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ORIGINAL RESEARCH

Associations Between ABO Blood Groups and Diseases in the Digestive System and Vein

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Purpose: The ABO blood type system is crucial for human blood transfusions. However, the relationships between ABO blood groups and diseases in the digestive system and vein have not been elucidated. We investigated the relationships between ABO blood groups and diseases in the digestive system and vein in this study.

Patients and Methods: A retrospective study on a Chinese population, including 1432 Crohn's disease (CD), 416 ulcerative colitis (UC), 1140 stomach cancer (SC), 841 colorectal cancer (CRC), 384 pancreatic cancer (PC), 520 liver cancer (LC), and 563 venous thrombosis (VT) patients, was performed. Furthermore, 896 healthy subjects were enrolled as normal controls (NC) in this study. The demographic characteristics of patients and NC were compared using the unpaired *t*-test and χ^2 test. Multivariate logistic regression model was used to evaluate the association between ABO blood groups and CD and VT.

Results: ABO blood groups distributions in UC, SC, CRC, PC, and LC patients did not differ from that of NC, but CD and VT patients had significant difference of ABO blood group distribution from that of NC ($p = 0.015$ and $p = 0.002$, respectively). Patients with CD and VT had considerably lower rates of type O blood ($p = 0.011$ and $p = 0.001$, respectively) and significantly higher rates of type AB blood ($p = 0.013$ and $p = 0.022$, respectively) than those with NC. Multivariate logistic regression analysis showed the association of CD and VT with non-O blood types was still significant with a higher risk than with blood group O after adjusting for age and gender (OR = 1.355, 95% CI = 1.100–1.670, $p = 0.004$ and OR = 1.465, 95% CI = 1.131–1.903, $p = 0.004$, respectively).

Conclusion: ABO blood groups distributions in CD and VT patients significantly differed from that of NC. Non-O blood group could be a new predictor for CD and VT.

Keywords: ABO blood groups, non-O blood group, CD, VT

Introduction

The most crucial blood group system used in human blood transfusions is the ABO blood type system,[1–4] which Karl Landsteiner initially identified in 1900.[5] ABO gene regulates the expression of the ABO blood group system's antigens (A, B, and H determinants), and it encodes a glycosyltransferase that changes complex carbohydrates on the surface of human cells and tissues in addition to the red blood cell (RBC) surface, including platelets, the epithelium, the vascular endothelium, and sensory neurons.[4,6] ABO blood group system has been reported that it was associated with many human diseases.[4,7] However, the relationships between ABO blood groups and diseases in the digestive system and vein have not been elucidated. Thus, we investigated the relationships between ABO blood groups and diseases in the digestive system and vein, among which digestive system diseases included CD, UC, SC, CRC, PC, and LC, and vein diseases included VT in this study.

Inflammatory bowel disease (IBD), clinically presenting as Crohn's disease (CD) or ulcerative colitis (UC), is a collection of inflammatory, relapsing, and chronic gastrointestinal illnesses.[8] It has been a worldwide healthy problem with increasing incidence of IBD and hospitalization of IBD patients.[8] In addition, Cancer[9] and cardiovascular disease (CVD)[10] are two of the leading causes of death in China. Thus, it is vital to identify the mechanism of these diseases as aforesaid. There was growing interest in the connection between ABO blood types and human disorders. ABO blood type

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is genetically linked to a number of autoimmune illnesses, cancer risk factors, and cardiovascular diseases, according to mounting evidence.[4,11,12] In particular, according to several researches, there was a substantial link between non-O blood type and IBD. A previous study had shown that the risk of developing CD was higher in Caucasus region for non-O blood group.[13] Similarly, Cheng et al recently discovered a statistically significant link between the non-O blood type and an increased chance of getting CD in Chinese Han.[12] However, there was a research had shown that ABO blood type was not related to the prevalence of CD in southern China.[14] The impact of non-O blood type on CD was inconsistent, making it more interesting. Rarely studies found a connection between UC and non-O blood type. In addition, some studies have found a meaningful relationship between non-O blood type and other diseases. There was a higher risk in stomach cancer (SC),[15] colorectal cancer (CRC),[16,17] pancreatic cancer (PC),[18] and liver cancer (LC)[19,20] with non-O blood types. Several systematic reviews, meta-analyses and clinical researches have consistently confirmed that non-O blood types alone contributed to an approximately twofold increased risk of venous thromboembolism (VTE).[21–25] However, the exact relationship and the underlying mechanism between non-O blood group and the aforementioned diseases have not yet been clear.

The distributions of ABO blood types in patients with digestive system diseases (CD, UC, SC, CRC, PC, and LC) and vein disorders (VT) and NC were examined in this retrospective study. Additionally, the relationships between non-O blood type and several disorders were examined.

Materials and Methods

Patients

Between January 2019 and February 2021, a retrospective research was conducted at Sir Run Run Shaw Hospital, Zhejiang University School of Medicine. Patients with digestive system diseases (CD, UC, SC, CRC, PC, and LC) and vein disorders (VT) were enrolled in this study. Furthermore, healthy subjects were also enrolled as NC in this study. The volunteers were all Han Chinese. The diagnosis of IBD (CD and UC) met clinical, laboratory, radiological, endoscopic, and histopathologic criteria.[26] All cancers (SC, CRC, PC, and LC) were diagnosed based on confirmed histopathology. This study enrolled patients with the mentioned diseases, with an exclusion criterion that ensured the absence of any concurrent co-existing conditions among the mentioned diseases. Furthermore, exclusion criteria also included individuals with other autoimmune diseases, acute or chronic infections, other cancers, or other medical issues. In addition, no patients took anticoagulant medications. The electronic medical history of all volunteers had been extracted. The electronic medical record included data on age, gender proportion, and ABO blood types distribution among all patients and healthy subjects. The conventional agglutination procedure was used to identify ABO blood types. The Human Research Ethics Committee at Sir Run Run Shaw Hospital, Zhejiang University School of Medicine gave its approval for this study, which was carried out in line with the Declaration of Helsinki. The written informed consent of the subjects was waived due to the retrospective nature of this investigation. And all participants' data were anonymized.

Statistical Analysis

SPSS version 26.0 (IBM SPSS, Chicago, IL, USA) was used for all statistical analyses. An unpaired *t*-test was used to compare continuous normally distributed data, and the results were displayed as mean ± standard deviation. The χ^2 test was used to analyze categorical variables, which were expressed as counts (percentage). To determine the factors that significantly differed across the various illness groups and to determine odds ratios (OR) with 95% confidence intervals (95% CIs), univariate and multivariate logistic regression analyses were utilized. Statistical significance was defined as a double tailed $p < 0.05$.

Results

The Characteristics of Patients

The NC and patients' demographics were included in Table 1. The sum of 1432 CD, 416 UC, 1140 SC, 841 CRC, 384 PC, 520 LC, and 563 VT patients were recruited into this study. Furthermore, 896 healthy subjects were also enrolled as NC in this study. Compared to NC, the average ages of CD and UC patients were all younger than NC (35.1 ± 12.9 vs

Table 1 Demographic Characteristics of the Study Population

Characteristics	CD (n = 1432)	UC (n = 416)	SC (n = 1140)	CRC (n = 841)	PC (n = 384)	LC (n = 520)	VT (n = 563)	NC (n = 896)
Age (years)	35.1 ± 12.9**	44.9 ± 14.8**	64.5 ± 10.6**	63.2 ± 11.9**	63.6 ± 10.3**	61.0 ± 11.5**	61.8 ± 15.6**	49.0 ± 10.7
Gender								
Male	937 (65.4)	239 (57.5)	797 (69.9)**	529 (62.9)	245 (63.8)	433 (83.3)**	318 (56.5)*	565 (63.1)
Female	495 (34.6)	177 (42.5)	343 (30.1)	312 (37.1)	139 (36.2)	87 (16.7)	245 (43.5)	331 (36.9)

Notes: All values shown were mean ± standard deviation or counts (percentage). *p < 0.05; **p < 0.01 compared to NC.
Abbreviations: CD, Crohn's disease; UC, ulcerative colitis; SC, stomach cancer; CRC, colorectal cancer; PC, pancreatic cancer; LC, liver cancer; VT, venous thrombosis; NC, normal controls.

49.0 ± 10.7 years, p < 0.01 and 44.9 ± 14.8 vs 49.0 ± 10.7 years, p < 0.01, respectively). However, the mean ages of SC, CRC, PC, LC, and VT patients were all older than NC having differences that were all statistically significant (all p < 0.01). Regarding gender proportion, the proportion of males was higher than NC in SC (p < 0.01) and LC (p < 0.01). However, the proportion of males was lower than NC in VT patients (p < 0.01). And the gender percentage in CD, UC, CRC, and PC did not differ from that of NC.

ABO Blood Groups Distributions

Table 2 displayed that the distribution of ABO blood groups in UC, SC, CRC, PC, and LC patients did not differ from that of NC, but CD and VT patients had significant difference of ABO blood group distribution from that of NC (p = 0.015 and p = 0.002, respectively). Individuals with CD and VT had considerably lower rates of O blood type (p = 0.011 and 0.001, respectively) and had significantly higher rates of AB blood type (p = 0.013 and 0.022, respectively) than individuals with NC.

Relationship Between ABO Blood Types and CD

In this study, logistic regression analyses were carried out to examine the effect of ABO blood groups in CD risk (Table 3). With univariate regression analysis, the risk of CD was higher for non-O blood group than for O blood group (OR = 1.268, 95% CI = 1.056–1.521, p = 0.011); with multivariate regression analysis, the association of non-O blood types and CD was still significant with a higher risk compared to blood type O (OR = 1.355, 95% CI = 1.100–1.670, p = 0.004) after adjusting for age and gender. Furthermore, we found that AB blood group had the highest risk for CD among ABO blood group in both univariate regression analysis (OR = 1.639, 95% CI = 1.201–2.253, p = 0.002) and multivariate regression analysis (OR = 1.704, 95% CI = 1.198–2.436, p = 0.003). However, it was very interesting that we found B blood group was not associated with CD in both univariate regression analysis and multivariate regression analysis.

Table 2 Distributions of ABO Blood Groups in Patients with Different Diseases and NC

Groups	Blood Types, n (%)								P value
	A	P_A	B	P_B	O	P_O	AB	P_{AB}	
CD (n = 1432)	483 (33.7)	0.533	397 (27.7)	0.796	388 (27.1)	0.011*	164 (11.5)	0.013*	0.015*
UC (n = 416)	132 (31.7)	0.788	125 (30.0)	0.291	118 (28.4)	0.181	41 (9.9)	0.341	0.405
SC (n = 1140)	381 (33.4)	0.653	268 (23.5)	0.055	394 (34.6)	0.230	97 (8.5)	0.840	0.273
CRC (n = 841)	265 (31.5)	0.666	215 (25.6)	0.431	285 (33.9)	0.411	76 (9.0)	0.564	0.719
PC (n = 384)	112 (29.2)	0.242	102 (26.6)	0.805	131 (34.1)	0.466	39 (10.1)	0.273	0.487
LC (n = 520)	185 (35.6)	0.234	126 (24.2)	0.215	167 (32.1)	0.974	42 (8.1)	0.904	0.554
VT (n = 563)	208 (36.9)	0.080	155 (27.5)	0.901	133 (23.6)	0.001**	67 (11.9)	0.022*	0.002**
NC (n = 896)	291 (32.5)	Ref	244 (27.2)	Ref	287 (32.0)	Ref	74 (8.3)	Ref	Ref

Notes: All values shown were counts (percentage). *p < 0.05; **p < 0.01.
Abbreviations: Ref, reference; CD, Crohn's disease; UC, ulcerative colitis; SC, stomach cancer; CRC, colorectal cancer; PC, pancreatic cancer; LC, liver cancer; VT, venous thrombosis; NC, normal controls; P_A, p value of distribution difference of blood group A between aforesaid diseases patients and NC; P_B, p value of distribution difference of blood group B between aforesaid diseases patients and NC; P_O, p value of distribution difference of blood group O between aforesaid diseases patients and NC; P_{AB}, p value of distribution difference of blood group AB between aforesaid diseases patients and NC; P value, p value of distribution difference of ABO blood group between aforesaid diseases patients and NC.

Table 3 Results of Univariate and Multivariate Analyses on ABO Blood Groups and Risk of CD

	Univariate OR (95% CI)	P value	Multivariate OR (95% CI)	P value
Age[a]	0.118 (0.096–0.143)	<0.001**	1.297 (1.062–1.586)	0.011*
Gender[b]	0.902 (0.758–1.073)	0.244	0.111 (0.091–0.136)	<0.001**
A[c]	1.228 (0.994–1.516)	0.056	1.387 (1.091–1.765)	0.008**
B[c]	1.204 (0.965–1.501)	0.100	1.215 (0.945–1.563)	0.129
AB[c]	1.639 (1.201–2.253)	0.002**	1.704 (1.198–2.436)	0.003**
Non-O[c]	1.268 (1.056–1.521)	0.011*	1.355 (1.100–1.670)	0.004**

Notes: All values shown were OR (95% CI). *p < 0.05; **p < 0.01. [a]High age group compared to low age group. [b]Female group compared to male group. [c]Compared to blood group O.
Abbreviations: CD, Crohn's disease; OR, odds ratio; CI, confidence interval.

Relationship Between ABO Blood Types and VT

Similarly, logistic regression analyses were conducted to further investigate the possible contribution of ABO blood group to VT risk (Table 4). Using univariate regression analysis, the risk of VT was found to be higher in non-O blood type than in O blood type (OR = 1.520, 95% CI = 1.198–1.936, p = 0.001); using multivariate regression analysis, the association of non-O blood types and VT was still significant with a higher risk compared to blood type O (OR = 1.465, 95% CI = 1.131–1.903, p = 0.004) after adjusting for age and gender. Furthermore, we found that AB blood group had the highest risk for VT among ABO blood group in both univariate regression analysis (OR = 1.954, 95% CI = 1.323–2.885, p = 0.001) and multivariate regression analysis (OR = 2.225, 95% CI = 1.450–3.420, p = 0.000). We similarly found B blood group was not associated with VT in multivariate regression analysis.

Discussion

In this investigation, there were significant variations in the distribution of ABO blood types in CD and VT patients compared to NC (p = 0.015 and 0.002, respectively). Regarding the distributions of ABO blood types, there were no statistically significant difference in UC, SC, CRC, PC, and LC patients compared to NC. The relationships between ABO blood type and UC, SC, CRC, PC, and LC were inconsistent with other studies.[15,17,18,20] This may be due to differences in the number of populations and ethnicities studied. Furthermore, we found that the proportion of males was lower in VT patients than NC (p < 0.01). And there was no difference in the sex ratio of CD patients compared to NC. However, the proportion of males was higher than the proportion of females in CD patients in this study. Researches on gender predisposition of CD were inconsistent. Some studies have showed that CD had no specific gender preference.[27,28] And a pooled analysis revealed that females were susceptible to CD from adolescence to middle-age in the Western countries.[29] However, it differed markedly from what occurred in Asian countries, where males predominated among CD patients in the range of 10–50 years old.[30,31] Female sex hormones was considered to the main cause that female had a higher risk of CD in

Table 4 Results of Univariate and Multivariate Analyses on ABO Blood Groups and Risk of VT

	Univariate OR (95% CI)	P value	Multivariate OR (95% CI)	P value
Age[a]	5.777(4.569–7.342)	<0.001**	5.852 (4.615–7.460)	<0.001**
Gender[b]	1.310 (1.056–1.624)	0.014*	1.271 (1.004–1.609)	0.047*
A[c]	1.542 (1.176–2.027)	0.002**	1.495 (1.113–2.013)	0.008**
B[c]	1.362 (1.022–1.818)	0.036*	1.232 (0.901–1.686)	0.191
AB[c]	1.954 (1.323–2.885)	0.001**	2.225 (1.450–3.420)	0.000**
Non-O[c]	1.520 (1.198–1.936)	0.001**	1.465 (1.131–1.903)	0.004**

Notes: All values shown were OR (95% CI). *p < 0.05; **p < 0.01. [a]High age group compared to low age group. [b]Female group compared to male group. [c]Compared to blood group O.
Abbreviations: VT, venous thrombosis; OR, odds ratio; CI, confidence interval.

West,[32] while gender predisposition of CD maybe not dependent on hormonal influences in Asia. Concomitant sex-based nonbiological determinants and hormone-independent mechanisms more likely played an important role in male predisposition of CD in Asia, like different types and levels of environmental exposures in females and males.[33] In addition, higher access of healthcare utilization in males may be another cause of male predominance of CD in Asia on account that males had higher healthcare utilization so that they could have more frequent diagnostic examination and be more exposed to antibiotics or other risk factors for CD compared to females in Asia.[34]

In a propensity score-matched study, individuals with non-O blood type had greater thrombosis[23,35,36] and CD[12] risk than patient with O blood type, which was consistent with findings from our study. We found that non-O blood types were significantly related to a higher CD (OR = 1.355, 95% CI = 1.100–1.670, p = 0.004) and VT (OR = 1.465, 95% CI = 1.131–1.903, p = 0.004) risk compared to blood group O in multivariate regression analysis. Furthermore, AB blood group had the highest risk for CD (OR = 1.704, 95% CI = 1.198–2.436, p = 0.003) and VT (OR = 2.225, 95% CI = 1.450–3.420, p = 0.000) among ABO blood group in multivariate regression analysis. It was worth noting that B blood group was not associated with CD and VT in multivariate regression analysis. Nevertheless, the exact underlying mechanisms involved remain unclear.

O blood type was obviously less common in CD and VT patients than it was in NC (p = 0.011 and 0.001, respectively). However, AB blood type was significantly more common in CD and VT patients than it was in NC (p = 0.013 and 0.022, respectively). A study showed staff with non-O blood type in hospital had significant higher rate of getting SARS-CoV compared to staff with O blood type in hospital.[37] And it may be the presence of natural anti-blood group antibodies, particularly anti-A antibody in the blood.[38] Thus, we speculated that patients with non-O blood group had higher risk of CD and VT compared with O-blood group because of fewer anti-A antibody in the blood of patients with non-O blood group. And this assumption could also explain why AB blood group had the highest risk for CD and VT among ABO blood group in multivariate regression analysis and why B blood group was not associated with CD and VT in multivariate regression analysis. This hypothesis needed to be further proved. There was also another hypothesis. As we well known, a group of enzymes known as Fucosyltransferases (FUTs) speed up the transfer of the sugar fucose to acceptor substrates such glycoproteins, glycolipids, and oligosaccharides.[39] The FUT2 locus encodes a human specific FUT enzyme, and its function in the production of blood type antigen ABO has been widely studied.[40,41] Recently, genome-wide association studies have identified FUT2 as involved in the genetic susceptibility of CD.[42] However, the role of FUT2 in the pathogenesis of UC have not been confirmed. There was no relationship between FUT2 and UC in a study,[43] while another study showed that the risk of UC was higher in the secretory status of FUT2.[44] More and more evidences suggest the mechanism of IBD occurrence is owing to a changed immune response to the gut microbiota in genetically predisposed people, and it is also influenced by certain modification in particular bacterial infections.[45,46] FUT2 is an essential factor influencing intestinal microbial diversity.[44,47] We speculated that ABO mutation may be served as a genetic risk factor for CD on account that there was functional correlation between FUT2 and ABO gene products. Furthermore, blood type antigens and the FUT2's secretory status played an important role in regulating gut microbiota composition. The ABO blood type is one of the first identified risk factors for VT.[48] Higher amounts of factor VIII and von Willebrand factor were found in non-O blood type patients; thus, patients of non-O blood type were more likely to develop VT than patients of O blood type.[49–52]

This study has some limitations. Firstly, due to retrospective studies' nature, a causal relationship could not be established. Secondly, only Chinese subjects were included in this study. Thus, the conclusions derived from this study should be carefully distributed to other races. However, the advantage of this study lies in the sufficient number of subjects.

Conclusion

This study found that the distribution of ABO blood type among patients with CD and VT was considerably different from that of NC. Non-O blood types were strongly associated with a higher CD and VT risk compared to blood group O. Furthermore, non-O blood group could be a new predictor for CD and VT. However, further in-depth investigations are needed to explore the exact underlying mechanisms.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors have no competing interests in this work.

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