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Review Article

COVID-19 Severity and ABO Blood Types; Association and Molecular Mechanisms A short Review

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Abstract
Genetically inherited characteristics of blood group phenotypes, whose association with certain infectious diseases have been debated for long. Growing evidence suggests that ABO blood group may play a role in the immunopathogenesis of SARS-CoV-2 infection. The level of evidence supporting an association between ABO type and COVID-19 ranges from small observational studies, to genome-wide-association-analyses and country-level meta-regression analyses. We tried to find out the molecular relations of SARS-CoV-2 infection and ABO blood groups. We discussed inherited associations and possible molecular mechanisms that drive the relationship between blood type and COVID-19. Similar and non-similar comments and demonstrations from several studies are simply notified here.

Introduction

The occurrence of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is considered a total devastation that has overwhelmed health care systems. From the beginning of the pandemic, identification of characteristics that might influence risk of infection and poor disease outcomes have been of supreme interest[1]. Identifying reliable risk factors is critical to ensure that those at higher risk of infection can take additional precautions to prevent attaining the infection. Furthermore, understanding those who are at greatest risk for severe outcome or death may help clinicians better predict patient consequences, allowing for more targeted allocation of limited critical care resources during epidemic outpourings[2]. Rising evidence suggests that the ABO blood group may play a role in the immuno-pathogenesis of SARS-CoV-2 infection, with group O being protective and group A conferring risks of higher disease predisposition and severity[3,4]. ABO blood type is an inborn, non-modifiable trait. According to the presence or absence of antigens on erythrocyte surfaces, individuals can be A, B, AB, or O. Blood types may also be classified as positive or negative depending on the presence of the Rhesus (Rh) factor protein. Several studies have previously found associations between ABO blood types and viral respiratory infections such as influenza A (H1N1) and acute respiratory syndrome (SARS)[5-7]. Recently, more than a few studies have proposed relationships between blood types and susceptibility to COVID-19, its implication in the course of the disease, and consequences[8-10].

Methodology

An online literature search was conducted using the keywords “SARS-CoV-2,” “COVID-19,” “2019-nCoV,” “ABO blood types,” “blood group,” “Rh factor,” “COVID-19 and ABO blood groups” on Google Scholar, PubMed and Elsevier. The search was restricted to English-language articles that were published in 2020 and 2021.

ABO blood groups recapitulation

Landsteiner discovered this most important blood group system[11]. The progressive additions of carbohydrates to an oligosaccharide backbone resulted in formation of three antigens, including A, B, and H[12]. ABO blood type is determined by the ABO gene which is located on the 9th chromosome. It contains 7 exons and codes for enzyme glycosyltransferases, which in turn forms the antigens in blood type A and/or B[4]. The ABH antigens which in reality

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are oligosaccharides (H antigen defines the O blood type), are exposed on RBCs and other cells; they are also found in body secretions. The A and B antigens are determined by allelic genes encrypting glycosyltransferases that transfer monosaccharides to the non-reducing ends of specific glycans on glycoproteins and glycolipids. For A this monosaccharide is N-acetyl-D-galactosamine and for B this is D-galactose. In group O individuals, the corresponding A and B glycosyltransferases are either absent or have been disabled by one of various polymorphisms, such that the non-reducing ends of the corresponding glycans indicate the H antigen. Antibodies of this system (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, remarkably the gut microbiota[13].

Each RBC expresses approximately 2 million copies of its genetically encoded ABH blood group antigens on its surface, although the concentration varies by antigen type. From plasma, other blood cells (e.g. platelets and lymphocytes) also adsorb ABH-expressing glycosphingolipids, where they circulate attached to lipoproteins. In addition, ABH antigens are manufactured and expressed on endothelial cells and some epithelial cells. Thus, although some blood group antigens are only on RBCs, ABH antigens are in different cells, body fluids and secretions. Hence, they are more acceptably denoted as 'histo-blood group antigens' (HBGA), not exclusively as blood group antigens[10,13,14].

ABO blood groups as risk factor

For years, blood group antigens were referred just to compatibility testing for blood transfusions. However, clinical significance has extended with relevance in pathogenesis of micro-organisms and even providing the first line of defense against infectious agents over corresponding natural antibodies. ABO and Rh blood groups, are among factors that may offer susceptibility or resistance to viral invasion and also influence prediction of infectious diseases[15]. Understanding the relationship between diseases that have caused pandemics and blood groups could be a useful risk factor to aid estimation of outcomes and launch efficient measures in contending the disease spread with respect to blood group distributions[1]. Consequently, multiple investigations have been conducted to identify the possible affiliation between blood groups as genetic risk factors for various human diseases, particularly infectious diseases[15]. In the case of infectious diseases, it has been shown that individuals with blood group O are with higher risk of being infected with *Vibrio cholerae*, Norovirus, Hepatitis B virus and Dengue virus[16,17]. Additionally, the efficacy of infectious disease related vaccines may be influenced by the distribution of blood groups in the target population[18,19].

Possible molecular mechanisms

Spike protein is the key component for the mechanism of SARS-CoV-2 infection since it utilizes angiotensin-converting enzyme 2 (ACE2) as receptor for cell entry. Several host proteases could help the virus to enter the cells more competently[20]. Expression of ACE2 on various human cell surfaces gives SARS-CoV-2 the capability to infect multiple tissues[21]. Viral interaction with ACE2 for simplifying cell entry might be possible with other host molecules such as blood group antigens, which in turn affect the predisposition of different blood type carriers to getting infected by SARS-CoV-2. A recent in vitro study specified 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 described the potential role of A antigen expressing on epithelial cells over the progress of SARS-CoV-2 infection[22].

Several hypotheses explain the differences in SARS-CoV-2 infection by ABO type. For instance, anti-A and/or anti-B antibodies (e.g. present in group O individuals) might bind to corresponding antigens on the viral envelope and contribute to viral neutralization, thus preventing target cell infection. The hurdle for this virus is the epithelium of the respiratory tract and, possibly, the digestive tract. Hence, to prevent infection, circulating antibodies may need to reach these cell surfaces; while, apparently, the most effective antibodies for this drive 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[23].

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 predilection to cardiovascular complications. Severe outcomes could also be elucidated by higher levels of Von Willebrand factor (VWF) and factor VIII in group A individuals. Moreover, VWF is an acute phase reactant with infection inducing even higher levels in group A individuals[24,25].

COVID-19 severity and ABO blood types; Comments from different studies

One of the initial studies in Wuhan, China, reported that there was an association between blood type A and COVID-19, noting that females with blood type A were more susceptible to infection[26]. Further studies also described that blood type A patients had significantly higher odds of attaining SARS-CoV-2 infection compared with non-A blood types. More than a few studies have also stated that blood type O patients have significantly lower odds of infection, suggesting that blood type O may be a protective factor against infection[27,28]. In one multivariate analysis of 14,112 patients who tested positive for COVID-19 in the New York Presbyterian hospital system, investigators conveyed that blood type A, AB, and B had higher prevalence than blood type O after adjusting for race and ethnicity[29]. A retrospective study at the First Hospital of Changsha in Changsha, Hunan, China, likewise showed that blood type is a strong risk factor for COVID-19. Blood type O patients had reduced risk of infection compared with non-O blood group patients and blood type A patients had higher risk than all other groups[30].

Various reports concluded 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[31-33]. For example, in a French study by Gallian et al. that included 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)[34]. A previous systematic review and meta- analysis of seven studies confirmed 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)[27].

Ray et al. have enrolled 225, 556 cases of COVID-19 for the evaluation of relationship between blood groups and risk of severe disease or death. They reported that blood group O and Rh negative carriers signified lower risk of developing sever. 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[35].

Most studies acknowledged a higher proportion of group A, and a lower proportion of group O, among COVID-19 patients, as compared to healthy controls[36-38]. These studies involved patients with SARS-CoV-2 pneumonia ranging in severity from mild to critically ill requiring mechanical ventilation or intensive care unit admission[37,39]. 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%, $P < 0.001$); yet, group A patients had higher frequencies of underlying comorbidities[40]. Another retrospective study had comparable findings, but did not describe comorbidities[38]. Another study defined a higher rate of infection in group AB patients and a lower rate in group O patients[32]. On the contrary, 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[41]. One probable reason for these varying results is that many such studies did not account for various confounders (e.g. age), including co morbidities. Another likely 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 numerousness due to blood collectors who are selectively recruited group O donors. Significantly, volunteer blood donors are not necessarily representative of general populations; although convenient, their use as a control group is not optimum[42,43]. It has also been hypothesized that anti-A and anti-B antibodies could restrict 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 related 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 amplified presence of IgG anti-A, B in group O plasma[44]. Studies have also proved the relationship between the Rhesus blood group (e.g. Rh (D) type) and COVID-19. One study proposed that Rh (D)-positive individuals were more likely to test positive for SARS-CoV-2[41]. Another study stated significant associations between Rh (D) blood group status, group B, and SARS-CoV-2[30].

Conclusion

Further preclinical and clinical studies are necessary to draw a detailed conclusion on the association between blood groups and SARS-CoV-2 infection. Several studies recommend that blood type may be a risk factor for COVID-19 infection and outcome. Findings related to the highest risk of infection vary from researchers to

researchers. The majority of researchers account that the chief risk for susceptibility to COVID-19 infection is among individuals with blood type A, while some others report that individuals with blood type B are the most susceptible group to infection. Even though some researchers state that there is no relation between blood type and COVID-19 severity or mortality, blood types A and AB had higher risk of severe illness or death in maximum studies, while blood type O was protective against death or severe outcomes. The role of ABO blood group in SARS-CoV-2 infectivity and COVID-19 disease severity necessitates additional study; however, accumulating evidence suggests that, at biochemical and physiological levels, there might be an involvement of ABO blood type to disease biology. It also must be recognized that host factors already identified as contributory to COVID-19 severity, play a leading role, coupled with timely access to suitable medical care. By contrast, the role of ABO type is likely tributary and non-modifiable.

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