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BRIEF REVIEW

ABO Blood Group Type and Susceptibility to COVID-19 Infection: A Brief Review

Rafael Fernandez-Botran[1], Ph.D.

[1]Department of Pathology and Laboratory Medicine, University of Louisville, Louisville, KY, USA

*gabino.fernandez-botran@louisville.edu

Abstract

Since December 2019, the SARS-CoV2 (COVID-19) pandemic has continued to extend over most of the world, infecting over four million people and causing well over 300,000 deaths so far (https://coronavirus.jhu.edu/map.html, accessed on May 14, 2020). A significant percentage of infected patients develop severe symptoms and life-threatening conditions. While COVID-19 infection can affect all ages, available evidence points to older age and pre-existing comorbidities such as hypertension, diabetes and coronary heart disease, as important risk factors related to increased mortality rates. [1-3] Moreover, recent reports from China and the U.S. have suggested that the susceptibility, and perhaps even mortality, to Covid-19 infection might be influenced by the ABO blood type. The purpose of the present minireview is to analyze the evidence published in the COVID-19 literature and to put it in the context of the existing knowledge about the association of blood group types and disease.

Introduction

A report from Zhao et al. analyzing data from 2,173 patients with confirmed COVID-19 infection from three hospitals in Shenzen and Wuhan, China, reported that persons with blood type A made a significantly higher proportion of the total infected and deceased patients compared to persons with blood type O, implying that people with blood type A may be more vulnerable 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 blood group A had a significantly higher risk for COVID-19 infection, with an odds ratio (OR) of 1.28 (95% confidence interval: 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, with an OR of 0.68 (95% confidence interval: 0.60-0.75, p<0.001) compared with non-O blood groups.

In a retrospective cohort study including 265 patients diagnosed with COVID-19 pneumonia in the Central Hospital of Wuhan, Li et al similarly reported a distribution of approximately 39%, 25%, 10% and 26% for patients with blood groups A, B, AB and O, respectively. [5] The proportion of patients with blood group A infected with COVID-19 proved again to be significantly higher than that for the control group (39 % *vs.*32%, p=0.017). The proportion of patients with blood group O was significantly lower when 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.

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 patients with blood group A in both groups (36% and 39% respectively), compared to a reference population, confirming that individuals with blood group type A were more susceptible to COVID-19 infection. [6] The calculated OD was 1.40 (95% CI:

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1.01-1.96) and 1.63 (1.10-2.42) for the mild and severe cohorts, respectively. However, the authors did not find significant associations of the blood type with a higher risk for outcomes, such as acute respiratory syndrome (ARDS), acute kidney injury or death. The latter is in contrast to a retrospective study in 101 death cases from COVID-19 infection, also in China, that reported a significant difference in the proportion of patients with blood type A that died *vs.* controls. [7]

An association between type A blood group and increased susceptibility has also been recently reported outside China. A study including 1,559 individuals tested for SARS-CoV2 (of which 62% were positive) in New York's Presbyterian Hospital, found a higher proportion of individuals with blood type A and a lower proportion of blood type O among those that tested positive compared to negatives. [8] However, the authors report that the significance was only present in those with Rh positive blood types. Consistent with the previous reports, the effect of the blood type was not explained by age, gender or comorbidities. Also, there was no strong association of the blood type with intubation or death among the cases studied.

Thus, evidence from China and the U.S. supports the conclusion that individuals with type A blood group have an increased susceptibility to infection by the COVID-19 virus. However, evidence is still controversial whether having type A blood group increases the risk of death from the infection. Interestingly, evidence of a negative association of type O blood group and susceptibility to infection with SARS-CoV1, a close relative of COVID-19, had been previously reported in 2005. [9]

Blood Groups and Susceptibility to Infection and Disease

While the data regarding the association of ABO blood group types and susceptibility to COVID-19 is new, the associations of different blood types and disease have been well established, having been studied since the early 1900s (Rev. in 10,11). In fact, solid evidence has accumulated indicating that susceptibility to many diseases and infectious agents is influenced by the blood type, including not only ABO but many other blood group systems, such as Rh, Duffy, Lewis and many more. [10,11] In fact, many infectious agents have acted as selective pressure affecting the expression of blood groups in different regions of the world, the classic example being malaria in Africa. [10] Thus, the relationship between blood type and susceptibility to COVID-19 does not appear to be an isolated case. **Table 1** shows some examples of reported disease susceptibilities by ABO group type. [11]

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). 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. These are the same antibodies that can cause transfusion reaction, transplant rejections or spontaneous abortions. Pathogens sometimes disguise themselves, mimicking our own antigens in order to evade immune detection and destruction, and blood group antigens are no exception. 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 the increased susceptibility of individuals with blood type A to COVID-19 infection still needs to be investigated. Interestingly, a report by Guillon et al. found that anti-A antibodies were able to block 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). [12] 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 Von Willebrand factor and factor VIII, express blood type antigens (e.g., A, B) that can affect their 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 increased in blood when compared to other groups. [11] 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.

Discussion

In conclusion, susceptibility to certain diseases and pathogens can be influenced by blood group types through a variety of mechanisms, some of which may include isohemagglutinin antibodies and effects on the coagulation system, but

Table 1. Examples of associations of ABO blood types with increased susceptibilities to infectious agents and other diseases.

Blood group	Increased susceptibility to:
O	*Yersinia pestis* (plague), *Vibrio cholerae* (cholera), *Mycobacterium tuberculosis* (tuberculosis), Mumps
A	*Pseudomonas aeruginosa*, Smallpox, COVID-19
B	*Streptococcus pneumoniae, Neisseria gonorrhoeae, E. coli, Salmonella sp.*
A>AB>B	Vascular disorders, thromboembolism, coronary heart disease. Ischemic stroke (this is due to differences in the levels and clearance of von Willebrand factor and factor VIII, which express blood group antigens)
AB>B>A	Dementia, cognitive impairment (also related to coagulation factors)

many others remain to be characterized. Evidence so far is consistent with an increased susceptibility of individuals with blood type A, and reduced susceptibility of type O individuals to COVID-19 infection. However, additional studies are needed to elucidate the underlying mechanisms.

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