The relationship between blood groups and risk of infection with SARS-CoV-2 or development of severe outcomes: A review

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Summary
The outbreak of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is considered a global catastrophe that has overwhelmed health care systems. Since initiation of the pandemic, identification of characteristics that might influence risk of infection and poor disease outcomes have been of paramount interest. Blood group phenotypes are genetically inherited characteristics whose association with certain infectious diseases have long been debated. The aim of this review is to identify whether a certain type of blood group may influence an individual’s susceptibility to SARS-CoV-2 infection and developing severe outcomes. Our review shows that blood group O protects individuals against SARS-CoV-2, whereas blood group A predisposes them to being infected. Although the association between blood groups and outcomes of COVID-19 is not consistent, it is speculated that non-O blood group carriers with COVID-19 are at higher risk of developing severe outcomes in comparison to O blood group. The interaction between blood groups and SARS-CoV-2 infection is hypothesized to be as result of natural antibodies against blood group antigens that may act as part of innate immune response to neutralize viral particles. Alternatively, blood group antigens could serve as additional receptors for the virus and individuals who are capable of expressing these antigens on epithelial cells, which are known as secretors, would then have a high propensity to be affected by SARS-CoV-2.

KEYWORDS
ABO blood groups, blood groups, COVID-19, Rh blood groups, SARS-CoV-2

Abbreviations: ACE, Angiotensin-converting enzyme; ACE2, Angiotensin-converting enzyme 2; COVID-19, Coronavirus disease 2019; FUT2, Fucosyltransferase 2; ICU, Intensive care units; MERS-CoV, Middle East respiratory syndrome coronavirus; MeSH, Medical Subject Heading; RBC, Red blood cell; RBD, Receptor binding domain; SARS-CoV, Severe acute respiratory syndrome coronavirus; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; WHO, World Health Organization.

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1 | INTRODUCTION

In late December 2019, the outbreak of coronavirus disease 2019 (COVID-19) was observed with an unusual pneumonia in Wuhan, China. It rapidly spread worldwide and was declared as a pandemic by the World Health Organization (WHO) on 11 March 2020. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the current global health crisis, and it has affected more than 143 million individuals and led to almost 3 million deaths across the world as of late April 2021. COVID-19 primarily involves the lower respiratory tract and is characterized through a dry cough, fever, dyspnea, and bilateral pneumonia. It has been estimated that 23% of infected cases develop severe symptoms and 6% die due to complications of the disease, such as pneumonia and end-organ failure. Advanced age, male sex, and comorbidities such as diabetes, hypertension, and renal disorders are related to the high SARS-CoV-2 infection rate.

The mechanism of SARS-CoV-2 infection mainly depends on spike protein since it utilizes angiotensin-converting enzyme 2 (ACE2) as receptor for cell entry. Several host proteases could help the virus to invade the cells more efficiently. Expression of ACE2 on various human cell surfaces gives SARS-CoV-2 the ability to infect multiple tissues.

The two other zoonotic coronaviruses that have caused epidemic infections in the past two decades are severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). The long incubation period and highly contagious nature of COVID-19 are purported to be the primary reason for the substantially high death toll, despite the lower case mortality rate of SARS-CoV-2 in comparison with SARS-CoV and MERS-CoV.

For decades, blood group antigens were relegated just to compatibility testing for blood transfusions. However, clinical significance has expanded with relevance in pathogenesis of microorganisms and even providing the first line of defence against infectious agents through corresponding natural antibodies. ABO and Rh blood groups, are among factors that may offer susceptibility or resistance to viral invasion and also influence prognosis of infectious diseases. Understanding the relationship between diseases that have caused pandemics and blood groups could be a useful risk factor to aid prediction of outcomes and establish efficient measures in combating the disease spread with respect to blood group distributions.

In this review, we sought to describe the relationship between blood groups and risk of infection with SARS-CoV-2 and developing unfavourable outcomes.

2 | METHODS

We searched PubMed database to identify publications from peer-reviewed journals. We used Medical Subject Heading (MeSH) terms, including ‘ABO Blood-Group System,’ ‘Rh-Hr Blood-Group System,’ ‘SARS-CoV-2,’ and ‘COVID-19’ in combination with other free terms such as ‘COVID-19,’ ‘SARS-CoV-2,’ ‘2019-ncov,’ ‘ABO blood types,’ ‘ABO factor,’ ‘ABO phenotype,’ ‘blood group,’ ‘Rhesus Blood Group System,’ ‘Rh factor,’ ‘antigen D,’ and ‘blood group antigens.’ Also, medRxiv (https://www.medrxiv.org/) was searched for pre-prints articles with ‘blood group AND COVID-19’ key words. The search was conducted on March 11, 2021 and no search filters on publication type, language, time period, and other fields were implemented. Reference lists of all relevant publications were manually screened to identify further qualified studies.

3 | BLOOD GROUP ANTIGENS AND DISEASES

There are a number of carbohydrates and proteins on human red blood cell (RBC) membranes that are known as blood group antigens. According to the World Blood Transfusion Association, about 341 antigens have been identified and categorized into 41 blood group systems. ABO blood group system, as discovered by Landsteiner, is the most important blood group system. The sequential additions of carbohydrates to an oligosaccharide backbone resulted in formation of three antigens, including A, B, and H. Adding a terminal residue to the oligosaccharide backbone, creates the H antigen which then acts as a precursor for formation of A and B antigens. ABO gene encodes two glycosyltransferase enzymes that attach N-acetylgalactosamine or D-galactose to H antigen to produce A and B antigens, respectively. In the case of no glycosyltransferase expression, the H antigen serves as an O phenotype. Group O is the most frequent blood group globally, followed by group A, B, and then AB. However, the distribution of these phenotypes widely varies in different populations and is mostly attributed to epidemics that have occurred in the past, so blood groups that were more resistant against disease tended to be naturally selected over time.

ABO phenotypes are a common target of epidemiological studies since they are genetically determined traits and the frequency of their distribution varies noticeably across ancestry groups. Accordingly, multiple investigations have been conducted to identify the possible relationship between blood groups as genetic risk factors for various human diseases, especially infectious diseases. A relationship between blood groups and diseases was first postulated in 1917 to investigate an association between ABO blood types and tuberculosis. Since then, many studies have supported the hypothesis that blood groups could be related to the risk of occurrence and progression of several diseases, including cardiovascular disorders, diabetes, neurological diseases, and cancers of the gastrointestinal system. In the case of infectious diseases, it has been shown that individuals with blood group O are at higher risk of being infected with norovirus, HBV, Vibrio cholerae, and dengue virus. Conversely, individuals with non-O blood groups were at higher risk of severe Plasmodium falciparum infection than those with blood group O. Moreover, the efficacy of infectious disease related vaccines may be influenced by blood group distribution in the target population.
The mechanism in which blood group antigens may confer susceptibility or protection from infectious agents or influence the evolution of diseases have yet to be elucidated. However, there is some underlying evidence to suggest that blood group antigens may play a key role as receptors and/or cofactors for several infectious agents, including Norwalk virus and Helicobacter pylori which interact with ABO antigens to successfully bind with gastric mucosa. Furthermore, various pathogens are capable of expressing blood group antigens identical or cross-reactive epitopes on their surfaces. Therefore, natural antibodies against ABO antigens may act as part of innate immunity that can attenuate infection.

The next general blood group category is the Rhesus (Rh) system, determined by the presence or absence of Rh or D antigen. Unlike the ABO system, Rh phenotypes are associated with few diseases, most of which are haemolytic diseases of newborns that occur as a consequence of Rh mismatching between mother and offspring.

4 | BLOOD GROUPS AND RISK OF CONTRACTING WITH SARS-CoV-2

The initial idea of a relationship between blood groups and coronavirus infections refers to 2005, where Cheng et al. examined the association of ABO blood groups and risk of SARS-CoV infection on 45 health care staff who were not protected by relevant equipment in exposure to affected patients. The comparison revealed that individuals with blood group O had a lower risk of infection compared to non-O blood groups (odds ratio [OR] = 0.18; 95% confidence interval [CI]: 0.04–0.81; p = 0.03). Given that the epidemic was controlled rapidly, the former finding was not sufficiently debated nor corroborated by further research at the time. More investigations are now underway to better understand if there is the same association between blood groups and the emerging virus, due to SARS-CoV-2 and SARS-CoV sequences being very similar and given that both utilize ACE2 for cell entry.

A recent Italian-Spanish genome-wide association study found that polymorphisms at two susceptibility loci, including 9q34.2 and 3p21.31, contributed to SARS-CoV-2 induced respiratory failure that was significant at the genome-wide level. The ABO gene resides on 9q34.2 locus, which suggests that the ABO blood group system has potential implications for SARS-CoV-2 infection.

Several reports have come to a conclusion that O blood group subjects are at lower odds of testing positive for COVID-19, whereas those with non-O blood groups, particularly group A, have higher susceptibility to the infection. For instance, in a French study by Gallian et al. including 998 samples collected from blood donors, the seroprevalence values of SARS-CoV-2 neutralizing antibodies were lower in group O donors compared with other blood groups (1.32% vs. 3.86%; p = 0.014). A previous systematic review and meta-analysis of seven studies demonstrated that patients with COVID-19 were more likely to have 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). In addition, a retrospective cohort study using the data of 14,112 individuals tested for SARS-CoV-2, reported that patients with Rh negative phenotype presented 2.7% lower risk of initial infection (Risk ratio [RR] = 0.85; 95% CI: 0.73–0.96). Similarly, a large cohort enrolling 225,386 confirmed COVID-19 cases by PCR testing showed that patients with blood group O and negative Rh phenotype were less represented as compared to other blood groups (RR = 0.74; 95% CI: 0.66–0.83).

Moreover, populations living in endemic malaria regions appear to have a lower incidence of COVID-19. One potential explanation for this restricted spread is high prevalence of blood group O in malaria-endemic regions, which have been selected due to protective effects against Plasmodium falciparum. Therefore, since O blood group carriers are somewhat resistant to SARS-CoV-2 infection, reduced spread of the infection would reasonably be expected in these regions.

It is noteworthy to mention that the impact of blood groups on COVID-19 may differ by race/ethnicity. In a study including 2,033 COVID-19 patients in the United States of America (USA), the distribution of O phenotype was lower than expected and A phenotype was over-represented in White patients, while among Black and Hispanic patients the observed and expected ABO phenotype distribution showed no significant difference. This is in concordance with a previous observation that blood group A in White patients was associated with developing acute respiratory failure syndrome after severe sepsis or major trauma, unlike Black patients.

Although all studies in this area have been performed on adult patients, NCT04682912 is recruiting approximately 2,000 children under the age of 18 years who were documented positive for SARS-CoV-2 through PCR assay in order to examine the possible link of blood groups with SARS-CoV-2 infection in such groups of patients.

5 | SECRETOR STATUS OF BLOOD GROUP ANTIGENS AND SARS-CoV-2 INFECTION

ABO blood group antigens are expressed not only on erythrocytes but also widely distributed along the mucosal membrane of the gastrointestinal tract, respiratory and reproductive systems, and in their secretions. Expression of such antigens on epithelial cell surfaces and secretions is genetically determined by FUT2 gene, encoding fucosyltransferase 2 enzyme. Based on synthesis of this enzyme, approximately 80% of the population are ‘secretor’ and 20% are ‘non-secretors’. Expression of blood group antigens on mucosal cells have raised some questions about whether the interactions with infectious agents play a role on entry processes of pathogens. In this case, it was shown that in non-secretors, lack of blood type antigen expression on mucosal cells offers some degree of protection from several pathogens, which then potentially bind to these antigens on mucosal surfaces.

Recently, it has been shown that the receptor binding domain (RBD) of SARS-CoV-2 spike protein exhibited only low-level affinity for binding to A, B, and H antigens on RBCs but, when exposed to blood group antigens expressed on respiratory epithelial cells, a high
affinity was found toward binding to blood group A antigen in comparison with B and H antigens.68 Consistently, Valenti et al. determined that in non-O blood group patients affected by SARS-CoV-2, non-secretor phenotype was significantly associated with reduced need of mechanical ventilation and intensive care unit (ICU) admission as compared to secretor phenotypes (OR = 0.57; 95% CI: 0.37–0.87; p = 0.007), whereas it did not reach statistical significance for blood group O patients.69 Therefore, secretor phenotype in group A carriers may play a fundamental role in SARS-CoV-2 infection to host respiratory cells and further progression of the disease. However, this conclusion may be challenged by a previous study in which no correlation was found between FUT2 gene and COVID-19 prevalence nor mortality.70 Thus, clarifying the exact role of secretor status on SARS-CoV-2 infection requires further investigations.

6 BLOOD GROUPS AND PROGNOSIS OF COVID-19

The majority of studies concluded that ABO blood groups cannot influence the outcomes of COVID-19 and are not associated with mortality.17,39,41,50,51,60,71–78 However, those few studies that found a relationship between blood groups and evolution of COVID-19 were almost consistent in their results, reporting a higher risk of unfavourable outcomes in non-O blood groups compared to blood group O.

Evaluating the relationship between blood groups and risk of severe disease or death, Ray et al., have enrolled 225,556 cases of COVID-19.55 They reported that blood group O and Rh negative carriers represented lower risk of developing severe outcomes or death as compared to non-O blood groups (adjusted RR = 0.87; 95% CI: 0.78–0.97) and Rh positive (aRR: 0.82; 95%CI: 0.68–0.96) individuals, respectively.55 In a systematic review and meta-analysis of five studies, a statistically significant association has been found in the case of blood group A and a higher risk of mortality due to SARS-CoV-2 infection, while no association was observed in other blood groups.77 Takagi et al. performed a meta-regression analysis on data of 101 nations, with blood group distribution data available online.79 In addition to blood group proportions, total number of confirmed COVID-19 cases and deaths in these nations in a whole population of ~7 billion were almost 9 million and 450,000, respectively.79 It showed that blood group O was independently associated with lower SARS-CoV-2 mortality (p = 0.02).79 The data of all the studies evaluating this association are summarized in Table 1.

7 THE POSSIBLE MECHANISMS UNDERLYING THE ASSOCIATION BETWEEN BLOOD GROUPS AND SARS-CoV-2 INFECTION

The inherent mechanisms explaining protection from or predisposition to SARS-CoV-2 infection are not yet clear, although there are multiple possibilities.

7.1 ABO antigens as receptors for SARS-CoV-2 cell entry

Viral interaction with ACE2 for facilitating cell entry might be possible with other host molecules such as blood group antigens, which in turn affect the susceptibility of different blood type carriers to getting infected by SARS-CoV-2. A recent in vitro study indicated that when the SARS-CoV-2 exposed to ABO antigens expressed on respiratory epithelial cells, the RBD showed a significant preference for binding to A antigen compared to B and H antigens (p < 0.001). This highlights the potential role of A antigen expressing on epithelial cells over the development of SARS-CoV-2 infection.68

7.2 Antibodies against ABO antigens and neutralization of SARS-CoV-2 particles

In 2008, Guillon et al. demonstrated that the adhesion of SARS-CoV spike protein to ACE2 could be inhibited by natural anti-A antibodies.88 The same can be extended to SARS-CoV-2.89 Thus, one might assume that both blood group O and B should provide protection, while numerous studies revealed that blood group B do not alter the risk of acquiring COVID-19.38,49,90 For instance, Gerard et al. indicated that subjects with anti-A antibody (i.e. blood groups O and B) were significantly under-represented in COVID-19 in comparison with A and AB (p < 0.001), A (p < 0.001), or AB (p = 0.032).91 Then, they examined the hypothesis if there is a difference between group O and B anti-A antibody.91 As a result, the prevalence of group O carriers was significantly lower, whereas the prevalence of group B carriers was significantly higher in COVID-19 patients (p < 0.001), suggesting that anti-A from O blood groups are more protective than anti-A from B.91 Differences in the nature of anti-A antibodies from O and B are responsible for the predominant immunoglobulin isotypes of anti-A antibody, being IgG in blood group O and IgM in blood group B.39,92 A beneficial aspect of this theory would be implicated in convalescent plasma therapy, so that donors with higher titres of natural antibody based on their blood group could be recruited selectively in order to optimize the treatment.99

7.3 ABO blood group phenotypes and SARS-CoV-2 progression

Blood group O is associated with a lower risk of unfavourable outcomes in patients with COVID-19.55,79,80 A possible explanation may be attributed to lower levels of von Willebrand and VIII factors in blood group O individuals which may lead to decreased risk of cardiovascular diseases.93–96 Coagulopathy and vasculopathy features of COVID-19 are reported to be substantial contributors to development of acute respiratory distress syndrome.97 Therefore, lower risk of disease progression shown in blood group O patients is
| First author       | Country          | Study design     | Age (Mean or Median) | Gender (% female) | Number of COVID-19 participants | Adjustment | Outcomes                                                                                     |
|--------------------|------------------|------------------|----------------------|------------------|-------------------------------|------------|--------------------------------------------------------------------------------------------|
| Hoiland et al.     | Canada           | Retrospective cohort | 68                   | 35.7             | 95                            | Yes        | (i) A greater proportion of A or AB patients required mechanical ventilation compared with O or B patients (adjusted HR = 1.76; 95% CI: 1.17–2.65; p = 0.007).
|                    |                  |                  |                      |                  |                               |            | (ii) A greater proportion of A or AB patients required CRRT compared with O or B patients (adjusted HR = 3.75; 95% CI: 1.28–10.9; p = 0.02) |
|                    |                  |                  |                      |                  |                               |            | (iii) Median ICU length of stay was longer in A or AB patients (13.5 days) than in O or B patients (9 days; p = 0.03), but there were no differences in the probability of ICU discharge after adjustment (adjusted HR = 0.63; 95% CI: 0.39–1.03; p = 0.06). |
|                    |                  |                  |                      |                  |                               |            | Comorbidities                                                                                     |
|                    |                  |                  |                      |                  |                               |            | No                                                                                               |
| Muñiz-Diaz et al.  | Spain            | Case-control study | 69                   | 40.9             | 965                           | Yes        | Risk of mortality in group A individuals was higher than in group O individuals (OR = 1.75; 95% CI: 1.22–2.51; p = 0.00) |
|                    |                  |                  |                      |                  |                               |            | (i) Patients with blood group A have a higher risk of death than the rest of the ABO blood groups (OR = 1.35; 95% CI: 1.03–1.78; p = 0.029). |
|                    |                  |                  |                      |                  |                               |            | (ii) Patients with blood group O showed a lower risk of death than non-O blood group patients (OR = 0.75; 95% CI: 0.56–0.99; p = 0.044) |
|                    |                  |                  |                      |                  |                               |            | Comorbidities                                                                                     |
|                    |                  |                  |                      |                  |                               |            | No                                                                                               |
| Mannan et al.      | Bangladesh       | Cross-sectional  | 40                   | 25               | 1021                          | No         | A significant relationship was found between blood groups and being symptomatic or asymptomatic (p 0.009). |
|                    |                  |                  |                      |                  |                               |            | Comorbidities                                                                                     |
| Kim et al.         | South Korea      | Retrospective cohort | 49                   | 49               | 2840                          | No         | COVID-19 patients with blood type A were more prone to progress severe outcomes (p < 0.001). |
| El-Shitany et al.  | Egypt and Saudi Arabia | Cross-sectional | 33                   | 84               | 726                           | No         | (i) Blood group O showed the highest percentage of patients who experienced an oxygen saturation range of 70%–80% (p = 0.025) |
|                    |                  |                  |                      |                  |                               |            | (ii) Blood group O and A showed the highest and lowest percentage of patients who required artificial respiration (p = 0.05 and p = 0.05, respectively) |

(Continues)
| First author | Country | Study design | Age (Mean or Median) | Gender (% female) | Number of COVID-19 participants | Adjustment | Outcomes |
|--------------|---------|--------------|----------------------|-------------------|-------------------------------|------------|----------|
| Kotila et al. | Nigeria | Cross-sectional | 38.8 | 33.1 | 302 | No | (iii) Blood group B showed the lowest percentage of patients who experienced myalgia ($p = 0.039$)  
(iv) Blood group B showed the lowest percentage of patients who needed 3 weeks or more to recover ($p = 0.045$)  
Patients with blood group O and B were more presented in symptomatic COVID-19 group than asymptomatic group ($p = 0.03$). |
| Ad’hiah et al. | Iraq | Case-control | 49.8 | 40.3 | 300 | Yes | Sex  
Age | Significantly increased risk of death in COVID-19 cases was associated with groups A (OR = 14.60; 95% CI: 2.85–74.88; $p = 0.001$), AB (OR = 12.92; 95% CI: 2.11–79.29; $p = 0.006$), A + AB (OR = 14.67; 95% CI: 2.98–72.33; $p = 0.001$), and A + B + AB (OR = 9.67; 95% CI: 2.85–74.88; $p = 0.005$). |
| Aktimur et al. | Turkey | Retrospective cohort | 53.3 | 50.8 | 179 | No | (ii) Duration of ICU stay was longer in patient with blood group A ($p = 0.013$).  
(iii) Mortality was higher in patients with group A ($p = 0.027$). |
| Belaouni et al. | Morocco | Cross-sectional | 35.13 | 0 | 242 | No | Covid-19 patients with blood group AB were more at risk of developing headache ($p < 0.001$). |
| Zalba Marcos et al. | Spain | Retrospective cohort | 70.9 | 36 | 226 | Yes | Sex  
Age | Group B and AB developed more thrombosis ($p = 0.012$), required more admission to the ICU ($p = 0.037$), and had elevated fibrinogen level ($p = 0.005$). |
| Ray et al. | Canada | Retrospective cohort | 53.8 | 71 | 225,556 | Yes | (i) Patients with blood type B were at higher risk for severe illness or death than type A (adjusted RR = 1.21; 95% CI: 1.04–1.40)  
(ii) Patients with blood type O were at lower risk for severe illness or death than all others types (adjusted RR = 0.87; 95% CI: 0.78–0.97)  
(iii) Patients with Rh blood type were at lower risk for severe illness or death than Rh + blood type (adjusted RR = 0.82; 95% CI: 0.68–0.96)  
(iv) Type O blood with negative Rh phenotype versus other blood types was protective against SARS-CoV-2 positivity without severe illness or death (adjusted OR = 0.72; 95% CI: 0.63–0.83) and also SARS-CoV-2 positivity with severe illness or death (adjusted OR = 0.49; 95% CI: 0.40–0.60). |
| First author | Country | Study design | Age (Mean or Median) | Gender (% female) | Number of COVID-19 participants | Adjustment | Outcomes |
|--------------|---------|--------------|----------------------|-------------------|--------------------------------|------------|----------|
| Kibler et al. | France  | Retrospective cohort | 82 ± 8.4            | 68.2              | 22                             | Yes Sex Age Comorbidities | Blood group A versus other blood groups were associated with COVID-19 severity (hospitalization and/or death) (OR = 0.84; 95% CI: 0.65–1.08). |
| Schetelig et al. | Germany | Cross-sectional | 50                  | 66.9              | 6919                           | Yes Sex Age BMI Comorbidities | Blood group B was associated with a higher risk of severe respiratory infections (OR = 1.24; 95% CI: 1.01–1.53; p = 0.038) and hospitalizations (OR = 1.78; 95% CI: 1.18–2.68; p = 0.006) compared to blood group O. |
| Takagi et al. | 101 nations across the world | Cross-sectional | -                   | -                 | 6.8 billion                    | Yes Age Comorbidities Tobacco and alcohol use Life expectancy at birth Medical doctor/nursing/midwifery personnel density GDP/GNI per capita–PPP Annual PM2.5 concentration Daily ambient ultraviolet radiation | Blood group O (p = 0.022) were associated with lower mortality. |
| Pahdi et al. | 33 states and union territories in India | Cross-sectional | -                   | -                 | -                              | No | (i) Blood group B (p = 0.004) and O (p < 0.001) were associated with lower mortality. (ii) Blood group A (p = 0.001) was associated with higher mortality. |

**Abbreviations:** BMI, body mass index; COVID-19, coronavirus disease 2019; GDP, gross domestic product; GNI, gross national income; HR, hazard ratio; ICU, intensive care unit; OR, odds ratio; PPP, purchasing; RR, risk ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
assumed to be a result of this phenomenon. Moreover, it was reported that levels of angiotensin-converting enzyme (ACE), which is responsible for converting angiotensin I to angiotensin II, is lower in blood group O carriers. Angiotensin II could promote inflammatory responses and also induce high blood pressure. Therefore, low levels of ACE in group O patients infected with SARS-CoV-2 may be accompanied by presentation of milder symptoms.

8 | BLOOD GROUP DISTRIBUTIONS AND DYNAMIC OF COVID-19 PANDEMIC

To examine the relationship between dynamics of COVID-19 pandemic and distribution of blood groups, Liu et al. analysed a large data set from WHO and Johns Hopkins University, representing nearly 5.4 billion people across the world. They identified that infection case growth factor and death case growth factor per day were positively associated with proportion of individuals with blood group A. In order to assess other parameters related to the dynamic of the COVID-19 pandemic, countries were divided into two groups based on a known higher (≥30%) and lower (<30%) proportion of blood group A. At initiation of the exponential phase of the COVID-19 pandemic, there was no difference in infection cases between these two groups, while the number of infections and deaths 26 days after the beginning of the pandemic were significantly higher for countries with high proportions of individuals with blood group A. In addition, death cases doubling time per day was significantly shorter for higher blood group A countries (p < 0.05). While the impact of confounder variables was not considered in this study, it provided valuable results on association of blood groups and the dynamic of the COVID-19 pandemic.

9 | COVID-19 PANDEMIC AND AN ONGOING INCREASE IN THE RATE OF PUBLICATIONS

Since the initiation of COVID-19 pandemic, there has been a great deal of concern regarding rapid expansion of low-quality research and investigations. This is especially evident in literature attempting to identify a possible link between blood types and susceptibility to COVID-19 or risk of developing severe outcomes. The effect of cofounding variables such as age, sex, ethnicity, genetic variations, and underlying comorbidities are often neglected, meaning associations that have been discovered using this approach are somewhat questioned. In this regard, Delanghe et al. found a significant correlation between A allele and both COVID-19 prevalence and mortality in univariate analysis, but A allele lost its significance when genetic variants, including polymorphisms of ACE and complement component 3 (C3) were added to the multivariate regression model. This suggesting that the role of blood groups in COVID-19 appear to be secondary to other variables rather than independent.

Moreover, in the case of blood group comparison between infected and non-infected individuals, a great number of studies obtained the control population from blood donors that are typically recruited from people in group O due to their universal compatibility, therefore it may have resulted in overestimation of O carriers in control groups. Consequently, the results of such studies should be interpreted with great caution.

Taken together, if we assume that there is a real connection between blood groups and SARS-CoV-2 infection, then it might be helpful in risk stratification of a target population to prioritize vaccination programs for the most susceptible groups. It should also be taken into account that individuals with blood group A must strengthen protection for minimizing their exposure to the virus. However, this finding does not guarantee O blood carriers become fully protected, hence, they should still observe precaution to avoid increasing the risk of SARS-CoV-2 infection. Furthermore, biological differentiation as the basis for policy decisions need to be weighed against ethical and social implications in a real-world public health setting. On a larger scale, countries with higher proportions of individuals with blood group A could consider implementing restriction measures more actively and earlier, while if the proportion of people with blood type O is predominant, a less intensive and slower restriction strategy could be implemented due to the reduced dynamic of COVID-19.

10 | CONCLUSION

Although the association between blood groups and outcomes of COVID-19 is not certain, it is speculated that non-O blood group carriers with COVID-19 are at higher risk of developing severe outcomes. The interaction between blood groups and SARS-CoV-2 infection is hypothesized to be as result of natural antibodies against blood group antigens. Also, the severity of disease and disease complications may be influenced by secretor status and ABO antibody titer. Further preclinical and clinical studies are warranted to draw a precise conclusion on the association between blood groups and SARS-CoV-2 infection.

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