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ABO Blood Groups and COVID-19

This rapid review of the science of different blood groups and COVID-19 from the Royal Society is provided to assist in the understanding of COVID-19.

This paper is a pre-print and has not been subject to formal peer-review.

Summary

- Blood group O reduces the risk of acquiring SARS-CoV-2 infection and COVID-19 (high confidence).
- The mechanism of protection is unknown but may be due to the natural antibodies to blood group A and B antigens that are observed in people with blood group O (moderate confidence).
- Blood group A is associated with a higher risk of infection and of severe disease (high confidence).
- People with blood group O also have a lower risk of venous thromboembolism (high confidence). This may contribute to a lower risk of death from COVID-19, in which widespread blood clotting is a major factor, but further evidence of a reduction in COVID-19 severity in blood group O patients is required (low confidence).
- No immediate policy implications are identified.

For reviews see Anstee[1]; Cooling[2]; Arend[3].

1. Are ABO blood groups associated with the risk of COVID-19?

Zhao *et* al[4] compared the ABO blood group distribution in 2173 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. The results were consistent in all three hospitals; the pooled results showed an odds ratio (OR) of COVID-19 for blood group A of 1.21 and for blood group O of 0.67. In the largest hospital sample studied (Jinyintan Hospital), blood group A was also associated with a higher risk of death compared with non-A groups, with an OR of 1.48, and blood group O was associated with a lower risk of death compared with non-O groups, with an OR of 0.66.

Zietz & Tatonetti[5] studied 1559 individuals in New York with known blood groups who received a SARS-CoV-2 test; about half were positive for the virus. Blood group A were associated with increased odds of testing positive for SARS-CoV-2 (OR 1.34), and blood group O was protective (OR 0.80). These observations could not be explained by known risk factors: age, sex, overweight status, diabetes mellitus, hypertension, pulmonary diseases, and cardiovascular diseases, and the effect of ABO blood group was independent of these risk factors. A meta-analysis of these results together with those of Zhao *et al*[4] confirmed the conclusions, despite the highly significant difference between the two populations in the distribution of blood group gene frequencies:

TABLE 1

Meta-analysis of the odds of testing positive for COVID-19 for different blood groups[6, 7].

Blood Group	Odds Ratio (infection)	P (chi-sq)
A	1.16	0.029
AB	1.25	0.272
B	1.11	0.036
O	0.73	0.001

These authors did not identify any significant relationships between blood group and intubation or death due to COVID-19.

Ellinghaus *et al*[8] carried out a genome-wide single-nucleotide polymorphism association study in two large case-control cohorts of COVID-19 patients with respiratory failure, respectively in Italy and Spain (total N= 1610 patients and 2205 controls). Two genetic loci were significantly associated with COVID-19, one of which coincided with the ABO locus on chromosome 9. The odds ratio of disease in blood group A individuals was 1.45 (95% CI 1.20-1.75) and in blood group O individuals 0.65 (95% CI 0.53 to 0.79). HLA genes were not associated with COVID-19.

Further evidence that blood group O is associated with a lower risk of SARS-CoV-2 infection was obtained by Li *et al*[9] in a study of 265 patients with SARS-CoV-2 in Wuhan, and by Wu *et al*[10] in a study of 187 patients with COVID-19 and 1991 controls. Fever and cough were significantly more frequent in patients with blood group A; and dyspnoea, myalgia or fatigue, and sore throat were commoner in those with blood group B[8].

In SARS-CoV-1 infection in Hong Kong, Cheng *et al*[11] studied 45 hospital workers of whom 34 contracted SARS after exposure to a single index patient. Most of the infected individuals (23/34) were non-group O (groups A, B, and AB). The OR of infection associated with group O was 0.18 (95% CI, 0.04 to 0.81; P <0.03).

2. How might this protection work?

2.1 ABO blood group antigens

These are carbohydrate antigens, expressed on glycosphingolipids (GSLs) and glycoproteins: blood group O individuals express the H antigen. In addition to red cells, ABH antigens are expressed in many tissues and secretions, including intestinal mucosa, endothelium, kidney, heart, and other organs. ABH antigens can be expressed on both N-linked and O-linked glycoproteins[2]; viral glycoproteins may also be either N-linked or O-linked[12]. Glycoproteins on viruses that are produced by cells from an individual of blood group A can display the A antigen, and similarly for B.

2.2 Natural antibodies against A and B antigens

About half of the species of Gram-negative bacteria in the gut express carbohydrate antigens with ABO activity[2, 13]. The bacteria in the gut flora stimulate the production of so-called natural antibodies to A and B antigens in people who are not blood group A or blood group B, respectively. Blood group O individuals can develop both anti-A and anti-B natural antibodies.

These natural antibodies can recognize A and B antigens on virus glycoproteins, raising the possibility that natural antibodies protect against infection with certain viruses. There is evidence to support this hypothesis in in vitro infection with HIV-1[14, 15] and measles virus[16], but epidemiological evidence is lacking for a protective effect on these infections.

Guillon *et al*[17] obtained evidence that both monoclonal anti-A antibodies and natural anti-A antibodies could block the interaction between the ACE2 receptor and the SARS spike (S) protein. But the effect depended strongly on the titre of antibody: less than 1:256 was ineffective.

To test the hypothesis that natural anti-A antibodies protect against COVID-19, Gérard *et al*[18] re-analysed the data from Zhao *et al*[4] according to the expected presence (in B and O individuals) or absence (in A and AB individuals) of anti-A antibodies (in total N=1888 patients with COVID-19; N=3694 controls). The results showed that those with anti-A were indeed under-represented in COVID-19 patients; anti-B did not appear to confer protection. N.B. Anti-A antibodies from O individuals appeared to be protective, but anti-A from B individuals were not. The authors suggest that this difference is because A and B individuals produce mainly IgM anti-B or anti-A respectively, whereas O individuals make mainly IgG.

3. ABO and blood clotting

Subjects of blood group A, B, or AB are more susceptible than those of group O to arterial and venous thromboembolism[1], and have higher levels of von Willebrand factor (vWF) and factor VIII[19, 20]. Therefore the lower risk of venous thromboembolism in O individuals may contribute to the better outcome in COVID-19. ABH antigens are expressed on some plasma glycoproteins, including von Willebrand factor[21].

4. ABO and other diseases

ABO blood group genotype has been associated with the risk of several infectious diseases[2], including virus diseases: e.g. norovirus[22] and hepatitis virus[23]. The most important association is with malaria: blood group O is associated with protection against severe malaria, which is believed to be the main selection force that has driven the evolution of the ABO system[24]. Blood group O is also associated with a lower incidence of many types of solid cancer (especially stomach & pancreas) and chronic lymphocytic leukaemia[25].

Conclusions

- Individuals with blood group O have about two-thirds to three-quarters of the odds of acquiring SARS-CoV-2 infection of non-group O individuals, and a lower risk of COVID-19. It is less clear whether blood group O individuals who have become infected with the virus have a lower risk of severe disease.
- Blood group A is associated with significantly increased odds of SARS-CoV-2 infection, and with a greater risk of severe disease.
- The protection conferred by blood group O may be mediated by natural anti-A antibodies (and less clearly anti-B antibodies). If so, this implies that blood group O individuals are more likely to resist infection acquired from blood group A or blood group B individuals.
- Further evidence is needed to demonstrate whether A or B antigens are expressed on the S antigen of SARS-CoV-2 and that natural antibodies can inhibit infection by the virus in vitro.
- Whether or not natural antibodies can protect against infection by a given virus will depend on the titre of the antibody[15] and the presence and position of the appropriate glycan groups on the viral glycoprotein, for example near the receptor-binding site.
- It would be of great interest to test for epidemiological evidence of protection associated with blood group O against other viral infections, such as measles.

Policy implications

There are few direct implications for policy, because the effect sizes are small and the effects are genetically determined. The main implications are for understanding the molecular mechanisms of infection.

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DISCLAIMER

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