Relationship between the ABO Blood Group and the COVID-19 Susceptibility

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Abstract:

OBJECTIVE

To investigate the relationship between the ABO blood group and the COVID-19 susceptibility.

DESIGN

The study was conducted by comparing the blood group distribution in 2,173 patients with COVID-19 confirmed by SARS-CoV-2 test from three hospitals in Wuhan and Shenzhen, China with that in normal people from the corresponding regions. Data were analyzed using one-way ANOVA and 2-tailed χ^2 and a meta-analysis was performed by random effects models.

SETTING

Three tertiary hospitals in Wuhan and Shenzhen, China.

PARTICIPANTS

A total of 1,775 patients with COVID-19, including 206 dead cases, from Wuhan Jinyintan Hospital, Wuhan, China were recruited. Another 113 and 285 patients with COVID-19 were respectively recruited from Renmin Hospital of Wuhan University, Wuhan and Shenzhen Third People's Hospital, Shenzhen, China.

MAIN OUTCOME MEASURES

Detection of ABO blood groups, infection occurrence of SARS-CoV-2, and patient death.

RESULTS

The ABO group in 3694 normal people in Wuhan showed a distribution of 32.16%, 24.90%, 9.10% and 33.84% for A, B, AB and O, respectively, versus the distribution of 37.75%, 26.42%, 10.03% and 25.80% for A, B, AB and O, respectively, in 1,775 COVID-19 patients from Wuhan Jinyintan Hospital. The proportion of blood group A and O in COVID-19 patients were significantly higher and lower, respectively, than that in normal people (both $P < 0.001$). Similar ABO distribution pattern was observed in 398 patients from another two hospitals in Wuhan and Shenzhen. Meta-analyses on the pooled data showed that blood group A had a significantly higher risk for COVID-19 (odds ratio-OR, 1.20; 95% confidence interval-*CI* 1.02~1.43, $P = 0.02$) compared with non-A blood groups, whereas blood group O had a significantly lower risk for the infectious disease (OR, 0.67; 95% *CI* 0.60~0.75, $P < 0.001$) compared with non-O blood groups. In addition, the influence of age and gender on the ABO blood group distribution in patients with COVID-19 from two Wuhan hospitals (1,888 patients) were analyzed and found that age and gender do not have much effect on the distribution.

CONCLUSION

People with blood group A have a significantly higher risk for acquiring COVID-19 compared with non-A blood groups, whereas blood group O has a significantly lower risk for the infection compared with non-O blood groups.

INTRODUCTION

The novel coronavirus SARS-CoV-2, causing the new infectious disease COVID-19, is currently spreading rapidly around the world. Current clinical observation suggest that people's age and gender are two risk factors in the susceptibility to COVID-19[1]. Older people and men are more susceptible to infection and development of more severe disease. However, no biological markers have been identified to predict the susceptibility to COVID-19 so far. Landsteiner's ABO blood types are carbohydrate epitopes that are present on the surface of human cells. The antigenic determinants of A and B blood groups are trisaccharide moieties GalNAcα1-3-(Fucα1,2)-Galβ- and Galα1-3-(Fucα1,2)-Galβ-, while O blood group antigen is Fucα1,2-Galβ-. While blood types are genetically inherited, the environment factors can potentially influence which blood types in a population will be passed on more frequently to the next generation. Susceptibility of viral infection has been found to be related to ABO blood group. For example, Norwalk virus and Hepatitis B have clear blood group susceptibility[2,3]. It was also reported that blood group O individuals were less likely to become infected by SARS coronavirus[4]. Here, we investigated the relationship between the ABO blood type and the susceptibility to COVID-19 in patients from three hospitals in Wuhan and Shenzhen, China to test if the former may function as a biomarker for the latter.

METHODS

We collected and ABO-typed blood samples from 1775 patients infected with

SARS-CoV-2, including 206 dead cases, at the Jinyintan Hospital in Wuhan, Hubei province, China. Another 113 and 285 patients with COVID-19 were respectively recruited from Renmin Hospital of Wuhan University, Hubei province and Shenzhen Third People's Hospital, Guangdong province, China. The diagnosis of COVID-19 was confirmed by a positive real-time reverse transcriptase polymerase-chain-reaction test of SARS-CoV-2 on nasal and pharyngeal swab specimens from patients. Two recent surveys of ABO blood group distribution of 3,694 normal people from Wuhan City and 23,386 normal people from Shenzhen City were used as comparison controls for the Wuhan and Shenzhen patients with COVID-19, respectively[5-6]. Statistical analyses were performed using one-way ANOVA and 2-tailed χ^2. Data from different hospitals were meta-analyzed using random effects models, with calculation of odds ratio (OR) and 95% confidence interval (*CI*). Statistical analyses were performed using SPSS software (version 16.0) and STATA software (version 13).

RESULTS

The ABO blood group in 3,694 normal people in Wuhan displayed a percentage distribution of 32.16%, 24.90%, 9.10% and 33.84% for A, B, AB and O, respectively, while the 1,775 patients with COVID-19 from Wuhan Jinyintan Hospital showed an ABO distribution of 37.75%, 26.42%, 10.03% and 25.80% for A, B, AB and O, respectively. The proportion of blood group A in patients with COVID-19 was significantly higher than that in normal people, being 37.75% in the former vs 32.16% in the later ($P < 0.001$). The proportion of blood group O in patients with COVID-19

was significantly lower than that in normal people, being 25.80% in the former vs 33.84% in the later (P < 0.001, Table 1). These results corresponded to a significantly increased risk of blood group A for COVID-19 with an OR of 1.279 (95% *CI* 1.136~1.440) and decreased risk of blood group O for COVID-19 with an OR of 0.680 (95% *CI* 0.599~0.771, Table 1) in comparison with non-A groups and non-O groups, respectively.

A similar distribution pattern of high-risk blood group A and low-risk blood group O was observed in the dead patients. Specifically, the proportions of blood groups A, B, AB and O in the 206 dead patients were 41.26%, 24.27%, 9.22% and 25.24%, respectively. Blood group O was associated with a lower risk of death compared with non-O groups, with an OR of 0.660 (95% *CI* 0.479~0.911, *P* = 0.014, Table 1). To the contrary, blood group A was associated with a higher risk of death compared with non-A groups, with an OR of 1.482 (95% *CI* 1.113~1.972, *P* = 0.008, Table 1).

We next examined 113 patients with COVID-19 from another hospital in Wuhan City, the Renmin Hospital of Wuhan University, and found a similar risk distribution trend of ABO blood groups for the infection. Specifically, compared with non-O groups, blood group O were significantly associated with a lower risk of infection, with an OR of 0.644 (95% *CI* 0.418~0.993, *P* = 0.045, Table 1). Compared with non-A blood groups, blood group A displayed higher relative risk (OR=1.396; 95% *CI* 0.952~2.048) than those observed in patients from Wuhan Jinyintan Hospital, although the associations did not reach statistical significance likely due to the small

sample size.

The ABO blood group in 23368 normal people in Shenzhen displayed a percentage distribution of 28.77%, 25.14%, 7.32% and 38.77% for A, B, AB and O, respectively. Analysis of 285 patients with COVID-19 from Shenzhen showed proportions of blood groups A, B, AB and O to be 28.77%, 29.12%, 13.68% and 28.42%, respectively. Similarly, a significantly lower risk of infection was associated with blood group O (OR, 0.627; 95% *CI* 0.484~0.812). Additionally, we found that blood group AB had an increased risk of infection (OR, 2.008; 95% *CI* 1.427~2.824, Table 1). Also, the average age of the 285 patients was 45.1±18.6 years, including 147 men and 138 women. We found no significant difference in patient age among different ABO groups (F = 0.135 ; *P* = 0.939).

Figure 1 shows the estimates of ORs of the risk of ABO blood groups for COVID-19 on the pooled data from the three hospitals by random effects models. Again, the results showed that blood group A was associated with a significantly higher risk for COVID-19 (OR, 1.21; 95% *CI* 1.02~1.43, *P* = 0.027) compared with non-A blood groups, whereas blood group O was associated with a significantly lower risk for the infection (OR, 0.67; 95% *CI* 0.60~0.75, *P* < 0.001) compared with non-O blood groups. Compared with other ABO blood groups, AB blood group (OR, 1.48, 95% *CI* 0.97~2.24) and B blood group (OR, 1.09, 95% *CI* 0.98~1.22) seemed to have a higher risk of infection, although the associations did not reach statistical significance.

We next investigate whether the people's age and gender as two risk factors

influence the ABO blood group distribution among patients with COVID-19. The distribution of ABO blood groups is known to have no sex and age predilections. For example, by analyzing the blood type of more than ninety thousands normal people, it was out that the percentage of A, B, AB and O blood types were essentially the same among different age groups and among different genders.[7] Thus we used the ABO blood group distribution of 3,694 normal people in Wuhan area as control to compare with different age groups and gender groups. When all patients from Jinyintan Hospital and Renmin Hospital in Wuhan city were combined together (1,888 patients together) and grouped into three age groups (less 40, 41-59, over 60 years old ages), the ABO blood group distribution did not change among the three age groups (Table S1). Similarly, the ABO blood group distribution did not have much change when men and woman of patient with COVID-19 were considered separately (Table S1).

DISCUSSION

In this study, we found that ABO blood groups displayed different association risks for the infection with SARS-CoV-2 resulting in COVID-19. Specifically, blood group A was associated with an increased risk whereas blood group O was associated with a decreased risk, thus demonstrating that the ABO blood type is a biomarker for differential susceptibility of COVID-19. These findings are consistent with similar risk patterns of ABO blood groups for other coronavirus infection found in previous studies. For example, Cheng *et al.* reported that the SARS-CoV infection

susceptibility in Hong Kong was differentiated by the ABO blood group systems[4]. The authors found that compared with non-O blood group hospital staff, blood group O hospital staff had a lower chance of getting infected. Patrice *et al.* found that anti-A antibodies specifically inhibited the adhesion of SARS-CoV S protein-expressing cells to ACE2-expressing cell lines[8]. Given the nucleic acid sequence similarity[9] and receptor angiotensin-converting enzyme 2 (ACE2) binding similarity between SARS-CoV and SARS-CoV-2[10-12], the lower susceptibility of blood group O and higher susceptibility of blood group A for COVID-19 could be linked to the presence of natural anti-blood group antibodies, particularly anti-A antibody, in the blood. This hypothesis will need direct studies to prove. There may also be other mechanisms underlying the ABO blood group-differentiated susceptibility for COVID-19 that require further studies to elucidate.

Conclusion

In summary, we for the first time report a link between COVID-19 susceptibility and the ABO blood group, demonstrating the latter to be a biomarker differentiating the former. Specifically, people with blood group A have a higher risk whereas people with blood group O have a lower risk for SARS-Cov-2 infection and COVID-19 severity. This study may have potential clinical implications given the current COVID-19 crisis: (1) People with blood group A might need particularly strengthened personal protection to reduce the chance of infection; (2) SARS-CoV-2-infected patients with blood group A might need to receive more vigilant surveillance and

aggressive treatment; (3) It might be helpful to introduce ABO blood typing in both patients and medical personal as a routine part of the management of SARS-CoV-2 and other coronavirus infections, to help define the management options and assess risk exposure levels of people. It should be emphasized that due to the imitations discussed above, one should be cautious to use this study to guide clinical practice at this time. This study encourages further studies.

Author contributions statement

P.G.W. and G.Y.Y. conceived, designed and supervised the overall study. P.G.W., M.X., G.Y.Y., L.Z., and X.Y.Z. supervised and administered the project. L.Z., H.P.H. and T.L. collected and verified ABO blood types of patients from Wuhan Jinyintan Hospital. X.Y.Z. and D.L. collected and verified ABO blood types of patients from Renmin Hospital of Wuhan University. Z.Z., L.L. and Y.Y. collected and verified ABO blood types of patients from Second Affiliated Hospital, Southern University of Science and Technology. Y.J.H., B.S., Y.R.L., X.H.W. and M.L.W. collected and verified the data. D.F.G., X.F.L., Y.K.L., Z.J., M.X., and P.G.W. analyzed the data. P.G.W., J.Z., G.Y.Y. and M.X., wrote and revised the paper. All authors read and approved the final manuscript.

PATIENTS AND PUBLIC INVOLVEMENT

This was a retrospective case series study and no patients were directly involved in the study design, setting the research questions, or the outcome measures directly. No

patients were asked to advise on interpretation or writing up of results.

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Competing interest statement

The authors declare that they have no competing financial interests.

Ethical approval

This study received approval from the Research Ethics Committees of the participating institutions, which waivered informed patient consent because the study only involved retrospective review of clinical data and because of the urgent nature of the study to investigate a new serious infections disease.

Patient consent: Waived

Data sharing: No additional data available.

Data Availability Statement

The data used to support the findings of this study are included within the article.

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Table 1. The ABO blood group distribution in patients with COVID-19 and normal controls.

	Blood Group			
	A	B	AB	O
Controls (Wuhan Area)				
3694	1188 (32.16%)	920 (24.90%)	336 (9.10%)	1250 (33.84%)
Wuhan Jinyintan Hospital				
Patients				
1775	670 (37.75%)	469 (26.42%)	178 (10.03%)	458 (25.80%)
$\chi 2$	16.431	1.378	1.117	35.674
P	**<0.001**	0.240	0.291	**<0.001**
OR	1.279	1.083	1.114	0.680
95%CI	1.136~1.440	0.952~1.232	0.920~1.349	0.599~0.771
Deaths				
206	85 (41.26%)	50 (24.27%)	19 (9.22%)	52 (25.24%)
$\chi 2$	6.944	0.015	0.000	6.102
P	**0.008**	0.903	1.000	**0.014**
OR	1.482	0.966	1.015	0.660
95%CI	1.113~1.972	0.697~1.340	0.625~1.649	0.479~0.911
Renmin Hospital of Wuhan University				
113	45 (39.82%)	25 (22.12%)	15 (13.3%)	28 (24.78%)
patients				
$\chi 2$	2.601	0.318	1.815	3.640
P	0.107	0.573	0.178	0.045
OR	1.396	0.857	1.530	0.644
95%CI	0.952~2.048	0.546~1.344	0.878~2.664	0.418~0.993
Controls (Shenzhen area)				
23386	6728 (28.77%)	5880 (25.14%)	1712 (7.32%)	9066 (38.77%)
Patients from Shenzhen Third People's Hospital				
285	82 (28.77%)	83 (29.12%)	39 (13.68%)	81 (28.42%)
$\chi 2$	0.000	2.160	15.729	12.278
P	1.000	0.142	**<0.001**	0.001
OR	1.000	1.223	2.008	0.627
95%CI	0.773~1.294	0.946~1.582	1.427~2.824	0.484~0.812

CI, confidence interval; OR, odds ratio; **P* value was calculated by 2-tailed $\chi 2$

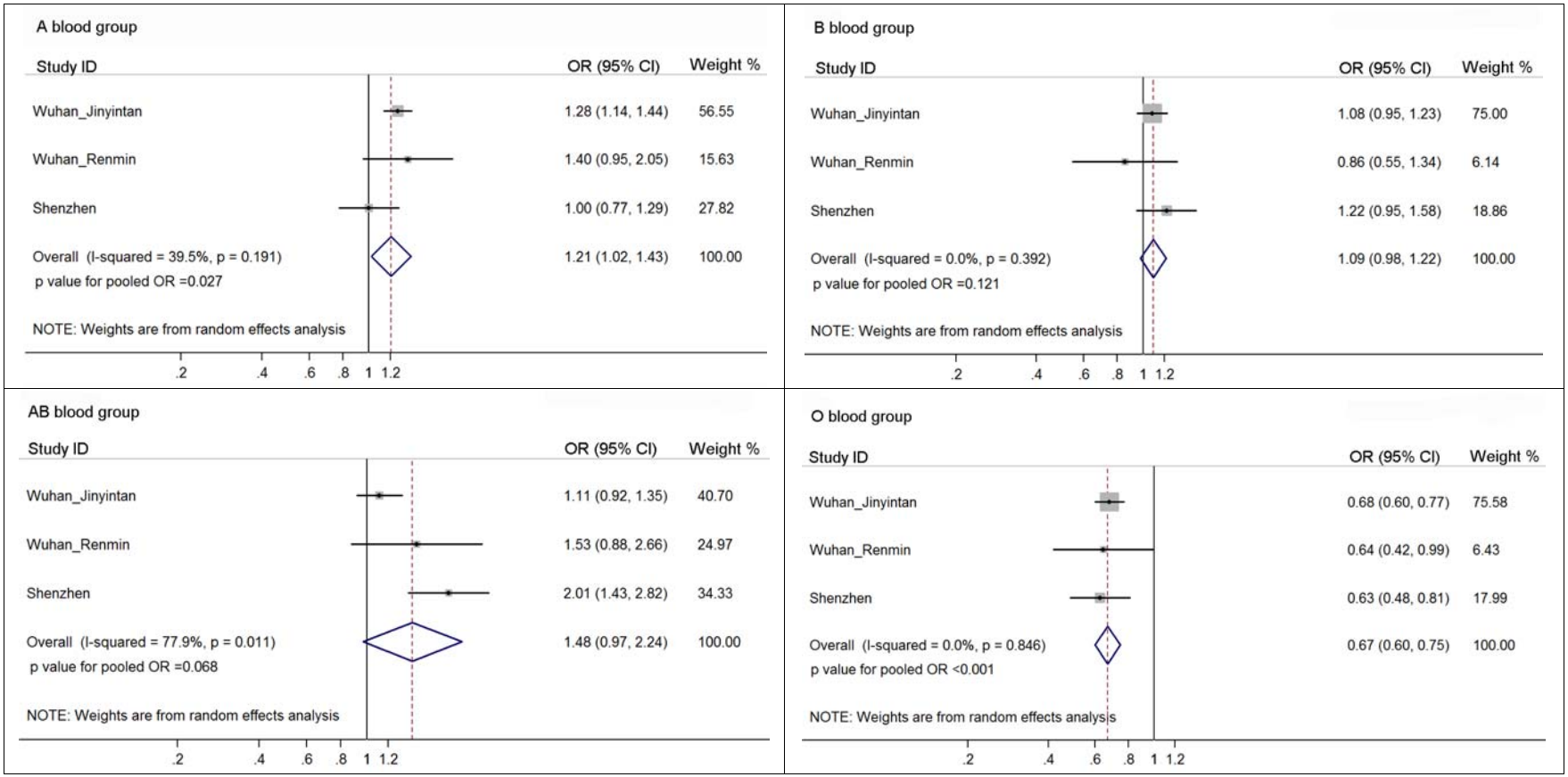

Figure 1. Meta-analysis of the risk of ABO blood groups for COVID-19 in three hospitals.

The X-axis represents the point estimate of odds ratio and corresponding 95% confidence interval; the Y-axis represents the source of study patients. OR, odds ratio. *CI*, confidence interval.

Table S1. Influence of age and gender on the ABO blood group distribution in patients with COVID-19 from two Wuhan hospitals.

	Blood Group			
	A	B	AB	O
3694 Control (Wuhan area)	1188 (32.16%)	920 (24.90%)	336 (9.10%)	1250 (33.84%)
Wuhan				
1888 patients	715 (37.87%)	494 (26.17%)	193 (10.22%)	486 (25.74%)
$\chi 2$	17.880	0.983	1.720	37.852
P	**<0.001**	0.321	0.190	**<0.001**
OR	1.286	1.069	1.138	0.678
95%CI	1.145~1.444	0.941~1.213	0.944~1.371	0.599~0.767
Less than 40 years	100 (36.63%)	78 (28.57%)	21 (7.69%)	74 (27.11%)
$\chi 2$	2.117	1.625	0.452	4.883
P	**0.146**	0.202	0.501	**0.027**
OR	1.219	1.206	0.833	0.727
95%CI	0.944~1.575	0.918~1.585	0.526~1.318	0.552~0.958
Between 41-59 years	275 (39.01%)	176 (24.96%)	71 (10.07%)	183 (25.96%)
$\chi 2$	12.197	<0.001	0.559	16.385
P	**<0.001**	1.000	0.455	**<0.001**
OR	1.349	1.003	1.119	0.685
95%CI	1.142~1.593	0.833~1.208	0.855~1.466	0.572~0.822
Over 60 years	340 (37.36%)	240 (26.37%)	101 (11.10%)	229 (25.16%)
$\chi 2$	8.679	0.759	3.181	24.797
P	**0.003**	0.384	**0.075**	**<0.001**
OR	1.258	1.080	1.248	0.657
95%CI	1.082~1.463	0.916~1.274	0.986~1.579	0.558~0.775
male 1030	403 (39.13%)	275 (26.70%)	101 (9.81%)	251 (24.37%)
$\chi 2$	17.187	1.278	0.403	32.883
P	**<0.001**	0.258	0.526	**<0.001**
OR	1.356	1.098	1.087	0.630
95%CI	1.175~1.564	0.939~1.285	0.860~1.373	0.538~0.738
female 858	312 (36.36%)	219 (25.52%)	92 (10.72%)	235 (27.39%)
$\chi 2$	5.379	0.111	1.976	12.884
P	**0.020**	0.739	0.160	**<0.001**
OR	1.205	1.033	1.200	0.738
95%CI	1.032~1.408	0.871~1.226	0.941~1.531	0.625~0.870

CI, confidence interval; OR, odds ratio; **P* value was calculated by 2-tailed $\chi 2$