Mini Review

Massimo Franchini, Fabrizio Maggi* and Daniele Focosi

**ABO blood group-related mechanism of infection of SARS-CoV-2: an overview of systematic reviews**

https://doi.org/10.1515/cclm-2023-0825
Received August 2, 2023; accepted August 23, 2023; published online September 21, 2023

**Abstract:** Among the host genetic factors playing a role in the susceptibility to infectious diseases, the ABO blood group system is of utmost importance. Following the first reports in early 2020, the association between ABO blood groups and SARS-CoV-2 infection or COVID-19 severity has been thoroughly investigated. The aim of this narrative review is to provide an overview of systematic reviews regarding the link between ABO blood groups and such risks. The possible molecular mechanisms underlying these associations will also be discussed. ABO blood group has a robust association with susceptibility to infection but not with disease severity, and studies on long COVID are still missing. Prov.

**Keywords:** ABO blood group; SARS-CoV-2; COVID-19; infection

**Introduction**

The ABO blood group is the most important human blood group system and consists of carbohydrate antigens located at the extracellular surface of the red blood cell (RBC) membrane [1]. While the A and B alleles of the ABO locus encode the A and B glycosyltransferase activities, respectively, which convert precursor H antigen into either A or B determinants by adding an extra saccharide unit, group O individuals lack such transferase enzymes and express unchanged H-antigen [2]. Along with their expression on RBCs, ABH blood group antigens (H antigen defining the O blood type) are also highly expressed on the surface of a variety of human cells and tissues [3]. Different precursor structures exist according to expression of the specific fucosyltransferase (FUT2 leading to type 1 precursors in genitourinary and gastrointestinal epithelia and secretions, and FUT1 leading to type 2 precursors in RBCs and endothelium).

Although the physiologic role of ABH antigens and anti-A and anti-B natural isoagglutinins is still largely unknown, they play a prominent role in blood transfusion and cell and organ transplantation [4].

Several studies have documented over the last 50 years a close link between ABO blood groups and a wide array of diseases, including cancers and cardiovascular disorders [5]. The latter association is particularly relevant, considering the profound influence of ABH antigens on hemostasis, particularly in modulating von Willebrand factor (VWF) and factor VIII (FVIII) circulating levels (blood group O individuals have 20–30 % lower VWF and FVIII levels compared with individuals with non-O blood groups) [6].

Finally, it is well documented how the ABO blood group affects susceptibility to various types of bacterial (e.g., *Vibrio cholerae*, enterotoxigenic *Escherichia coli*, and *Streptococcus*), fungal (e.g., Candida), parasite (e.g., malaria and *Schistosoma*), and viral infections (e.g., norovirus, rotavirus, influenza, and HIV) is well documented [7]. This issue has recently gained a renewed interest thanks to the observation of the association between ABO blood type and the Coronavirus Disease 2019 (COVID-19) pandemic caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) [8].

The aim of this narrative review is to perform an update of the literature data regarding the link between ABO blood group, COVID-19 infection, and disease outcome. The mechanisms underlying such association are also explored. A literature search through MEDLINE and PubMed electronic databases was performed for publications during the period from December 1, 2019 to July 31, 2023 using the following key words: “COVID-19”, “SARS-CoV-2”, “ABO blood groups” and “ABO blood type”. We also screened the reference lists of the most relevant review articles for additional studies not captured in our initial literature search.
Molecular relationships between SARS-CoV-2 and ABO antigens

As previously mentioned, ABH blood group antigens are implicated in the pathogenesis of multiple infections, including tuberculosis, malaria, cholera, Chikungunya virus, *Helicobacter pylori* and *E. coli* [7]. The underlying potential mechanisms include ABH antigens as receptors for pathogens, and natural antibodies (isoagglutinins) cross-reacting with pathogen antigen (molecular mimicry) [9]. As an example of the first type of causation, individuals with A blood type have been found to be highly susceptible to *Plasmodium falciparum* malaria whereas low parasitemia and uncomplicated *P. falciparum* malaria cases have been observed more frequently among blood type O individuals [10]. Such better malaria outcomes in blood group O have been attributed to decreased RBC rosetting (binding of parasitized RBCs to healthy RBCs, which is directly implicated in the pathogenesis of severe malaria) [10].

Regarding the link between ABH antigens and susceptibility to SARS-CoV-2 infection, an initial genome-wide association study (GWAS) study of more than 2,200 controls and 1,600 patients with severe COVID-19 disease found a protective effect (OR 0.65, 95 % CI 0.53–0.79) of blood group O compared with non-O [11]. However, a GWAS meta-analysis of more than 50,000 individuals with COVID-19 and 700,000 with no record of SARS-CoV-2 infection found that the ABO gene was not associated with COVID-19 severity [12]. Another meta-analysis of more than 125,000 COVID-19 cases and 2.5 million controls found a statistically significant association after correction for multiple factors between the ABO locus and COVID-19 [13]. A recent study by Wu and colleagues unraveled the possible underlying molecular mechanism [14], i.e., a significant similarity between SARS-CoV-2 receptor-binding domains (RBD) within the Spike protein (which is responsible for recognizing host ACE2 and cell entry) and human galectins (a family of carbohydrate binding proteins able to engage ABH antigens). Pre-incubation of blood group A cells with a galectin selective for this blood type specifically inhibited SARS-CoV-2 infection of blood group A expressing cells (“shielding”), while similar incubation with a galectin that did not recognize blood group antigens failed to impact SARS-CoV-2 infection [14]. These results confirmed the previous observation that SARS-CoV-2 preferentially recognizes and infects blood group A cells, providing thus a direct link between ABO blood group expression and SARS-CoV-2 infection [15, 16]. Similarly, in a cellular model, SARS-CoV Spike protein/ACE2 dependent adhesion to ACE2-expressing cell lines was specifically inhibited by monoclonal or natural human anti-A antibodies [17]. Another possible mechanism involves the presence on the virion surface of blood group A antigens [9]: such carbohydrate epitopes, acquired from cell membranes of previously infected group A or AB hosts. Thus, individuals with non-A blood types, specifically O or B blood types (which produce anti-A antibodies), may be less susceptible to SARS-CoV-2 infection due to the inhibitory effects of anti-A isoagglutinins that block viral attachment to cells, the entrance of SARS-CoV-2 into the host cells and the consequent viral infection [17]. In other words, these naturally occurring antibodies function as viral neutralizing antibodies [18] (Figure 1). *In vitro* studies could not detect any virus-neutralizing activity in prepandemic sera, but this could be explained by the lack of ABO antigens on cell type used in viral neutralization assays (https://pubmed.ncbi.nlm.nih.gov/35262018/). However, many additional factors may play a role in modulating the host sensitivity to SARS-CoV-2, including variations in ACE2 levels, blood group A antigen expression, and additional polymorphisms of other blood group systems, such as Lewis antigens [20].

![Figure 1: Mechanisms of action of ABO blood group-associated COVID-19 infection.](image-url)
**Association between ABO blood group and SARS-CoV-2 infection**

Soon after the onset of the COVID-19 pandemic, an association between the ABO blood group and SARS-CoV-2 infection was firstly documented in China by Zhao and colleagues, in which blood type A was significantly related to higher risk of COVID-19 infection in comparison to non-A blood types; while blood type O was significantly related to lower risk of COVID-19 infection compared to non-O blood types [21]. In addition, other studies found that ABO antibody levels were significantly lower in COVID-19 patients compared to controls, indicating that patients with low levels of ABO antibodies (i.e., elderly and immunocompromised patients) could be at higher risk of being infected by SARS-CoV-2 [19]. Subsequently, several studies have reported significant associations between blood type A and higher susceptibility to SARS-CoV-2 infection and/or blood type O and lower susceptibility [22]. The largest study was conducted in Spain in a cohort of 87,090 subjects and found a protective role against the risk of SARS-CoV-2 infection. The study, which included that evaluating the largest number of trials [32], however, did not find a significant association, suggesting a possible protective role of O blood group against COVID-19-related death and a deleterious effect of B blood type [39]. In a study conducted in patients admitted to ICU for severe COVID-19, a significantly higher risk of requiring mechanical ventilation as well as a higher ICU length of stay was observed for A and AB groups, while B and O groups were negatively associated with these outcomes [40]. The majority of the studies, however, were unable to identify any trend in the outcomes according to the type of ABO blood group. In the overview of the systematic review reported in Table 1, 6 [27, 28, 31, 32, 35, 37] out of the 13 reviews reported analyzed the relationship between the ABO blood group and COVID-19 severity and mortality. The majority of them [27, 28, 32, 35], however, did not find a significant association, including that evaluating the largest number of trials [32].

**Conclusions**

While the association between ABO blood group and virus infection is well known since many years, the finding of a lower susceptibility of people with O blood group to get infected by coronaviruses had already been reported nearly 20 years ago for SARS-CoV. Further evidence from the recent COVID-19 pandemic has reinforced this finding, evoking, as a susceptibility to COVID-19 infection, while those with blood group O have a lower risk.
possible main molecular mechanism, both the ability of Spike to bind to A antigens and the ability of anti-A antibodies at neutralizing the virions. Overall, the analysis of the published literature data evidences that individuals with blood group O and those with group A are at lower and increase risk of becoming infected by SARS-CoV-2, respectively. By contrast, no convincing evidence is available regarding the association between ABO blood group and
COVID-19 severity and outcome. No study has been reported yet on the association between ABO blood groups and post-acute sequelae of COVID-19.

Further studies are also needed to verify whether in COVID-19 clinical responses to plasma-derived antibody-based treatments (i.e., convalescent plasma and polyclonal IgGs) are driven, in addition to the levels of neutralizing antibodies, also by the presence of natural occurring ABO antibodies.

**Research ethics:** Not applicable

**Informed consent:** Not applicable.

**Author contributions:** M.F. and D.F. wrote the manuscript. F.M. revised the manuscript. The authors have accepted responsibility for the entire content of this manuscript and approved its submission.

**Competing interests:** The authors state no conflict of interest.

**Research funding:** None declared.

**Data availability:** Not applicable.

**References**


