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Association between ABO blood group and risk of Crohn's disease: A case-control study in the Chinese Han population

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Abstract

Background: Blood group O has been reported to be a potentially protective factor for Crohn's disease (CD) susceptibility in Caucasian and Korean populations, but a similar conclusion was not found in a Chinese study. The present study investigated the potential association in the Chinese Han population.

Methods: We included 275 CD patients, 132 ulcerative colitis (UC) patients and 1201 healthy individuals in this case-control study. The demographic characteristics and ABO blood group were compared among the three groups. The clinical characteristics and treatment of CD were further investigated according to the blood group distribution.

Results: The blood group distribution in CD patients was significantly different from healthy controls, and the frequency of O blood in CD patients was significantly lower compared to healthy controls. After adjusting for age and gender, the non-O blood groups remained significantly associated with CD susceptibility in propensity score-adjusted and propensity score-matched analyses. Compared to CD patients with non-O blood groups, patients with O blood were at a lower risk of developing penetrating disease, more likely to receive immunosuppressant treatment and less likely to receive biological treatment.

Conclusion: Our results confirmed that non-O blood groups were significantly associated with an increased risk of CD in the Chinese Han population.

KEYWORDS
ABO blood group, biomarkers, Crohn's disease, immunology, inflammatory bowel disease

1 | INTRODUCTION

Inflammatory bowel disease (IBD), which encompasses ulcerative colitis (UC) and Crohn's disease (CD), is a group of chronic and relapsing inflammatory disorders of the intestine.[1] Although the exact pathogenic mechanisms of IBD are not clear, it is widely accepted that IBD results from a dysregulated immune response to intestinal environmental antigens, such as intestinal microbiota and food antigens in genetically susceptible individuals.

The ABO blood group system, which was the first genetic trait discovered by Karl Landersteiner in the early 20th century, is divided into four phenotypic groups named A, B, AB and O. Red blood cells (RBCs) and various human cells express ABO antigens, including the intestinal epithelium.[2] The ABO blood groups are relevant to immunohaematology and transfusion medicine, and it is associated with the risk of various diseases, including cardiovascular diseases,[3-5] gastrointestinal cancers[6,7] and autoimmune diseases.[8-10] Some studies addressed the potential role of ABO blood groups in IBD development.

A previous study in a Caucasian population revealed that patients with non-O blood groups had a higher risk for CD.[11] This study also found that the non-O blood groups were associated with a higher risk of developing a stricturing or penetrating disease. A recent study in a Korean population showed a similar result that the O blood group was a protective factor against CD.[12] However, the conclusions on the influence of ABO blood groups on CD are not consistent. Yu et al. found that the ABO blood groups were not associated with CD risk in Southern China.[13] The present study investigated the prevalence of blood groups in patients with CD and healthy controls in the Chinese Han population from Fujian Province in Southeast China. We also evaluated the association between the ABO blood groups and the disease characteristics of CD.

2 | MATERIALS AND METHODS

2.1 | Subjects

The present study included 275 CD patients, 132 UC patients and 1201 healthy controls. All subjects were recruited from the First Affiliated Hospital of Fujian Medical University, which is a tertiary care centre for the management of IBD in Fujian, between January 2016 and December 2017. All subjects were of Chinese Han descent. The diagnosis of IBD was established using clinical, endoscopic, radiological and histological criteria.[14] Disease activity in CD patients was evaluated using the CD activity index (CDAI) score. Patients with a CDAI score less than 150 were considered inactive, and a CDAI score higher than 150 indicated active disease.[15] The data, including demographic, body mass index (BMI), smoking status, history of intestinal surgery, disease duration and disease location and behaviour, were collected from electronic medical records for each patient during hospitalization. Information on medical treatment was also collected. The ABO blood groups were tested using the standard agglutination method. The ABO blood group distribution is different between populations and ethnicities. Therefore, healthy subjects with Chinese Han ethnicity who received routine health checks, including blood group testing, in our centre were selected as controls. Patients with autoimmune diseases, tumours and IBD family history were excluded. Patients who did not authorize the use of their medical records for research were also excluded from the study.

2.2 | Statistical analysis

Statistical analyses were performed using SPSS software (Version 22.0; IBM SPSS, Chicago, IL, USA). Continuous normally distributed variables are presented as means $\pm$ standard deviation (SD) and were compared using Student's t-test. Categorical variables are presented as counts and proportion and were assessed using the Chi-squared or Fisher's exact test, as appropriate. Logistic regression was used for analysis of risk factors. Factors with p values less than 0.10 in the univariate analysis were included in the multivariate analysis.

Propensity score-adjusted and propensity score-matched analyses were used to control the confounding factors. Logistic regression analysis was performed using age and sex to calculate propensity scores. Subsequently, a 1:1 case-control propensity score matching without replacement was carried out using nearest-neighbour matching approach, with a calliper of 0.2 SD of the logit of the propensity score. A p values less than 0.05 was considered significant.

3 | RESULTS

3.1 | Baseline characteristics

A total of 275 patients with Crohn's Disease (CD), 132 patients with ulcerative colitis (UC) and 1201 healthy subjects who received blood group testing during a routine health check were included in our study. Compared to the healthy controls, the mean age of CD patients was younger (30.2 $\pm$ 12.0 vs. 33.7 $\pm$ 15.0 years, $p < 0.001$). The mean age of UC patients was older than the healthy controls (45.7 $\pm$ 14.4 years, $p < 0.001$). The proportion of females in the CD and UC groups was lower than the control group (36.0% vs. 54.7%, $p < 0.001$ and 34.8% vs. 54.7%, $p < 0.001$ respectively).

3.2 | Distribution of ABO blood groups in different groups

The distribution of ABO blood groups in our study population is presented in Table 1. There were 94 (34.2%) CD patients with blood group A, 76 (27.6%) patients with blood group B, 28 (10.2%) patients with blood group AB and 77 (28.0%) patients with blood group O in the CD group. Among the 132 UC patients, there were 35 (26.5%) patients with blood group A, 37 (28.0%) patients with blood group B, 6 (4.5%) patients with blood group AB and 54 (40.9%) patients with blood group O. In the healthy control group, there were 359 (29.9%) subjects with blood group A, 300 (25.0%) subjects with blood group B, 89 (7.4%) subjects with blood group AB and 453 (37.7%) subjects with blood group O. The ABO blood group distribution was statistically comparable between the UC group and the control group ($p = 0.46$). However, the blood group distribution in CD patients compared to healthy controls was significantly different. The proportion of blood group O in CD patients was significantly lower compared to healthy controls ($p = 0.002$).

3.3 | Association of ABO blood groups and risk of Crohn's disease

To investigate the possible role of ABO blood groups in the risk of CD, logistic regression analyses were performed (Table 2). Univariate

regression analysis revealed that age, gender and blood group O were significantly associated with the presence of CD. After adjusting for age and gender, blood group O remained significantly associated with lower risk of CD in multivariate analysis (OR = 0.562, 95% CI: 0.342 ~ 0.924, p = 0.023). These results suggest that blood group O may be an independent protective factor for CD.

3.4 | Propensity score analyses on ABO blood groups and risk of Crohn's disease

To estimate the effect sizes of the overall study population and increase the statistical power of our analysis, a propensity score-adjusted analysis was first performed (Table 3). Propensity score adjusted analysis revealed that individuals with non-O blood groups had a significantly higher risk of suffering from CD than those with blood group O (OR = 1.482, 95 CI: 1.106 ~ 1.985, p = 0.008). Of the different non-O blood groups, both blood groups A (OR = 1.475,

95 CI: 1.052 ~ 2.068, p = 0.024) and AB (OR = 1.781, 95 CI: 1.083 ~ 2.928, p = 0.023) were also had an increased risk of developing CD.

To further reduce the confounding effect of age and gender, a propensity score-matched analysis was then conducted. In total, 275 CD cases and 275 controls were successfully matched. Both gender and age were well balanced between cases and controls after matching. In the matched cohort, the positive association between non-O blood groups and risk of CD was replicated (OR = 1.794, 95 CI: 1.256 ~ 2.562, p = 0.001). Similar results for blood groups A, B and AB were also obtained in the propensity score-matched analysis (Table 3).

3.5 | Clinical characteristics of Crohn's disease patients according to blood phenotype

The clinical characteristics of CD patients were divided into an O blood group and Non-O blood groups, as shown in Table 4. Patients

TABLE 1 Distribution of ABO groups in patients with Crohn's disease, ulcerative colitis and healthy controls

Groups	Blood type, n (%)				
	A	B	AB	O	p
CD (n = 275)	94 (34.2)	76 (27.6)	28 (10.2)	77 (28.0)	0.002[*]
UC (n = 132)	35 (26.5)	37 (28.0)	6 (4.5)	54 (40.9)	0.460[*]
Control (n = 1201)	359 (29.9)	300 (25.0)	89 (7.4)	453 (37.7)	

Abbreviations: CD, Crohn's disease; Control, Healthy controls; UC, Ulcerative colitis.
*Compared to the Control group.

TABLE 2 Results of univariate and multivariate analyses on ABO blood groups and risk of Crohn's disease

	Univariate		Multivariate	
	OR (95% CI)	p	OR (95% CI)	p
Age	0.982 (0.973 ~ 0.992)	0.000	0.984 (0.975 ~ 0.994)	0.001
Gender (Male)	2.147 (1.637 ~ 2.816)	0.000	2.128 (1.619 ~ 2.798)	0.000
A	1.218 (0.922 ~ 1.609)	0.165	0.827 (0.507 ~ 1.350)	0.447
B	1.147 (0.854 ~ 1.540)	0.362	0.787 (0.476 ~ 1.301)	0.350
AB	1.416 (0.906 ~ 2.214)	0.127	1.271 (0.769 ~ 2.100)	0.350
O	0.642 (0.481 ~ 0.856)	0.003	0.562 (0.342 ~ 0.924)	0.023

Abbreviations: CD, Crohn's disease; CI, confidence interval; OR, odds ratio.

TABLE 3 Results of propensity score analyses on ABO blood groups and risk of Crohn's disease

Blood group	Propensity score-adjusted [a]				Propensity score-matched			
	CD[b]	Control[b]	OR (95% CI)	p	CD[b]	Control[b]	OR (95% CI)	p
O	77 (28.0)	453 (37.7)	1.0 (reference)		77 (28.0)	113 (41.1)	1.0 (reference)	
A	94 (34.2)	359 (29.9)	1.475 (1.052 ~ 2.068)	0.024	94 (34.2)	79 (28.7)	1.746 (1.151 ~ 2.648)	0.009
B	76 (27.6)	300 (25.0)	1.403 (0.984 ~ 1.999)	0.061	76 (27.6)	64 (23.3)	1.743 (1.121 ~ 2.709)	0.014
AB	28 (10.2)	89 (7.4)	1.781 (1.083 ~ 2.928)	0.023	28 (10.2)	19 (6.9)	2.163 (1.128 ~ 4.145)	0.020
Non-O	198 (72.0)	748 (62.3)	1.482 (1.106 ~ 1.985)	0.008	198 (72.0)	162 (58.9)	1.794 (1.256 ~ 2.562)	0.001

Abbreviations: CD, Crohn's disease; CI, confidence interval; OR, odds ratio.
[a]Propensity score as a continuous covariate was integrated in the logistic regression model.
[b]Data were expressed as N(%).

with O blood had a lower risk of developing penetrating disease compared to the non-O blood groups (OR = 0.425 95% CI: 0.197 ~ 0.917, $p = 0.026$). Patients with O blood were more likely to receive immunosuppressant treatment (OR = 2.326, 95% CI: 1.325 ~ 4.004, $p = 0.002$) and less likely to receive biological treatment (OR = 0.351, 95% CI: 0.196 ~ 0.627, $p < 0.001$), which suggests that patients with O blood had a lower progressive disease behaviour.

4 | DISCUSSION/CONCLUSION

The ABO blood group system was well established in the early 1990s. ABO blood antigens are specific carbohydrate sugars, which are expressed on the surface of RBCs and various human cells and tissues, such as the gastrointestinal epithelium, vascular endothelium, platelets and sensory neurons.[2] Therefore, beyond

TABLE 4 Clinical characteristics of Crohn's disease patients according to blood type

Patient characteristics	Total	Non-O groups (n = 198)	O group (n = 77)	p
	275	198 (72.0)	77 (28.0)	
Gender, n (%)				
Male	176 (64.0)	124 (62.6)	52 (67.5)	0.447
Female	99 (36.0)	74 (37.4)	25 (32.5)	
BMI (kg/m^2), n (%)				
<18.5	140 (50.9)	102 (51.5)	38 (49.4)	0.764
18.5 ~ 23.9	115 (41.8)	83 (41.9)	32 (41.6)	
≥24	20 (7.3)	13 (6.6)	7 (9.1)	
Disease duration, (mean ± SD), Mo		47.4 ± 53.0	46.5 ± 41.4	0.172
Disease activity, n (%)				
Active disease	102 (37.2)	73 (37.1)	29 (37.7)	0.926
Inactive disease	172 (62.8)	124 (62.9)	48 (62.3)	
Age at diagnosis, n (%)				
A1(≤16 years)	41 (14.9)	33 (16.7)	8 (10.4)	0.342
A2(17 ~ 40 years)	198 (72.0)	138 (69.7)	60 (77.9)	
A3 (>40 years)	36 (13.1)	27 (13.6)	9 (11.7)	
Disease behaviour, n (%)				
B1 (inflammatory)	121 (44.0)	84 (42.4)	37 (48.1)	0.399
B2 (stricturing)	98 (35.6)	67 (33.8)	31 (40.3)	0.318
B3 (penetrating)	56 (20.4)	47 (23.7)	9 (11.7)	**0.026**
Perianal disease	127 (46.2)	89 (44.9)	38 (49.4)	0.551
Disease location, n (%)				
L1 (ileal)	26 (9.5)	16 (8.1)	10 (13.0)	
L2 (colonic)	17 (6.2)	16 (8.1)	1 (1.3)	0.062
L3 (ileocolonic)	232 (84.4)	166 (83.8)	66 (85.7)	
L4 (upper disease)	91 (33.1)	62 (31.3)	29 (37.7)	0.315
Smoking status, n (%)				
Non-smoker	243 (88.4)	179 (90.4)	64 (83.1)	0.185
Current smoker	17 (6.2)	11 (5.6)	6 (7.8)	
Former smoker	15 (5.5)	8 (4.0)	7 (9.1)	
Medical treatment, n (%)				
5-ASA	144 (52.4)	100 (50.4)	44 (57.1)	0.322
Steroids	48 (17.5)	35 (17.7)	13 (16.9)	0.867
Immunosuppressants	134 (48.7)	85 (42.9)	49 (63.6)	**0.002**
Biologicals	119 (43.3)	99 (50.0)	20 (26.0)	**0.000**
Intestinal surgery history	46 (16.7)	35 (17.7)	11 (14.3)	0.499

Abbreviations: 5-ASA, 5-aminosalicylic acid; BMI, Body mass index; Mo, Month;SD, standard deviation; y, years.

its role in transfusion medicine, a growing body of studies examined the role of ABO blood groups in the susceptibility to various diseases, including cancers,[6,7] cardiovascular diseases,[3-5] infectious diseases[16,17] and autoimmune diseases.[8-10] Previous studies revealed that patients with non-O blood groups had a higher risk for CD in the Caucasian population[11] and Korean population.[12] Forni et al.[11] found that non-O blood groups predisposed to developing a more severe disease behaviour. Our study also revealed similar results that individuals with non-O blood groups had a higher risk of developing CD, even after adjusting for potential confounders, which was repeated in both propensity score-adjusted and propensity-score-matched analyses. Moreover, we also found that CD patients with non-O blood groups had had a higher risk of developing penetrating disease and increased probability of receiving immunosuppressant treatment and lower probability of biological treatment. However, a study in Southern China failed to draw similar conclusions about the influence of ABO blood groups on CD.[13] This discrepancy may be attributed to the different ABO blood group distributions between regions and different inclusion criteria between these studies.

The exact underlying mechanisms of how ABO blood antigens affect the pathogenesis and progression of CD remain mostly unclear. The intestinal microbiota composition is an important aspect of the pathogenesis of IBD, and host genetic factors influence this composition to some extent. Previous investigations revealed that ABO blood groups modulated gut microbiota composition in healthy subjects.[18,19] Galactoside 2-α-L-fucosyltransferase 2 (FUT2) is encoded by the FUT2 gene, and it is a membrane protein that is responsible for the formation of ABO antigens, their gastrointestinal tract presentations and body secretions.[20] Loss-of-function mutation of the FUT2 gene was significantly associated with the predisposition to CD.[11,21] Two recent large cohort studies failed to identify any association between FUT2 genotype and faecal microbiota composition,[22,23] but the FUT2 genotype affects the composition and function of intestinal mucosa-associated microbiota in CD patients and healthy individuals.[24,25]

Genetic variants of the ABO gene contribute to circulating inflammatory marker levels, which provide a plausible mechanism for the association of ABO blood groups in CD susceptibility. A genome-wide association study (GWAS) of 6145 subjects confirmed that single-nucleotide polymorphisms (SNPs) in the ABO gene were significantly associated with circulating interleukin-6 (IL-6) levels, which is a pro-inflammatory molecule that is involved in the development of CD.[26] Another GWAS in a British population demonstrated a similar association between variants in the ABO gene and IL-6 levels.[27]

The present study had several limitations. Firstly, due to the nature of retrospective studies, some additional information about risk factors and clinical outcomes were unavailable in the medical records. Secondly, it is a single-centre study that included a relatively small sample size, which may not be sufficient to reach significant statistical differences in subgroup comparisons. Thirdly, the distribution of ABO blood group differs geographically and between ethnicities. Therefore, our results may not be extended to other ethnicities.

In conclusion, our results confirmed that non-O blood groups were significantly associated with an increased risk of CD in this Chinese Han population, similar to the results in the Caucasian and Korean populations. Additional investigations are warranted to further elucidate the exact mechanisms of how ABO blood groups affect the pathogenesis and progression of CD.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS
J.T.C designed the study, conceived the survey and wrote the manuscript. H.N.C and Y.L assessed the participants and collected clinical data. W.W.Z conducted the statistical analysis. C.D.W designed and supervised the study, and revised the manuscript. All authors read and approved the final manuscript.

ETHICS STATEMENT
The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Fujian Medical University, China (MRCTA, ECFAH of FMU [2019]221). All subjects signed informed consent forms.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author Chengdang Wang (wangcdhl@fjmu.edu.cn) upon reasonable request.

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REFERENCES
1. Xavier RJ, Podolsky DK. Unravelling the pathogenesis of inflammatory bowel disease. *Nature*. 2007;448(7152):427-434.
2. Franchini M, Liumbruno GM. ABO blood group: old dogma, new perspectives. *Clin Chem Lab Med*. 2013;51(8):1545-1553.
3. Chen Y, Chen C, Ke X, et al. Analysis of circulating cholesterol levels as a mediator of an association between ABO blood group and coronary heart disease. *Circ Cardiovasc Genet*. 2014;7(1):43-48.
4. Sun X, Feng J, Wu W, Peng M, Shi J. ABO blood types associated with the risk of venous thromboembolism in Han Chinese people: A hospital-based study of 200,000 patients. *Sci Rep*. 2017;7:42925.
5. Gotsman I, Keren A, Zwas DR, Lotan C, Admon D. Clinical impact of ABO and rhesus D blood type groups in patients with chronic heart failure. *Am J Cardiol*. 2018;122(3):413-419.
6. Liu M, Ji S, Xu W, et al. ABO blood group and the risk of pancreatic neoplasms in Chinese Han Population: a study at shanghai pancreatic cancer institute. *Pancreas*. 2019;48(9):e65-e66.

7. Song HR, Shin MH, Kim HN, et al. Sex-specific differences in the association between ABO genotype and gastric cancer risk in a Korean population. *Gastric Cancer*. 2013;16(2):254-260.

8. Islamoglu ZGK, Unal M. Is there an association of ABO blood groups and Rhesus factor with alopecia areata? *J Cosmet Dermatol*. 2018;17(6):1271-1274.

9. Ozyurt K, Ozturk P, Gul M, Benderli YC, Colgecen E, Inci R. ABO blood groups, Rhesus factor, and Behcet's disease. *Acta Dermatovenerol Alp Pannonica Adriat*. 2013;22(3):63-64.

10. Lopetegi I, Munoz-Lopetegi A, Arruti M, et al. ABO blood group distributions in multiple sclerosis patients from Basque Country; O(-) as a protective factor. *Mult Scler J Exp Transl Clin*. 2019;5(4):2055217319888957.

11. Forni D, Cleynen I, Ferrante M, et al. ABO histo-blood group might modulate predisposition to Crohn's disease and affect disease behavior. *J Crohns Colitis*. 2014;8(6):489-494.

12. Ye BD, Kim BM, Jung S, et al. Association of FUT2 and ABO with Crohn's disease in Koreans. *J Gastroenterol Hepatol*. 2020;35(1):104-109.

13. Yu Q, Wang L, Zhang S, et al. The role of ABO blood groups in Crohn's disease and in monitoring response to infliximab treatment. *Blood Transfus*. 2016;14(5):460-464.

14. Lennard-Jones JE. Classification of inflammatory bowel disease. *Scand J Gastroenterol Suppl*. 1989;24(sup170):2-6.

15. Best WR, Becktel JM, Singleton JW, Kern F Jr. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. *Gastroenterology*. 1976;70(3):439-444.

16. Fry AE, Griffiths MJ, Auburn S, et al. Common variation in the ABO glycosyltransferase is associated with susceptibility to severe Plasmodium falciparum malaria. *Hum Mol Genet*. 2008;17(4):567-576.

17. Hutson AM, Atmar RL, Graham DY, Estes MK. Norwalk virus infection and disease is associated with ABO histo-blood group type. *J Infect Dis*. 2002;185(9):1335-1337.

18. Makivuokko H, Lahtinen SJ, Wacklin P, et al. Association between the ABO blood group and the human intestinal microbiota composition. *BMC Microbiol*. 2012;12:94.

19. Gampa A, Engen PA, Shobar R, Mutlu EA. Relationships between gastrointestinal microbiota and blood group antigens. *Physiol Genomics*. 2017;49(9):473-483.

20. Watkins WM. Biochemistry and Genetics of the ABO, Lewis, and P blood group systems. *Adv Hum Genet*. 1980;10(1–136):379-185.

21. McGovern DP, Jones MR, Taylor KD, et al. Fucosyltransferase 2 (FUT2) non-secretor status is associated with Crohn's disease. *Hum Mol Genet*. 2010;19(17):3468-3476.

22. Turpin W, Bedrani L, Espin-Garcia O, et al. FUT2 genotype and secretory status are not associated with fecal microbial composition and inferred function in healthy subjects. *Gut Microbes*. 2018;9(4):357-368.

23. Davenport ER, Goodrich JK, Bell JT, Spector TD, Ley RE, Clark AG. ABO antigen and secretor statuses are not associated with gut microbiota composition in 1,500 twins. *BMC Genom*. 2016;17(1):941.

24. Rausch P, Rehman A, Kunzel S, et al. Colonic mucosa-associated microbiota is influenced by an interaction of Crohn disease and FUT2 (Secretor) genotype. *Proc Natl Acad Sci USA*. 2011;108(47):19030-19035.

25. Tong M, McHardy I, Ruegger P, et al. Reprograming of gut microbiome energy metabolism by the FUT2 Crohn's disease risk polymorphism. *ISME J*. 2014;8(11):2193-2206.

26. Naitza S, Porcu E, Steri M, et al. A genome-wide association scan on the levels of markers of inflammation in Sardinians reveals associations that underpin its complex regulation. *PLoS Genet*. 2012;8(1):e1002480.

27. Shah T, Zabaneh D, Gaunt T, et al. Gene-centric analysis identifies variants associated with interleukin-6 levels and shared pathways with other inflammation markers. *Circ Cardiovasc Genet*. 2013;6(2):163-170.