REVIEW ARTICLE

THE CONNECTION BETWEEN COVID-19 AND ABO BLOOD GROUP: A BRIEF REVIEW

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ABSTRACT

The COVID-19 pandemic started in December 2019, and is still spreading throughout the world affecting 96, 53,048 people, and caused 4, 91,128 deaths so far last accessed on June 27, 2020). A significant percentage of patients develop severe and life-threatening symptoms among infected COVID-19 patients. Although COVID-19 infection can occur in all groups, studies suggest that the mortality rate is high in older age and patients having comorbidities such as diabetes, hypertension, and coronary heart diseases. Studies reports from the United States (US) and China suggested that the ABO blood group types can influence susceptibility and mortality rate of COVID-19. The O blood group individuals are less affected by SAR-CoV-2 due to the presence of anti-A antibodies more specifically IgG anti-A antibody in the serum should be the considered factor compared to the blood groups itself, as far as the association between susceptibility to COVID-19 and blood group is concerned. This brief review was done to analyze the published reports on COVID-19 and add it to the existing knowledge about the association of COVID-19 and ABO blood types.

Key Words: ABO blood groups, COVID-19, Coronavirus, SARS-CoV-2.

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INTRODUCTION

The COVID-19 pandemic (caused by SARS-CoV-2) has been rapidly spreading across the world and infected 96, 53,048 individuals and 4, 91,128 deaths globally as of June 27, 2020 report of WHO.[1] Many risk factors contribute to COVID-19 infection and death rate including sex, age, laboratory findings, and other comorbidities.[2] The role of ABO blood type has been reported among the risk factors for many infectious diseases. To date, many studies have investigated blood group type susceptibility to Coronaviridae viruses, Hepadnaviridae, and Retroviridae infections.[1,3] A report from Zhao et al. analyzing data from 2,173 patients with confirmed COVID-19 infection from 3 different hospitals in Shenzhen and Wuhan, China, the identified association between COVID-19 infection and ABO blood group.[4] It has been reported that persons with A blood type made a significantly higher proportion of the total infected and deceased patients compared to

persons with blood type O, implying that people with A blood type may be more prone to the virus.[4] According to the report, while in the studied regions approximately 31 % of the population had blood type A, they represented approximately 37% of the cases and 41% of the mortalities. Meanwhile, while making approximately 34% of the population, people with blood type O made up only about 26% of cases and about the same percentage for deaths. Meta-analyses on the pooled data from Wuhan and Shenzhen showed that A blood group type persons had significantly higher risk of COVID-19 infection, with an odds ratio (OR) of 1.28 (95% confidence interval: 1.02 to 1.43, p=0.02) compared to other blood group types. In contrast the O blood group individuals had relatively lower risk for this disease, with an OR of 0.68 (95% confidence interval: 0.60 to 0.75, p<0.001) compared to other blood groups (non-O blood groups).[4] In another study from China, a report by Zeng et al. comparing a cohort of COVID-19 patients with mild symptoms to another with severe symptoms, showed higher proportions of blood group A patients within both groups (36% and 39% respectively), compared to a reference population, confirming that individuals with A-type blood group were more prone to COVID-19 infection.[5] The calculated OD was 1.40 (95% CI: 1.01 to 1.96) and 1.63 (1.10 to 2.42) for the mild and severe cohorts, respectively. A retrospective cohort study done in Central Hospital of Wuhan (China) has reported 39%, 26%, 25%, and 10% of patients diagnosed with COVID-19 pneumonia had blood groups A, O, B, and AB respectively.[6] The proportion of patients with blood group (A) infected with the COVID-19 was significantly higher than the control group (39% *vs* 32%, p=0.017), whereas a significantly low number of blood group O patients were affected compared to the control group (26% *vs.* 34%, p<0.01). These distributions by blood groups were consistent across age and gender. However, no significant differences by blood group were found in the mortality rates. An association between type A blood group and increased susceptibility has also been recently reported outside China. A study carried out in Presbyterian Hospital (New York) including 1559 patients tested for SARS-CoV-2 (of which 62% patients were positive), the proportion of blood group A patients was high whereas lower proportion of blood group O was infected among the positive COVID-19 cases.[7] However, the authors reported that the significance was only present in those with Rh-positive blood types. Consistent with the previous reports, the effect of blood type was not linked to age, gender, or comorbidities. There was no strong association of the blood type with intubation or death among the cases studied. Thus, evidence from China and the US supports the conclusion that individuals with type A blood group have high susceptibility and O blood group have low susceptibility of getting infected with SARS-CoV-2.

The table shows data meta-analysis from the Shenzhen, Wuhan, and NYP/CUIMC. Blood group distribution among data from New York City, Shenzhen, and Wuhan. The meta-analysis associations for the ABO blood types in comparison to positive COVID-19 cases vs the general population is shown using the random model effect. [7]

MECHANISMS OF INCREASED SUSCEPTIBILITY

The mechanisms responsible for the differences in susceptibility depending on the ABO blood type are still not completely clear. Blood group antigens are present in erythrocytes, platelets, leukocytes, plasma proteins, other cells, and other body fluids. In the case of the ABO groups, in addition to the antigens, people with a determined blood group may also have isohemagglutinins

(antibodies that react with other groups, such as anti-A and anti-B).[8] For example, an individual with blood type A will have antibodies against blood type B antigens; a type B individual against type A and a type O individual against both type A and type B antigens. Thus, if a pathogen happens to express antigens similar to blood type A, individuals with type B or O, would have antibodies against type A antigens, and thus be less susceptible. In contrast, individuals with blood type A or AB, which lack anti-A antibodies, would show more susceptibility. Whether this mechanism explains individuals' higher susceptibility with A blood type to COVID-19 infection still needs to be investigated.[8] Interestingly, a report by Guillon et al. found that anti-A antibodies were able to hinder the interaction of angiotensin-converting enzyme-2 (ACE2)-expressing cell lines with the S protein of SARS-CoV1 (a relative of COVID-19 which also uses ACE2 as its cellular receptor).[9] Thus, it is possible that anti-A isohemagglutinins present in persons with blood type O (or non-A) might indeed exert a protective role.

Another potential way blood group types might influence susceptibility and disease severity is through their relationship with the coagulation system. Certain coagulation proteins, such as the Von Willebrand factor and factor VIII, express blood type antigens (e.g., A, B) that can affect theirs in vivo half-life and clearance. In people with blood group type A, the half-life is longer and the concentration of these factors is high in blood when compared to other groups.[10] This is an explanation for their increased susceptibility to conditions related to coagulation. Again, whether this plays a role in the increased susceptibility and mortality to COVID-19, which also appears to activate the coagulation system leading to multi-organ damage, [2] still needs to be studied. Furthermore, for one the blood groups are composed of sugars and the coronaviruses in animals have a surface protein that attaches to the sugars of the blood group antigen during infection. The extra N-acetyl galactosamine (sugar) might be of importance in blood group A, suggesting frequent contact with the pathogen, and this sugar is not present in O blood group type individuals.[11] Another possible explanation for the relatively exposed and protective characteristics of the non-O and O blood groups type is the formation of evolutionary phenotype; the epitopes in the antigens are exposed to ancestral, non-immune antibodies IgM and its high isoagglutinin activities against the glycan of ABO. This property of IgM is down-regulated by the glycosylation in non-O blood groups, whereas the blood group O maintains its isoagglutinin property and power of IgM ancestral antibodies, the immunity vanguard.[12] The replication SARS-CoV-2 occurs in epithelial cells of the respiratory and gastrointestinal tract[13], which can synthesize glycan A and B antigens, that depends on the phenotypes. If protein S of blood groups A, B, or AB individuals carry the respective glycan antigen, then it is possible that binding of antibodies can easily block the interaction between S protein and angiotensin-converting enzyme 2 (ACE2) thereby offer incomplete or complete protection.[12] Hence the infectivity between the ABO blood groups can be presumably predicted e.g. virus produced in the B blood group individuals will carry B antigen and there is a maximum chance of infecting blood B or AB individuals as compared to the blood O or A. This can be the explanation for the least number of COVID-19 cases O blood groups that contain both antibodies A and B. It is believed that once SARS-CoV-2 infection is established it then replicates in epithelial cells and thus exhibits that individuals' antigens and the antibodies

are left ineffective.[12] A study was done by Gérard et al., suggested that presence of anti A antibodies more specifically IgG anti A antibody in the serum should be considered factor compared to the blood groups itself, as far as the association between susceptibility to COVID-19 and blood group is concerned.[14] It is still not clear whether these assumptions are true or not. However, in past the association of other infections and ABO blood groups cannot be ignored.[11]

Table 1: Summary of the literature

Blood group	NYP general Pop.	NYP COV+	Shenzhen general Pop.		Wuhan general Pop.	Wuhan Jinyintan COV+	Wuhan Renmin COV+	OR	95% CI	p-value
A	32.7% (35643)	34.2% (233)	28.8% (6728)	28.8% (82)	32.2% (1188)	37.7% (670)	39.8% (45)	1.164	1.015 - 1.333	0.02
AB	4.2% (4582)	3.1% (21)	7.3% (1712)	13.7% (39)	9.1% (336)	10% (178)	13.3% (15)	1.2519	0.8384 -1.8694	0.27
B	14.9% (16229)	17% (116)	25.1% (5880)	29.1% (83)	24.9% (920)	26.4% (469)	22.1% (25)	1.1101	1.0068 -1.2240	0.03
O	48.1% (52406)	45.7% (312)	38.8% (9066)	28.4% (81)	33.8% (1250)	25.8% (458)	24.8% (28)	0.7252	0.5971 -0.8807	0.00

CONCLUSION

This the first brief review in which we have has compiled data from the published reports on the susceptibility to COVID-19 and ABO blood group types. The O blood group individuals have a lower risk of SARS-CoV-2 infection and severity COVID-19 compared to blood group A individuals. If this review is verified by studies in the future, then its findings will have several significant clinical implications:

1) Blood group A individuals may need strict personal protective measures to decrease the chances of SARS-CoV-2 infection.
2) Blood group A of individuals might need good surveillance and more aggressive treatment.
3) It may be very useful to include the ABO blood group typing in the management of COVID-19 patients.

Further studies should be done to draw inferences about the association of ABO blood type and COVID-19 and verify the current findings. However, any blood group individual needs to follow preventive measures to avoid COVID-19. The associations between many viral diseases and ABO blood groups have been shown in the past. Studies on SARS-CoV had shown association (positive) of A blood group type with a high number of positive cases. The O blood group had lesser chances of infection

than other blood groups. Similarly, two studies from the USA and China have reported the same pattern of association between the COVID-19 and ABO blood type. Therefore, we believe that this link should be investigated to understand the COVID-19 pathophysiology as well as the effectiveness of convalescent plasma therapy (CPT) in clinical trials.

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