











REVIEW

ABO blood group and COVID-19: a review on behalf of the ISBT COVID-19 Working Group

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Vox Sanguinis

Abstract

Growing evidence suggests that ABO blood group may play a role in the immunopathogenesis of SARS-CoV-2 infection, with group O individuals less likely to test positive and group A conferring a higher susceptibility to infection and propensity to severe disease. The level of evidence supporting an association between ABO type and SARS-CoV-2/COVID-19 ranges from small observational studies, to genome-wide-association-analyses and country-level meta-regression analyses. ABO blood group antigens are oligosaccharides expressed on red cells and other tissues (notably endothelium). There are several hypotheses to explain the differences in SARS-CoV-2 infection by ABO type. For example, anti-A and/

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or anti-B antibodies (e.g. present in group O individuals) could bind to corresponding antigens on the viral envelope and contribute to viral neutralization, thereby preventing target cell infection. The SARS-CoV-2 virus and SARS-CoV spike (S) proteins may be bound by anti-A isoagglutinins (e.g. present in group O and group B individuals), which may block interactions between virus and angiotensin-converting-enzyme-2-receptor, thereby preventing entry into lung epithelial cells. ABO type-associated variations in angiotensin-converting enzyme-1 activity and levels of von Willebrand factor (VWF) and factor VIII could also influence adverse outcomes, notably in group A individuals who express high VWF levels. In conclusion, group O may be associated with a lower risk of SARS-CoV-2 infection and group A may be associated with a higher risk of SARS-CoV-2 infection along with severe disease. However, prospective and mechanistic studies are needed to verify several of the proposed associations. Based on the strength of available studies, there are insufficient data for guiding policy in this regard.

Key words: COVID-19, SARS-CoV-2, ABO blood groups, disease susceptibility, disease severity.

Introduction

The COVID-19 pandemic spurred a crisis that is unprecedented in modern times [1]. The disease course varies substantially among individuals, from mild or even sub-clinical infection to severe disease [2]. Indeed, more than 1 million COVID-19-related deaths have been reported globally. There is interest in potential risk factors that affect susceptibility to infection and disease progression. Multiple medical (e.g. diabetes, hypertension) and sociodemographic (e.g. sex, age and race/ethnicity) risk factors for severe outcomes were already established [2]. Growing evidence suggests that the ABO blood group may also play a role in the immunopathogenesis of SARS-CoV-2 infection, with group O being protective and group A conferring risks of higher disease susceptibility and severity [3–7].

An international group of experts in transfusion medicine and haematology were assembled by the International Society of Blood Transfusion (ISBT) to review and summarize the literature with a view of offering recommendations pertaining to ABO type and COVID-19. To this end, we provide an overview of the ABO blood group system, ABO population frequencies and distributions, its role as a histo-blood group antigen, not just a blood group antigen, and the known associations between ABO type and various infectious and non-infectious diseases. Finally, we present a scoping review of the literature on the associations of ABO type with COVID-19 and propose mechanistic pathways that could potentially explain these observations.

Search strategy and selection criteria

A combination of searching using Medline's controlled vocabulary/indexing, [Mesh]/[Supplemental Concept], and keyword searching titles and abstracts [tiab] features was used to search articles on ABO blood group and infectious diseases and ABO blood group and COVID-19 or SARS-CoV-2 to (a) pull articles either specifically indexed about our topic/concept as well as (b) pull articles wherever our topic/concept of interest was mentioned. Furthermore, we also searched all the Web of Science (WOS) databases using the same keyword searching as for PubMed/Medline. WOS in addition supports the NEAR operator (searches for words that appear near one another in the text without requiring an exact phrase match). The search was confined to English-language articles that were published prior to 10 November 2020. Pre-print articles were also included on a case-by-case basis.

ABO blood group overview

Of the 39 blood group systems and 350 antigens recognized by the ISBT [8], the ABO system is clinically the most important [9]. The A and B antigens are inherited co-dominantly over O [10]. The ABH antigens (H antigen defines the O blood type) are oligosaccharides exposed on RBCs and other cells; they are also found in body secretions. The A and B antigens are determined by allelic genes encoding glycosyltransferases that transfer monosaccharides to the non-reducing ends of specific glycans on glycoproteins and glycolipids. For A and B,

this monosaccharide is N-acetyl-D-galactosamine and D-galactose, respectively. In group O individuals, the corresponding A and B glycosyltransferases are either not present or have been inactivated by one of various polymorphisms, such that the non-reducing ends of the corresponding glycans express the H antigen.

Antibodies in this system (i.e. anti-A and anti-B) develop in the first few months of life; they are typically 'naturally occurring' antibodies produced after contact with non-self A and/or B antigens, often found in food and micro-organisms, notably the gut microbiota [11]. Anti-A and anti-B, typically of the IgM isotype, circulate in almost all healthy individuals who lack the corresponding antigen; IgG anti-A,B is often found in group O individuals [12–14]. Transfusion of ABO-incompatible RBCs can provoke acute haemolytic transfusion reactions because the corresponding IgM antibodies bind complement efficiently, causing intravascular hemolysis of the transfused RBCs and activation of coagulation. IgG antibodies can also cause severe intravascular hemolysis in this setting, because of the very high density of ABH antigens on RBCs, leading to close proximity of anti-A and/or anti-B IgG molecules on the RBC surface with subsequent complement activation [15, 16]. If untreated, this medical emergency can induce acute renal failure, disseminated intravascular coagulation and death. Therefore, always transfusing ABO-compatible RBCs is a central focus of modern blood banking processes and procedures.

Population frequency of ABO blood groups

ABO blood group frequencies vary among human populations, suggesting that migration and the selective advantage of particular blood groups, perhaps relating to exposure to specific pathogens, might have contributed to these variations (Table 1). For example, group O is the most common globally, followed by A, then B, and then AB. Group O may have originated in Africa before early human migration, because it may have provided a selective advantage against malaria [17]. In contrast, group O individuals are at higher risk of developing severe cholera, perhaps explaining the lower prevalence of group O and higher prevalence of group B, in the Ganges Delta region of Bangladesh [18].

Indigenous populations show widely divergent ABO blood group distributions. For example, those in Australia and North and South America almost completely lack group B, whereas those in Asia show the highest rates of group B. In addition, group A is almost non-existent in indigenous populations of South and Central America,

but more prevalent (>30%) in Canada, Scandinavia and Central Europe, perhaps due to selective pressure provided by smallpox [18]. In contrast, ABO distributions of *current populations* in these same countries demonstrate the impact of migration; for example, although group A is virtually absent in indigenous populations in Central and South America, its current overall population frequency is as high as 30% [18].

ABO is not just a blood group antigen

Each RBC expresses ~2 million copies of its genetically encoded ABH blood group antigens on its surface, although the density varies by antigen type. Other blood cells (e.g. platelets and lymphocytes) also adsorb ABH-expressing glycosphingolipids from plasma, where they circulate attached to lipoproteins. In addition, ABH antigens are synthesized and expressed on endothelial cells and certain epithelial cells. Thus, although some blood group antigens are only on RBCs, ABH antigens are in various cells, body fluids and secretions. Therefore, they are more correctly denoted as 'histo-blood group antigens' (HBGA), not solely as blood group antigens [11, 19–23].

In addition to serving as antigenic barriers during transfusion, transplantation and pregnancy, ABH oligosaccharides physiologically influence hemostasis and, therefore, confer disease risks in this setting. For example, A and B glycosyltransferases modify H-active glycans on von Willebrand factor (VWF) [24]. Interestingly, VWF in group O individuals has a shorter half-life, accompanied by 25–30% reduced VWF and Factor VIII levels, as compared to group A or B individuals. However, independent of the ABO blood group, glycosyltransferase activity was also decreased in patients with venous thromboembolism, as compared to healthy controls [25]. In addition, higher VWF and factor VIII levels are associated with increased risks for coronary heart disease, arterial thrombosis and venous thrombosis [26, 27]. Therefore, perhaps not surprisingly, recent genome-wide association studies (GWAS) demonstrated that ABO locus variants correlate with increased plasma lipid and inflammatory marker levels [25, 28].

ABO expression may also not be stable over time, with lower levels in healthy children <2 years old [29] and changes in various diseases (e.g. necrotizing infection, thalassemia, malignancy) [20, 30]. In addition, as compared to group O, group A individuals have a higher prevalence of gastric cancer, and group A, AB or B individuals have a higher prevalence of pancreatic cancer; possible mechanisms include ABO blood group influences on regulating proinflammatory [31] and adhesion

Table 1 Table of ABO Geographic Distributions for the native and contemporary populations

Region	Native population			Current population			
	Type A %	Type O %	Type B %	Type A %	Type O %	Type B %	
North America	Canada	Up to 40	80–100	0–5	40+	40+	9
	United States	0–15*	80–100	0–5	40+	40+	~10
Central and South America	Absent	90–100	0–5	10–30	50–80	~10	
Greenland	Up to 40+						
Australia	Up to 40+ [†]	60–80 (North)	0–5	38	49	~10	
Africa	15–20	60–80	10–20	~20–25 [‡]	Up to 60	West > 20	
Middle East	15–20	60–80	5–15	~25	>40	>20	
Europe	Scandinavia	25–40 [‡]	50–70	0–10	40+	~40	10
	Western Europe	25–30	60–70	5–10	30–40	30–40	~10
	Eastern Europe	25–30	50–60	10–20	30–40	30–40	~10
Russia	15–20	50–60	15–30	~35	~35	~10	
Asia	China	20–25	60–70	15–25	~30	~50	~20
	Japan	15–25	50–70	10–15	40	30	20
	Pacific	15–20	60–70	15–25	25–30	>40	~30
India	15–20	56–60	Up to 30	22	29	38	

*Blackfoot of Montana: 30–35%.

[†]Aboriginal Australians: 40–53%.

[‡]Lapp: 50–90%.

[‡]Cameroon 38, Uganda 39, South Africa 32%.

Table 2 Potential mechanisms for relationships between histo-blood group antigen (HBGA) and infection

Action as a receptor or co-receptor for a given pathogen

Functions as a receptor for a virulence factor, toxin, or other pathogenic product

Interaction with a pathogen that is limited to a specific strain, specific organ system or disease state

Modification of a key target cell surface glycoprotein or glycolipid, thereby affecting important cellular functions (e.g. endocytosis, phagocytosis, signal transduction) in response to infection

molecules [32, 33], and the role of VWF in angiogenesis and apoptosis [22, 25, 34, 35].

Associations between blood groups and infectious diseases

HBGAs are implicated in the pathogenesis of multiple infections. In particular, the ABO blood type has been associated with, for example, tuberculosis, malaria, cholera, norovirus, retrovirus, Chikungunya virus, *Helicobacter pylori* (*H. pylori*) and *Escherichia coli* [36, 37]. The underlying mechanisms range from simple (e.g. receptor-ligand interactions) to complex and may be limited to a specific pathogenic product, strain or disease state. For ABO, possible explanations include ABH antigens as receptors for pathogens, natural antibodies and lectins as inhibitors, and molecular mimicry by blood group antigens between pathogen and host.

One specific example involves the P antigen in the Globoside blood group. This antigen is necessary, but not sufficient [38], for parvovirus B19 entry into RBCs, requiring a co-receptor for infection [39, 40]. The distribution of P antigen, including relatively high expression by RBCs and their precursors, is consistent with parvovirus B19 clinical syndromes, including aplastic anaemia [41]. Furthermore, individuals lacking the P antigen (i.e. the p phenotype) are resistant to this infection [42].

For other infections, HBGAs can be receptors for toxins, virulence factors or other pathogenic products without directly binding the implicated pathogen itself. In addition, HBGAs in secretions, body fluids or non-erythroid tissues can contribute to pathogenesis. For example, adhesion and colonization by *H. pylori*, the aetiologic agent of peptic ulcer disease and some forms of gastric cancer, are facilitated by Le^b/H oligosaccharides on gastric epithelial mucins [43, 44] with certain strains

having higher affinity for Le^b/H [45]; in addition, group O individuals, by expressing more H antigen, are more likely to be infected [46].

In summary, the relationship between HBGAs and a specific infection should ideally satisfy Koch's postulates. Nonetheless, this is often difficult to document fully in human studies. Typically, one can only show that individuals expressing a specific blood group or HBGA are more susceptible to infection, whereas individuals without it are completely resistant or, at least, protected from severe disease. Multiple examples demonstrate that HBGAs can interact with pathogens at initial infection, or alter disease progression/severity, or affect clinical presentation (Table 2).

ABO blood group and susceptibility to SARS-CoV-2

During the severe acute respiratory syndrome coronavirus (SARS-CoV-1) epidemic, several observations suggested that ABO type may contribute to disease, with less susceptibility in group O individuals [47]. This was also observed for SARS-CoV-2 (Table 3). Most studies identified a higher proportion of group A, and a lower proportion of group O, among COVID-19 patients, as compared to healthy controls [5, 7, 12, 48–52]. These studies included patients with SARS-CoV-2 pneumonia ranging in severity from mild to critically ill requiring mechanical ventilation or intensive care unit admission [48, 51]. For example, in one study, the proportion of group A infected patients was significantly higher than in healthy controls (38% vs. 32.2%, $P < 0.001$), whereas group O was significantly lower (25.7% vs. 33.8%, $P < 0.001$); however, group A patients had higher frequencies of underlying comorbidities [7]. Another retrospective study had similar findings, but did not describe comorbidities [52]. Another study described a higher rate of infection in group AB patients and a lower rate in group O patients [50]. In contrast, an additional study did not find any correlation between group A status and COVID-19; nonetheless, group O individuals had a lower risk of COVID-19 and group B and AB individuals had a higher risk [6]. One potential reason for these varying results is that many such studies did not account for various confounders (e.g. age), including comorbidities. Another potential confounder for some of the studies could be the use of randomly selected volunteer blood donors as controls, because of the risk of group O epidemiological predominance due to blood collectors selectively recruiting group O donors. Importantly, volunteer blood donors are not necessarily representative of general populations; although convenient, their use as a control group is not optimal [53, 54].

It has also been hypothesized that anti-A and anti-B antibodies could interfere with virus–cell interactions. In a secondary analysis of data from ~1900 patients with COVID-19, subjects with circulating anti-A were significantly less represented in the disease group as compared to those lacking anti-A. In addition, anti-A in group O individuals was more protective than anti-A in group B individuals; this may relate to the increased presence of IgG anti-A,B in group O plasma [13].

One study attempted a meta-regression analysis of 101 nations using their known blood group distributions, including ~9-million COVID-19 cases and ~450 000 deaths in a total population of ~7 billion. Although there was no association of group A or B with overall mortality, group O significantly correlated with lower mortality ($p = 0.02$). The authors proposed that COVID-19 mortality was lower in nations with higher group O prevalence because overall population ABO blood group prevalence was analysed as the control [55].

Studies have also examined the relationship between the Rhesus blood group (e.g. Rh(D) type) and COVID-19. One study suggested that Rh(D)-positive individuals were more likely to test positive for SARS-CoV-2 [6]. Another study found significant associations between Rh(D) blood group status, group B, and SARS-CoV-2 [56].

In summary, these mixed findings may be ascribed to the different populations, the controls that were used for comparison, the geographical locations and the confounders that were considered. The latter include age, comorbidities and using volunteer blood donors as controls.

ABO and COVID-19 disease severity

The effect of ABO type on COVID-19 disease severity also warrants analysis. As such, in one study, group A patients had a higher risk of hospitalization for SARS-CoV-2 infection, whereas group O patients were at lower risk [7]. However, the group A patients had more comorbid risk factors for severe disease, which were not adjusted for using a multivariate analysis. Another group performed a GWAS of COVID-19 patients with respiratory failure [57], detecting a statistically significant cross-replicating association at 9q34. The 9q34 signal was located at the ABO blood group locus and a blood type-specific analysis showed a higher risk of severe COVID-19 with respiratory failure for group A individuals and a protective effect for group O.

As another example, in a nested prospective observational study of critically ill patients with COVID-19 in Canada, using a multivariable adjustment of various risk factors, patients with blood group A or AB had an increased risk of requiring mechanical ventilation,

Table 3 Summary of reported studies assessing the association between blood groups and SARS-CoV-2 infection

Ref. Author (country)	COVID-19 study population	Controls(if applicable)	% group A patients (vs. control) P value (when applicable)	% group O patients (vs. control) P value (when applicable)	Blood group susceptibility to SARS-CoV-2 infection	Association with clinical outcomes and risk of death
Zhao J et al. [5] China	1775 patients	3694 normal individuals	37.75 (32-16) $P < 0.001$	25.80 (33-84) $P < 0.001$	Yes, group A	Group A associated with higher risk of mortality than non group A
Li J et al. [7] China	2153 patients with COVID-19 pneumonia	3694 healthy controls	38.0 (32-2) $P < 0.001$	25.7 (33-8) $P < 0.001$	Yes, group A	Group A patients at higher risk of hospitalization following SARS-CoV-2 infection. Association with risk of mortality not assessed.
Zeng X. et al. [51] China	137 patients with mild pneumonia 97 patients with severe pneumonia	Nil, Chinese population data used for comparison	35.76 (28-39) 39.22 (28-39)	32.45 (33-20) 26.47(33-20)	Yes, group A	Blood group A more susceptible to SARS-CoV-2. Blood groups not relevant to acute respiratory distress syndrome, acute kidney injury and mortality.
Zietz M & Tatonetti [56] USA	Observational data on 14,112 individuals tested for SARS-CoV-2	None	32.7 (32-7)	46.9 (48-2)	Yes, group B and Rh(D)	Risk of intubation decreased among group A and increased among groups AB and B. Risk of mortality increased for group AB and decreased for groups A and B. Rh-negative blood type protective for mortality.
GÖKER H, et al. [49] Turkey	186 patients	1881 healthy controls	57 (38) $P < 0.001$	24.8 (37-2) $P = 0.001$	Yes, group A	No significant effect of ABO and RhD on clinical outcomes including intubation, ICU stay and mortality
Wu et al. [52] China	187 patients	1991 non-COVID-19 hospitalized patients	36.9 (27-47) $P = 0.006$	21.92(30-19) $P = 0.018$	Yes, group A	Group A influenced clinical outcomes but no association with mortality
Leaf RK et al. [48] USA	561 critically ill patients.	Nil, local population data used for comparison	45.1 (39-8)	37.8 (45-2)	Yes, group A	No association with any ABO phenotype and mortality
Latz CA et al. [6] USA	1289 patients	Nil	34.2 (NA)	45.5 (NA)	Yes, positive correlation with group B , AB & Rh(D)Negative with group O	No association with risk of intubation, peak of inflammatory markers and death
Gerard C et al. [12]	1175 patients	3694 controls	37.7 (32-2) $P < 0.001$	49.4 (57-6)	Yes, presence of anti-A antibodies in serum and more specifically IgG anti-A-associated	Mortality risk not assessed

Table 3 (Continued)

Ref. Author (country)	COVID-19 study population	Controls(if applicable)	% group A patients (vs. control) P value (when applicable)	% group O patients (vs. control) P value (when applicable)	Blood group susceptibility to SARS-CoV-2 infection	Association with clinical outcomes and risk of death
Abdollahi A et al. [50] Iran	397 patients	500 normal controls	40.3 (36) P = 0.19	28 (38) P = 0.002	with higher susceptibility to SARS-CoV-2 infection. Yes, group AB with higher susceptibility than other groups.	No association of ABO or RHD phenotype with severity of disease. No association of ABO or RHD with mortality assessed.
Holland et al. [4] Canada	125 critically ill patients admitted to ICU	Nil, Comparison of blood group distributions between blood donor data was performed.	37 (35) p-0.60 No difference from blood donors	Group O 43% (n = 41) No difference from blood donors	Yes, group A and AB	Higher proportion of COVID-19 patients with blood group A or AB required mechanical ventilation, and continuous renal replacement therapy and had longer ICU stay compared with patients with blood group O or B.
Barrkobb et al. [3] Denmark	7422 COVID positive patients among 473 654 individuals tested	466 232 COVID-negative individuals	More A (P <0.001), B (P = 0.011), and AB (P = 0.091) individuals were COVID positive.	38.41% (95% CI, 37.30–39.50) group O compared with 41.70% (41.60–41.80) in controls	Yes, Decreased infection risk in group O	ABO blood group as a risk factor for SARS-CoV-2 infection but not for hospitalization or death from COVID-19.

continuous renal replacement therapy and prolonged intensive care unit admission, as compared to group O or B patients [4]. Another recent retrospective cohort analysis including nearly half a million Danish individuals tested for SARS-CoV-2, also showed reduced prevalence of SARS-CoV-2 infection in blood group O individuals. This study identified ABO blood group as a risk factor for SARS-CoV-2 infection but not for hospitalization or death from COVID-19 [3].

Taken together, these studies suggest that the risk of infection with SARS-CoV-2 and the risk of severe COVID-19 disease may be lower in group O individuals than non-group O individuals. Nonetheless, these results are not definitive and further studies are warranted.

Mechanisms for associations between ABO blood group and COVID-19

Several pathophysiological mechanisms were proposed to explain the association between ABO type and SARS-CoV-2 infection (Fig. 1, Table 4). Anti-A and/or anti-B antibodies might bind to A and/or B antigens expressed on the viral envelope, thereby preventing infection of target cells; that is, these naturally occurring antibodies could function as viral neutralizing antibodies. If true, this would help explain differences in initial susceptibility for SARS-CoV-2 infection. For example, an anti-A viral neutralizing antibody in a potentially susceptible group O host would bind the A antigen on virus produced by, and inhaled from, an infected group A (or group AB) host [58]. Why this mechanism would be relevant to disease severity *per se* is less obvious, because subsequent rounds of viral proliferation in a group O host would produce virus expressing the H antigen on its envelope. However, assuming that disease severity relates to the size of the infecting inoculum and yielding the subsequent viral load, a neutralizing isoagglutinin (e.g. anti-A) could attenuate infection, if not preventing infection altogether. Finally, the entry barrier for this virus is the epithelium of the respiratory tract and, possibly, the digestive tract. Thus, to prevent infection, circulating antibodies may need to reach these cell surfaces; although, presumably, the most effective antibodies for this purpose are of the secretory IgA isotype, to date, no data are available about the IgA isotype for either anti-A and/or anti-B in this regard.

Glycan structures at various N-glycosylation sites of the SARS-CoV S protein were previously described [59–61]. In addition, N-glycans of recombinant SARS-CoV-2 S protein were recently characterized [62]; although ABH antigen structures were not described, this may be due to the cell line used to produce the recombinant protein. Interestingly, the receptor-binding domains of the SARS-CoV-2 and SARS-CoV S proteins are structurally nearly

identical [63]; in addition, glycosylation yields S trimers in which the receptor-binding domains are covered by N-glycans. Thus, it is conceivable that SARS-CoV-2 S protein could be specifically bound by human anti-A antibodies, which could then block the interaction between the virus and the angiotensin-converting enzyme 2 receptor (ACE2R), thereby preventing entry into the lung epithelium. Relevant to this hypothesis, monoclonal or naturally occurring anti-A antibodies dose-dependently inhibited interaction between SARS-CoV S protein and ACE2R, in a model where the A antigen was associated with S protein [64]. Thus, if this is also true for SARS-CoV-2, it would support the hypothesis that anti-A blocks viral attachment and/or entry [65]. Although not definitive, currently available data could support the above mechanism. There is also emerging evidence that receptor-binding domain (RBD) of SARS-CoV-2 may share sequence similarity to an ancient lectin family known to bind blood group antigens. SARS-CoV-2 RBD binds the blood group A expressed on respiratory epithelial cells, which could explain the linkage between blood group A and SARS-CoV-2 [66].

Another potential mechanism for explaining an association between group A and severe COVID-19 is an increase in angiotensin-converting enzyme 1 (ACE-1) activity, with a predisposition to cardiovascular complications. Severe outcomes could also be explained by higher levels of VWF and factor VIII in group A individuals. Furthermore, VWF is an acute phase reactant with infection inducing even higher levels in group A individuals. Given that anti-A and anti-B antibody titres are highly variable among individuals [67, 68], the potential neutralizing effect of such antibodies is also expected to be highly variable [69], possibly obscuring the 'signal' in large population studies. This variability may be further compounded by the significantly higher binding affinity of SARS-CoV-2 S protein for ACE2R, as compared to SARS-CoV [70].

Studies to confirm this hypothesis *in vitro* would involve producing recombinant SARS-CoV-2 S protein in cell lines that can synthesize terminal ABH oligosaccharides to determine whether these are, indeed, on the recombinant protein. In addition, it is important to culture SARS-CoV-2 in cell lines capable of synthesizing ABH oligosaccharides, isolate the virus and determine whether anti-A and anti-B prevent infection of cell lines that do not express the corresponding ABH antigen. If successful, these experiments would also allow testing whether IgM, IgA or IgG anti-A (or anti-B) antibodies were equally effective [71]. To our knowledge, there are no published studies to date that address this.

Other potential mechanisms may explain the epidemiological results. For example, if ABH oligosaccharides are

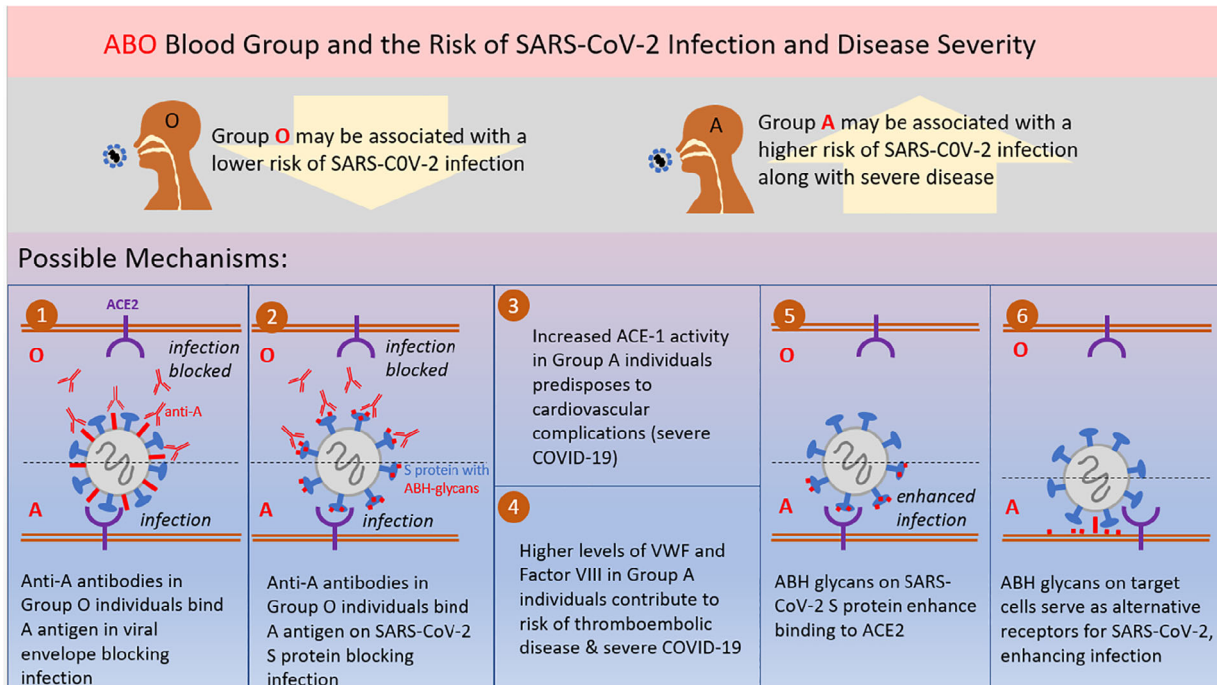


Fig. 1 Graphical summary of proposed mechanisms for association Between ABO blood groups and SARS-CoV-2 infection.

on SARS-CoV-2 S protein, they may modify the affinity of SARS-CoV-2 for ACE2R, its cellular receptor. This could be evaluated formally by producing recombinant S protein in otherwise identical host cell lines (e.g. by transfecting in the relevant glycosyltransferases) and then quantifying the affinity of the purified proteins for their receptor. Analogously, if the virus could be produced *in vitro* in these ABH-expressing cell lines and purified, the infectivity of a given target cell line could then be quantified. Given the published human population data, one might expect 'group O virions' to be less infectious in these experiments, thereby correlating with decreased COVID-19 disease severity.

A different, but not mutually exclusive, mechanism may involve ACE2R, which is also a glycoprotein and may express ABH glycans. It is possible that these glycans affect SARS-CoV-2 viral binding to ACE2R, the number of ACE2R proteins on a given cell surface, and/or the efficacy of internalization of the virus: receptor complex. In this case, ACE2R expressing H-antigen glycans may not be as effective at binding and internalizing SARS-CoV-2 produced by any source, irrespective of ABO type. This could also underlie COVID-19 disease severity.

It is also possible that the ABH glycans themselves could serve as (alternative) lower-affinity receptors for SARS-CoV-2 S protein or bind other viral envelope structures. Although current evidence suggests that this is

unlikely, if it were relevant, then ABH glycan levels on cell surfaces, in plasma, and in secretions would be important and could affect initial infection and disease severity. For this purpose, determining the 'secretor phenotype' and Lewis blood group types would be helpful [37, 72]. Moreover, secretor status and Lewis antigen frequencies can affect host immunity [37, 72].

Because COVID-19 severity relates significantly to cardiovascular [73], thromboembolic [74, 75] and inflammatory complications, the patient's ABO type may be a surrogate for these effects and have nothing to do with blood type *per se*, the presence of naturally occurring anti-A and/or anti-B or viral-target cell interactions. For example, as described above, ABO type influences circulating VWF and factor VIII levels, which influence cardiovascular risk and hemostatic function, even in the absence of infection [76].

Although an association between ABO blood group and the risk of susceptibility to COVID-19 disease or disease severity is compelling, the practical significance is uncertain. COVID-19 convalescent plasma (i.e. plasma collected from those who recover from COVID-19) is being employed as an investigational therapy for treating COVID-19 [77, 78]. One theoretical ramification of an association with ABO type could affect such a therapy; specifically, donors with higher titres of antibodies could be recruited selectively based on blood type [79].

Table 4 Proposed mechanisms, theoretical pathways and suggested experiments for studying the association Between ABO blood groups and SARS-CoV-2 infection**Proposed mechanisms for association between ABO blood type and SARS-CoV-2 infection**

Anti-A and/or anti-B antibodies serve as viral neutralizing antibodies by binding to A and/or B antigens expressed on the viral envelope, thereby preventing infection of target cells

The SARS-CoV-2 S protein is bound by human anti-A antibodies, which may block the interaction between the virus and ACE2R, thereby preventing entry into the lung epithelium

An increase in ACE-1 activity in group A individuals predisposes to cardiovascular complications, accounting for severe COVID-19

Variation of VWF and Factor VIII levels by ABO type with higher levels in group A individuals contributing to risk of thromboembolic disease and severe COVID-19

ABH glycans, if present on SARS-CoV-2 S protein, may modify the affinity of SARS-CoV-2 for ACE2R, its cellular receptor.

ABH glycans on target cells could serve as alternative, lower-affinity receptors for SARS-CoV-2 S protein or bind other viral envelope structures.

Suggested experiments to confirm the proposed associations between ABO blood groups and SARS-CoV-2 infection

In vitro production of recombinant SARS-CoV-2 S protein in cell lines that can synthesize ABH glycans to determine whether these are, indeed, on the recombinant protein.

Culturing SARS-CoV-2 in cell lines capable of synthesizing ABH glycans, isolating the virus and determining whether anti-A and anti-B prevent infection of cell lines that do not express the corresponding ABH antigen. These experiments would also allow testing whether IgM and IgG anti-A (or anti-B) antibodies were equally effective.

Producing recombinant SARS-CoV-2 S protein in identical host cell lines (e.g. by transfecting in the relevant glycosyltransferases) and then quantifying the affinity of the purified proteins for their receptor. This can determine if ABH glycans are present on SARS-CoV-2 S protein and if they modify the affinity of SARS-CoV-2 for ACE2R.

Produce SARS-CoV-2 *in vitro* in ABH-expressing cell lines; and quantify the infectivity of a given target cell line with purified virus.

Quantify IgA anti-A and/or anti-B and correlate with risk of susceptibility to infection by SARS-CoV-2 and severity COVID-19 illness.

Nonetheless, this would still require definitive proof of differential titres by ABO type. Routine ABO testing of COVID-19 patients could also guide decision-making, for example, by lowering thresholds for escalating care with higher risk blood groups. However, realistically, this is unlikely to happen given that risk, if present, is not sufficiently convincing to alter population-based care.

Conclusions

The role of ABO blood group in SARS-CoV-2 infectivity and COVID-19 disease severity requires additional study; however, accumulating evidence suggests that, at biochemical and physiological levels, there may be a contribution of ABO blood type to disease biology. It also must be recognized that host factors already identified as contributing to COVID-19 severity, play a dominant role, coupled with timely access to appropriate medical care. By contrast, the role of ABO type is likely secondary and non-modifiable.

Conflict of interest

RG serves on the medical advisory board of Rigel and reports personal consulting fees from Alexion Pharmaceuticals and TERUMO BCT outside of the submitted

work. EMB reports personal fees and non-financial support from Terumo BCT, personal fees and non-financial support from Grifols Diagnostics Solutions and Abbott Laboratories, outside of the submitted work; EMB is a member of the United States Food and Drug Administration (FDA) blood Products Advisory Committee. Any views or opinions that are expressed in this manuscript are that of the author's, based on his own scientific expertise and professional judgement; they do not necessarily represent the views of either the Blood Products Advisory Committee or the formal position of FDA and also do not bind or otherwise obligate or commit either Advisory Committee or the Agency to the views expressed. DVD serves on the advisory board of Macopharma. SLS serves on the advisory board of Hemanext, Inc. is a consultant with Tioma, Inc., and is the Executive Director of the Worldwide Initiative for Rh Disease Eradication (WIRhE).

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