Association between ABO blood group and HCV-related hepatocellular carcinoma risk in China
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Abstract
The ABO blood group has previously been reported to be associated with risk for certain malignancies; however, data about the risks for hepatocellular carcinoma (HCC) according to blood type are limited. Thus, we conducted a retrospective case–control study to investigate whether the ABO blood group contributes to hepatitis C virus (HCV) infection–induced HCC.

From January 2010 to June 2016, 447 consecutive patients with chronic HCV infection were recruited. Of these patients, 217 had HCV-related HCC, and 230 had chronic hepatitis C (CHC) without HCC. We performed multivariate logistic regression to probe the association between the ABO blood group and HCC risk.

Compared with subjects with blood type O, patients with blood type A had an adjusted odds ratio (AOR) of 3.301 (95% confidence interval [CI], 1.927–5.653) for HCC after adjusting for age and gender. We found statistically significant associations between blood type A and HCC risk for both men (AOR [95% CI] = 4.192 [1.959–8.973]) and women (AOR [95% CI] = 2.594 [1.231–5.460]), and for patients aged below 70 years (<60 years: AOR [95% CI] = 3.418 [1.338–8.734]; 60–69 years: AOR [95% CI] = 3.917 [1.730–8.867]).

Thus, HCC risk is associated with ABO blood type in Chinese CHC patients, and CHC patients with blood type A are more susceptible to HCV-related HCC than patients with other blood types.

Abbreviations:
AOR = adjusted odds ratio, CHC = chronic hepatitis C, CI = confidence interval, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, NAFLD = nonalcoholic fatty liver disease.

Keywords: ABO blood group, chronic hepatitis C, hepatocellular carcinoma

1. Introduction
Hepatocellular carcinoma (HCC) is estimated to be the sixth most frequently diagnosed cancer and the third most common cause of cancer-related death worldwide.\cite{1} In China, HCC remains the second most common cause of death from cancer. In addition, a 5-year survival rate of only 10% has been reported for patients with this disease. Major known risk factors for HCC include infection with hepatitis B virus (HBV), infection with hepatitis C virus (HCV), and excessive alcohol consumption.\cite{2} Moreover, increasing evidence suggests that obesity and diabetes are also associated with HCC risk.\cite{3–5}

Mounting evidence has suggested an association of ABO blood type with several malignancy risks, including gastric, pancreatic, and epithelial ovarian cancer.\cite{6–8} However, the precise biological mechanism by which the ABO blood group may influence certain cancers has not yet been elucidated in detail.\cite{9} One possibility is that this link between blood group and cancer involves the dysregulation of the enzymatic activity of the ABO glycosyltransferases, which are involved in the modification of intercellular adhesion and cellular membrane signaling as well as in malignant cell immunosurveillance.\cite{10–13} During tumorigenesis, the alteration of these surface molecules may promote carcinoma progression and spread through a mechanism similar to that utilized by the ABO glycosyltransferases to modulate circulating von Willebrand factor levels in the plasma, resulting in an increased risk for development of venous thromboembolism.\cite{16,17} This association is particularly intriguing because von Willebrand factor was recently found to be an important modulator of angiogenesis and apoptosis, which are processes intimately involved in tumorigenesis.\cite{18}

A second possible explanation for this relationship is that alterations in ABO blood group–related host inflammatory state can also trigger tumor progression and metastasis.\cite{19–21} Recently, several genome-wide association studies uncovered an association between single nucleotide polymorphisms within the locus for the ABO gene and the levels of soluble intercellular adhesion molecule (sICAM)-1, tumor necrosis factor-alpha, P-selectin, and E-selectin in the plasma, suggesting a link between malignancies and the ABO blood type. All these adhesion molecules are important mediators of the systemic inflammatory response and are essential for immune cell recruitment. Therefore, these data may offer a biological basis for the postulated relationship between ABO blood type and...
cancer cell survival via a direct link between ABO blood group genes and tumor initiation and spread.

Recently, a link between ABO blood type and the risk of HCC was suggested. However, no other data regarding the association between the ABO blood group and HCV-related HCC risk have been published. Thus, the present study was conducted to precisely analyze the associations between ABO blood type and HCV-related HCC in Chinese patients. Furthermore, we examined the potential associations between ABO blood group distribution and liver cirrhosis severity in untreated patients with HCV infection.

2. Patients and methods

2.1. Patients

We conducted a retrospective case-control study at The First Hospital of Jilin University in China. Patients with chronic HCV infection, which was diagnosed according to anti-HCV antibodies and HCV RNA in the serum for 26 months, were recruited for inclusion in our study. Subjects who met the following inclusion criteria between January 2010 and June 2016 were enrolled in this study: ≥18 years of age, no treatment for cancer or with direct-acting antiviral agents or interferon, Han population, and residence in Jilin Province.

Subjects were excluded due to the following criteria: coinfection with human immunodeficiency virus or HBV; history or evidence of any other cancer; evidence or history of hepatitis other than hepatitis C; and presence of other liver disease, such as nonalcoholic fatty liver disease (NAFLD) or alcoholic liver disease.

Diagnosis of liver cirrhosis was confirmed with a liver biopsy or based on a combination of clinical findings, biochemistry, and radiology. Histology was used for diagnosis of HCC, or alternatively, images from at least 2 sources (ultrasound, enhanced computed tomography, hepatic angiography, or magnetic resonance imaging) were used to confirm HCC diagnosis.

The Independent Institutional Review Board of The First Hospital of Jilin University approved the recruitment of human subjects as well as the study protocol. Each participant provided written informed consent before enrollment.

2.2. Study variables

We analyzed the following variables in this study: gender, age, family history of liver cancer (defined as liver cancer in any of the first-degree relatives), presence of type 2 diabetes, HBsAg, cirrhosis, and ABO blood group. We analyzed patient biochemical parameters, such as alanine aminotransferase, aspartate aminotransferase, bilirubin, albumin, and prothrombin time, because these factors reflect impaired liver function; these were used to assess the relationship between the ABO blood group and severity of liver cirrhosis. In addition, the Child–Pugh score was calculated in patients with liver cirrhosis who did not have HCC. Abdominal ultrasound was also performed to determine the amount of ascites and the presence of cirrhosis.

2.3. Statistical analysis

To determine the significance of our findings, we employed a chi-squared test for categorical variables and an independent sample t test for continuous variables that exhibited a normal distribution. All tests were 2-tailed. Multivariate logistic regression was employed to adjust for possible confounding effects among the variables. In addition, we calculated the adjusted odds ratios (AORs) and 95% confidence intervals (CIs) for these comparisons. SPSS v. 13.0 (SPSS Inc., Chicago, IL) was used for data analysis, and a P value <0.05 indicated statistical significance.

3. Results

3.1. Patient characteristics and blood group distribution

Baseline clinical and demographic characteristics of the subjects are shown in Table 1. A total of 447 consecutive eligible subjects were enrolled as either cases or controls and were matched according to the degree of liver fibrosis/cirrhosis. The case group comprised 217 patients with newly diagnosed HCV-related HCC and included 131 male and 86 female patients with a mean age of 65.12 ± 8.11 years. The majority of cases (99.5%) had no family history of liver cancer. In addition, 177 patients (81.6%) were cirrhotic, and 177 patients (81.6%) had a blood type other than O. The control group consisted of 230 hospital chronic hepatitis C (CHC) patients without HCC. This group was representative of patients in northeast China, with a median age of 60.24 ± 8.90 years and a predominance of females (64.3%). All of the study subjects tested positive for Rh D type.

3.2. ABO blood group and HCC risk

Univariate analysis suggested that the sex ratio (male/female) was significantly higher in the HCC patient group than in the control group and that the age and ABO blood type distributions were significantly different between the HCC patients and the controls. These factors were then considered for multivariable analysis. After adjusting for age and gender, the AOR for patients with non-O blood types (A, B, and AB) was 2.538 (95% CI, 1.595–4.039, P < 0.001) compared to patients with blood type O. Moreover, blood types A and B were significantly associated
with HCC according to both univariate and multivariate analyses (Table 2).

In addition, we further evaluated whether stratified age and sex impacted the link between ABO blood type and HCC risk (Table 3). A significant association was detected between HCV-related HCC and blood type A in both males and females. Furthermore, male patients with non-O blood types exhibited a greater risk of HCC than those with blood type O. A significant association between the ABO blood group and HCC risk was observed among patients who were younger than 70 years, but such an association was not evident for patients who were older than 70 years.

### Table 2

Univariate and multivariate analyses of the demographic and clinical characteristics of HCV-related cases of HCC and CHC controls.

| Variables                        | Univariate OR (95% CI) | P     | AOR (95% CI) | P     |
|----------------------------------|------------------------|-------|--------------|-------|
| Sex                              |                        |       |              |       |
| Female                           | 1                      | <0.001| 2.972 (1.963–4.499) | <0.001|
| Male                             | 2.749 (1.874–4.033)    | <0.001|              |       |
| Age, y                           |                        |       |              |       |
| <60                              | 2.014 (1.304–3.110)    | 1     |              |       |
| 60–69                            | 3.706 (2.188–6.277)    |       |              |       |
| ≥70                              |                        |       |              |       |
| Family history of liver cancer   |                        | 0.597 |              |       |
| No                               |                        |       |              |       |
| Yes                              | 0.528 (0.048–5.863)    | <0.001|              |       |
| History of smoking               |                        | 0.788 |              |       |
| No                               |                        |       |              |       |
| Yes                              | 1.072 (0.647–1.775)    |       |              |       |
| Diabetes                         |                        | 0.365 |              |       |
| No                               |                        |       |              |       |
| Yes                              | 1.252 (0.769–2.037)    | <0.001|              |       |
| Liver cirrhosis                  |                        | 0.117 |              |       |
| No                               |                        |       |              |       |
| Yes                              | 0.664 (0.397–1.111)    | <0.001|              |       |
| ABO blood types                  |                        |       |              |       |
| O                                |                        | <0.001| 2.538 (1.595–4.039) | <0.001|
| A                                | 2.498 (1.615–3.864)    | <0.001|              |       |
| B                                | 3.319 (2.002–5.506)    | <0.001|              |       |
| AB                               | 1.886 (0.924–3.850)    | <0.001|              |       |
|                  | 2.045 (1.237–3.382)    | <0.001|              |       |

AOR = adjusted odds ratio, CHC = chronic hepatitis C, CI = confidence interval, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, OR = odds ratio.

### Table 3

Stratified multivariate analyses of the association between ABO blood type and HCC risk in patients with CHC.

| Factors                        | 0  | Non-O | A    | AB   |
|-------------------------------|----|-------|------|------|
| Sex                           |    |       |      |      |
| Female                        | 19/50 | 67/98 | 32/22 | 25/50 | 10/16 |
| AOR (95% CI)                  | 1.738 (924–3.269) | 2.594 (1.231–5.466) | 1.194 (0.570–2.499) | 1.806 (0.676–4.821) | 0.628 |
| P                             | 0.086 | 0.012 | 0.638 | 0.829 |       |
| Male                          | 21/33 | 110/49 | 56/23 | 44/20 | 10/6  |
| AOR (95% CI)                  | 3.756 (1.924–7.332) | 4.192 (1.959–8.793) | 3.426 (1.599–7.528) | 3.196 (0.954–10.711) | 0.060 |
| P                             | <0.001 | <0.001 | 0.002 | 0.060 |       |
| Age, y                        |    |       |      |      |
| <60                           | 9/38 | 46/67 | 24/26 | 14/29 | 8/12  |
| AOR (95% CI)                  | 2.691 (1.164–6.263) | 3.418 (1.338–8.734) | 1.976 (0.734–5.323) | 2.750 (0.841–8.997) | 0.894 |
| P                             | 0.021 | 0.010 | 0.178 | 0.094 |       |
| 60–69                         | 19/33 | 77/58 | 42/20 | 28/31 | 7/7   |
| AOR (95% CI)                  | 2.624 (1.305–5.278) | 3.917 (1.730–8.867) | 1.722 (0.773–3.839) | 2.948 (0.844–10.300) | 0.090 |
| P                             | 0.007 | 0.001 | 0.184 | 0.090 |       |
| ≥70                           | 12/12 | 54/22 | 22/9  | 27/10 | 5/3   |
| AOR (95% CI)                  | 2.348 (0.897–6.150) | 2.277 (0.728–7.125) | 2.689 (0.890–8.121) | 1.463 (0.272–7.869) | 0.658 |
| P                             | 0.082 | 0.157 | 0.080 | 0.060 |       |

AOR = adjusted odds ratio, CHC = chronic hepatitis C, CI = confidence interval, HCC = hepatocellular carcinoma.
3.3. ABO blood type and liver disease severity

A total of 377 liver cirrhosis patients were included in our study. We sought to evaluate the association between ABO blood group and liver disease severity in chronic liver disease. However, hepatic function may be impacted by the size and location of the tumor in patients with HCC, and as such, the Child–Pugh will not reflect the real severity of liver cirrhosis, so we excluded liver cirrhosis patients in the HCC group. A total of 200 liver cirrhosis patients were included in the control group. The Child–Pugh scores were calculated for these patients; however, no significant associations between the Child–Pugh classes of liver cirrhosis and the various blood groups were found (Table 4).

4. Discussion

Here, we describe an association between ABO blood type and HCC risk in CHC patients. The results of our hospital-based case–control study revealed a significantly increased risk for development of HCC in Chinese CHC patients with blood type A compared to that in Chinese CHC patients with blood type O, as reported for gastric, pancreatic, and epithelial ovarian cancers.[6–8] Similarly, Trevisani et al.[28] provided evidence that non-O blood types and cirrhosis were the primary independent risk factors for multinodular HCC development in an Italian patient cohort. Moreover, in a study of 90,731 patients, Lavarone et al.[29] reported significantly increased HCC risk for patients with non-O blood types. In a similar case–control study of 1538 Korean patients with newly diagnosed HCC, the presence of blood group A and more specifically, the presence of the AA genotype exhibited the highest risk for HCC development compared to other blood types.[27]

Thus, these results suggest that non-O blood types (in particular blood type A) are associated with more aggressive disease. As recently demonstrated, serum concentrations of sICAM-1 are significantly reduced in patients with blood group A compared to patients with blood group O, as this factor functions to inhibit lymphocytes from attaching to endothelial cells by binding to circulating cells via ICAM ligands.[23,30] Decreased sICAM concentrations in the serum have been found to be associated with numerous diseases, including tumor development and progression.[31,32] For instance, the A and B antigens, which are expressed during the initial stages of carcinoma development, enhance the basal resistance to apoptosis in rat colon adenocarcinoma cells, and therefore these specific antigens may facilitate immune surveillance escape.[13] These results provide a potential explanation for our finding that blood group A is associated with a higher risk for HCC than blood group O in CHC patients.

In this study, the 2 sexes exhibited differences in the association between HCC risk and the ABO blood group, and this finding is in accordance with the work of Li et al.[26] This discrepancy in gender-related HCC risk is well known, as the male-to-female ratio of HCC cases is as high as 4:1, and a gender-based dimorphism has been documented for the associations between HCC and other risk factors.[34–36] In addition, the association between HCC risk and the ABO blood group differed according to age. Stratified analyses demonstrated that this association was significant in patients aged less than 70 years but not significant in patients aged over 70 years after adjusting for confounding factors. One possible explanation is that older individuals are more susceptible to gastrointestinal cancer, a notion that has been described by Gong et al.[37] and such increased susceptibility masks the difference induced by blood group type to some extent. Interestingly, in the present study, there was no significant association between ABO blood group and the severity of liver disease, which is different from previously published reports.[38] That might be because of the small number of patients with Child–Pugh class C, and the result should be considered with caution.

This study had some limitations. First, the number of cases in our study was not large, leading to a small number of subjects for the subgroup analysis. These numbers were affected by our desire to exclude the impact of liver injury induced by other factors, such as alcoholic liver disease and NAFLD, and thus the subgroup analysis. These numbers were affected by our desire to exclude the impact of liver injury induced by other factors, such as alcoholic liver disease and NAFLD, and thus the nonsignificant findings with respect to the severity of liver disease may be a reflection of these low numbers. Second, for the small subjects, also, all cases in our study tested positive for Rh D type, which induce us not to further analyze the impact of Rh blood group on HCV-related HCC risk.

In conclusion, we found that the risk of HCC in Chinese CHC patients was associated with the patient’s ABO blood type. Furthermore, we found that CHC patients with blood type A were more susceptible to HCC than patients with other blood types.

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