

The association of non-O blood group and severity of liver fibrosis in patients with chronic hepatitis C infection

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Background: The progression rate of liver fibrosis is variable among patients with hepatitis C virus (HCV) infection. It is affected by environmental and genetic factors. We determined the association between ABO blood groups and the severity of liver fibrosis in HCV patients. **Materials and Methods:** This cross-sectional study was conducted on adult patients with chronic HCV infection who referred to university clinics in Isfahan, Iran in 2009-10. Patients with positive hepatitis B surface antigen (HBS Ag), human immunodeficiency virus antibody (HIV Ab), or other liver disorders, as well as those who had received anti-HCV treatments were not included. Blood type was determined and liver biopsy was obtained from all patients. The severity of hepatic fibrosis was graded from F0 to F4 based on METAVIR system. **Results:** Non-O blood groups were present in 53.8%, 72.3%, 75%, 87.5%, and 90.4% of the patients with F0-F4 grades of liver fibrosis, respectively ($p = 0.019$). There was no relationship between the severity of hepatic fibrosis and age or gender. In ordinal regression analysis, only the viral load ($p = 0.028$) and non-O blood group ($p = 0.001$) were associated with the severity of hepatic fibrosis. **Conclusion:** Non-O blood group is a genetic risk factor for progression of liver fibrosis in patients with HCV infection. It can play an important role in determining the prognosis and appropriate treatment among these patients. The association between blood group and liver fibrosis is probably due to the increased risk of venous thrombosis. Such relation can be the goal of preventive/treatment strategies.

Key words: ABO Blood Groups, Hepatitis C, Liver Fibrosis, Thrombosis.

INTRODUCTION

Infection with hepatitis C virus (HCV) had a prevalence of nearly 0.14% in 2005 and 0.12% in 2007 among the blood donors in Iran.^[1] Rather than hepatitis B infection which is the most common cause of viral chronic liver dysfunction at the present, recent studies have shown the prevalence of HCV infection to have an increasing rate. It might thus be the most common cause of chronic viral liver disease in the near future.^[2] Hence, identifying the prognostic and associating factors, which predict the condition of the disease and its response to the treatment, can play an important role in determining the therapeutic strategies.

The progression of liver fibrosis in patients with HCV infection is a dynamic process that varies considerably in different patients. The rate of progression is affected by the interaction between genetic factors of the host and pathogen, and environmental factors. Alcohol consumption, smoking, and environmental pollutants are known environmental (external) factors, which affect the progression of the disease.^[3,4] Host-related factors are gender, du-

ration of infection, race, human leukocyte antigen (HLA) types, genetic polymorphisms (e.g. patatin-like phospholipase-3), and concurrent infections [e.g. hepatitis B virus (HBV) and human immunodeficiency virus (HIV)].^[4,5]

New evidence has suggested a role for the clotting process, which can provoke liver fibrosis in patients with HCV infection.^[6] A number of studies reported several risk factors for venous thrombosis in patients with extensive liver fibrosis, and early cirrhosis due to HCV infection.^[7,8] Furthermore, the risk of thrombosis in patients with non-alcoholic fatty liver disease was associated with advanced liver fibrosis and nonalcoholic steatohepatitis.^[9] In addition, several other studies have shown that the mutation in factor V Leiden (FvL), the most common genetic risk factor for venous thrombosis, may be an independent risk factor for progression of liver fibrosis in HCV infection, as well.^[10,11] Moreover, C protein deficiency, increased factor VIII expression, and hyperhomocysteinemia, as other risk factors for thrombosis, are associated with the rapid progression of cirrhosis in chronic hepatitis C infection.^[7] A

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cohort study showed that liver fibrosis in HCV infection progressed slowly in hemophilic patients. In fact, only 3% of these patients, who were heavy alcohol users, died due to liver dysfunction.^[12] It seems that hypercoagulant and thrombotic states can reveal fibrogenesis in liver. In addition, anti-thrombotic state is associated with slower progression of liver fibrosis.^[6]

Another genetic factor, which almost doubles the risk of venous thrombosis, is the non-O blood group.^[13-15] Recent studies have shown that in patients with a known risk of venous thrombosis, such as mutation in FvL, the presence of non-O blood group may significantly increase the risk of venous thrombosis.^[16,17] Despite several evidence suggesting the genetic factor of non-O blood group as a risk factor for venous thrombosis, there is only one study suggesting the role of non-O blood group for liver fibrosis in patients with HCV infection with the relative risk of 1.8.^[18] Regarding the interaction between the genetic and environmental factors in liver fibrosis in HCV, and the importance of understanding the factors increasing the risk of liver fibrosis, we aimed to determine the association of non-O blood group with liver fibrosis in Iranian patients with HCV infection.

MATERIALS AND METHODS

Study population

This cross-sectional study was conducted from 2009 to 2010 on Iranian patients with HCV infection. The study was held in the gastroenterology clinics of Isfahan University of Medical Sciences (Isfahan, Iran). Inclusion criteria were an age of 18 years or over, proven HCV infection based on viral load and HCV antibody (Ab), negative hepatitis B surface antigen (HBs Ag), negative HIV Ab, no other liver diseases confirmed by necessary laboratory tests such as ceruloplasmin, 24-hour urine copper, and liver autoantibodies, and no previous HCV antiviral therapy. With an alpha of 0.05 and power of 80% according to previous studies,^[18] 200 consecutive patients were enrolled. The study was approved by the Ethics Committee of Isfahan University of Medical Sciences and written informed consents

were obtained from all participants. Demographic information, including age and gender, and ABO blood group of the patients were collected through interviews and reviewing patient records at the time of liver biopsy.

Histopathological study

To determine the severity of hepatic fibrosis, liver biopsies were taken with a BARD needle. The samples were fixed in Bouin's fluid, embedded in paraffin, and then divided into small pieces and stained with hematoxylin and eosin. Histological fibrosis was measured by a pathologist who was blinded to the study and patients' information. Based on METAVIR system, histological fibrosis was classified as F0 (without cirrhosis), F1 (portal fibrosis without septa), F2 (portal fibrosis with rare septa), F3 (numerous septa without cirrhosis), or F4 (cirrhosis).^[19] Data was analyzed in SPSS_{16.0} (SPSS Inc., Chicago, IL, US) using univariate and multivariate tests. P values of less than 0.05 were considered as significant.

RESULTS

In our study, 200 HCV infected patients (mean age = 38.7 ± 10.0 years, 77.4% male) were included. Among these, 50 patients (25%) had O blood group and 150 (75%) had non-O blood groups. The distribution of liver fibrosis was F0: 26 patients (13.0%); F1: 65 (32.5%); F2: 56 (28%); F3: 32 (16%), and F4: 21 (10.5%). The severity of liver fibrosis according to the patients' profile is shown in the Table 1. Non-O blood group was associated with more severe liver fibrosis ($p = 0.019$). However, there was no significant relationship between the severity of hepatic fibrosis and patients' age or gender ($p > 0.05$).

Considering the possibility of multiple factors affecting the severity of liver fibrosis, ordinal regression analysis was used to determine the association of each factor independently (Table 2). Among these factors, only the viral load ($p = 0.028$) and non-O blood groups ($p = 0.001$) were associated with the severity of hepatic fibrosis.

Table 1. Severity of liver fibrosis according to patients characteristics and blood type

	F0 n = 26	F1 n = 65	F2 n = 56	F3 n = 32	F4 n = 21	p
Age (years)	42.8 ± 9.2	38.3 ± 10.4	38.4 ± 10.7	36.6 ± 8.5	38.3 ± 9.0	0.207*
Male/female	6/20	15/49	11/45	6/26	7/14	0.763**
Non-O blood groups	14 (53.8%)	47 (72.3%)	42(75%)	28 (87.5%)	19 (90.4%)	0.019**

* Analysis of variance (ANOVA)

** Chi-square test

Table 2. Ordinal regression analysis of factors associated with the severity of liver fibrosis

	T	B	CI 95%	p
Age	-1.887	-0.015	-0.032-0.001	0.061
Male/Female	-0.136	-0.026	-0.409-0.356	0.892
Non-O blood groups	3.484	0.662	0.287-1.036	0.001
Viral load	2.216	4.086	4.499-7.723	0.028

DISCUSSION

The aim of the present study was to evaluate the relationship between non-O blood group and the severity of liver fibrosis in Iranian patients with HCV infection. The study showed that non-O blood group had a direct and independent correlation with the severity of hepatic fibrosis. It is thus an independent genetic predictor for the severity of liver fibrosis. These results were similar to the results of Poujol-Robert et al. in France who reported male gender, duration of HCV infection, the amount of alcohol consumption, and non-O blood group to be independent factors associated with the severity of liver fibrosis in HCV infected patients.^[18] However, there was not any association between the severity of liver fibrosis and gender in our study. Moreover, the two factors of duration of HCV infection and the amount of alcohol consumption were not evaluated in our study since history taking is not reliable enough to calculate the infection duration based on the date of the first intravenous injection or first blood infusion. On the other hand, due to our cultural and legal characteristics, patients would not provide true information about their alcohol use. Despite these differences however, like our findings, Poujol-Robert et al. suggested non-O blood group as a predictor of liver fibrosis with a relative risk of 1.8, independent of other factors including the duration of HCV infection and the value of alcohol consumption.^[18]

The association between the progression of liver fibrosis and non-O blood group can be justified considering that the blood type itself is an independent risk factor for venous thrombosis which has an important role in the progression of liver fibrosis. In addition, the mutation of FvL, which is the most common genetic risk factor for venous thrombosis, is significantly associated with the progression of liver fibrosis in HCV patients. Likewise, in animal models, liver fibrosis treated with anticoagulants like warfarin has reduced the rate of fibrosis.^[20] Two general mechanisms have been proposed for the activation of coagulation pathways in the progression of liver fibrosis. The first is that the throm-

bosis in the microscopic vessels of the liver can cause fibrosis due to tissue ischemia. Another possible mechanism is the activation of stellate cell by thrombin, which initiates the process of liver fibrogenesis.^[6]

Thrombotic effects of non-O blood group can be due to its effect on plasma levels of factor VIII.^[21] Therefore, non-O blood group has an evidently higher level of this factor comparing to the O blood group.^[22] On the other hand, higher risk of venous thrombosis is associated with high levels of factor VIII.^[23] The mechanisms through which factor VIII levels and increased risk of thrombosis are significantly influenced by ABO blood group have not been well identified.^[24] Despite the evidence indicating the role of thrombosis in the progression of liver fibrosis, there have been a few clinical studies on the effectiveness of anticoagulation therapy as an anti-fibrotic treatment. Moreover, the evidence does not recommend the routine use of this type of treatments. Further clinical investigations are thus needed to determine the safety and efficacy of such medications.^[6]

CONCLUSIONS

According to this study, non-O blood group is an independent genetic risk factor for the progression of liver fibrosis in patients with HCV infection. It plays an important role in determining the prognosis and therapeutic strategies of the disease. The relationship between non-O blood group and liver fibrosis is probably due to increased risk of venous thrombosis, which can be a target to prevent the progression of liver fibrosis in non-O blood group patients with HCV infection in future studies.

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