Mini Review

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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 anre 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 (WVF) 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.

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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)s [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].

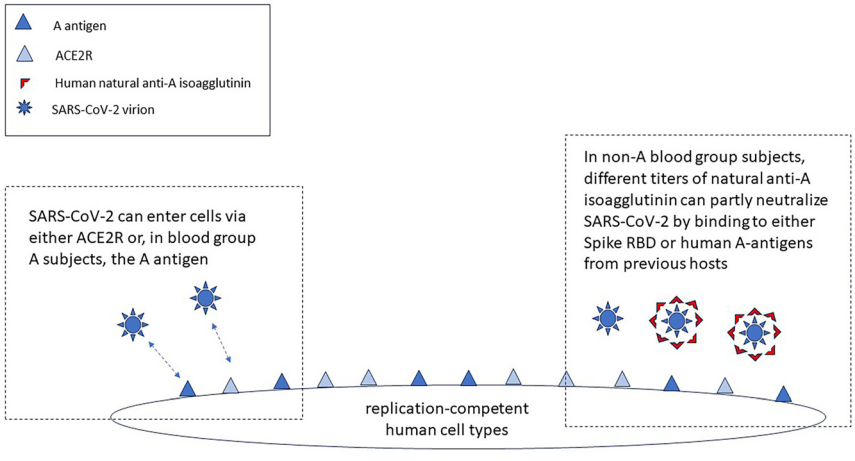

Figure 1: Mechanisms of action of ABO blood group-associated COVID-19 infection.

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 of blood group O vs. non-O groups (OR 0.94; 95 % CI 0.90–0.99) [23]. Other studies, however, were in disagreement with these findings [24, 25]. Table 1 summarizes the main results of the systematic reviews and meta-analyses exploring the association between ABO blood group and risk of COVID-19 infections and complications. Overall, 13 systematic reviews and meta-analyses were retrieved from the literature [26–38], published during the period 2020–2023 and including a variable number of trials, ranging from 4 studies for a meta-analysis published in 2020 [27] to 63 studies for a meta-analysis published in 2022 [32] with a consequent wide variability in the number of cases and controls evaluated (from 14,938 to 3,458,647). All but one [35] of the systematic review explored the association between the ABO blood group and the rick of SARS-CoV-2 infection. No prospective trials were included in these reviews, the majority of studies being retrospective. In almost all reviews, the qualitative study assessment found a large heterogeneity among the different studies, particularly in terms of study design and populations considered. Regarding the latter, the ethnicity difference among populations enrolled in the different studies (it is well known that ABO blood group distribution varies among different human races) could have generated an important bias hampering pooling estimate.

In spite of these limitations, however, all but one [37] of the systematic reviews analyzed found similar results: individuals with blood group A have an increased susceptibility to COVID-19 infection, while those with blood group O have a lower risk.

Association between ABO blood group and COVID-19 severity

While there is a general agreement on the link between the ABO blood group system and the predisposition to COVID-19 infection, more uncertainty arises from the analysis of the literature data regarding the association with COVID-19 severity and mortality [18]. The concomitant presence of confounding factors (i.e., comorbidities, disease stage, etc.) probably enhances the heterogeneity of the different studies, which appears even more marked that concerning the risk of infection.

Several studies have investigated the association between ABO blood group and COVID-19 severity or outcomes [18]. In an investigation conducted in the Indian population, a significant inverse correlation was observed between the frequency of O blood group and the COVID-19 mortality rate (Spearman r=−0.36, p=0.03), while the prevalence of blood group B was positively correlated with COVID-19 deaths/million (Spearman r=0.67, p<0.0001), 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

Table 1: Overview of the systematic reviews and meta-analyses on the association between SARS-CoV-2 infection and ABO blood group.

First author, year [reference]	Studies included, n (study design)	Cases/controls, n	Main results
Golinelli, 2020 [26]	7 (7 CC)	7,503/2,962,169	SARS-CoV-2 positive individuals are more likely to have a blood group A (OR 1.23; 95 % CI 1.09–1.40) and less likely to have blood group O (OR 0.77; 95 % CI 0.67–0.88)
Wu, 2020 [27]	4 (4 R)	31,100	Individuals with A and O blood type were at increased (OR 1.25; 95 % CI 1.11–1.44) and decreased (OR 0.7; 95 % CI 0.63–0.77) risk of COVID-19 infection, respectively. No correlation between ABO blood group and severity was found
Franchini, 2021 [28]	21 (11 CC, 8 R, 2 P)	29,649/892,496	A lower risk of SARS-CoV-2 infection was observed in subjects with O blood type vs. non-O blood types (OR 0.81; 95 % CI 0.75–0.86). No evidence was found indicating an effect of the O blood type on the disease severity in SARS-CoV-2 infected patients
Wang, 2021 [29]	18 (18 R)	13,600/3,445,047	O blood group was associated with a lower risk of COVID-19 infection compared with other blood groups (OR 0.76; 95 % CI 0.66–0.84), while blood group A and AB was associated with a higher risk (OR 1.25; 95 % CI 1.10–1.41 and OR 1.13; 95 % CI 1.04–1.23, respectively)
Kabrah, 2021 [30]	16 (14 R, 1 CC)	14,938	The COVID-19 infection rate was higher in persons with blood group A vs. the other blood groups (pooled p value <0.001)
Liu, 2021 [31]	10 (8 CC, 2 C)	9,383/44,835	Blood groups A and B were risk factor for COVID-19 (OR 1.33; 95 % CI 1.14–1.56 and OR 1.06; 95 % CI 1.00–1.13, respectively), while group O is protective (OR 0.61; 95 % CI 0.70–0.84). Blood group A was associated with an increased risk of COVID-19 mortality (OR 1.25; 95 % CI 1.02–1.52)
Gutierrez-Valencia, 2022 [32]	63 (26 C, 19 CC, 18 CS)	1,564,162 (infection), 39,542 (mortality)	The O blood group was associated with a lower risk of COVID-19 infection compared to the non-O blood group (OR 0.88; 95 % CI 0.82–0.94). The mortality risk was similar in O vs. non-O blood group (OR 0.99; 95 % CI 0.92–1.06)
Banchelli, 2023 [33]	23 (18 C, 5 CC)	74,563/1,166,717	The O blood group is associated with a slightly lower risk (OR 0.91; 95 % CI 0.85–0.99) and A blood group with a slightly higher risk (OR 1.06; 95 % CI 1.00–1.13) of COVID-19 infection as compared to the other blood groups
Balaouras, 2022 [34]	22 (13 R, 6 CC, 3 CS)	NR	Blood groups A, B and AB have a higher risk for COVID-19 infection compared to blood group O, which appears to have a protective effect. A group vs. O (OR 1.29; 95 % CI 1.15–1.44), B vs. O (OR 1.15; 95 % CI 1.06–1.25), AB vs. O (OR 1.32; 95 % CI 1.10–1.57)
Bhattacharjee, 2022 [35]	9 (9 O)	233,006	No significant differences in the unadjusted mortality and/or severity outcomes (defined by intubation or dyspnea) related to COVID-19 were found in patients with blood groups A/AB (with no anti-A antibodies) as compared with B/O groups (with anti-A antibodies) (OR 1.09; 95 % CI 0.91–1.29)
Gheshlagh, 2022 [36]	27	23,285/590,593	Individuals infected with COVID-19 have higher risk of having blood group A and lower risk of having blood group O. OR for blood groups A, O, B, and AB were 1.26 (95 % CI 1.13–1.40), 0.77 (95 % CI 0.71–0.82), 1.05 (95 % CI 0.99–1.12), and 1.11 (95 % CI 0.99–1.25), respectively
Leache, 2022 [37]	13 (6 CC, 6 C, 1 CS)	NR	In a population aged ≥60 years, blood group A was associated with a significantly higher mortality risk when compared to non-A (OR 1.23; 95 % CI 1.08–1.40), and a lower risk was found for the blood group B when compared to non-B (OR 0.83; 95 % CI 0.70–0.99). No significant association was found between any of the ABO blood groups and COVID-19 infection
Soo, 2022 [38]	23	53,835/1,328,484	Individuals with blood group A are more likely to be infected by COVID-19 (OR 1.16; 95 % CI 1.08–1.24), while individuals with blood group O are protected against COVID-19 infection (OR 0.78; 95 % CI 0.71–0.85)

OR, odds ratio; CC, case-control; R, retrospective; P, prospective; C, cohort study; CS cross-sectional; O, observational; NR, not reported.

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.

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