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Blood Groups as Biomarkers for Covid-19 in Pediatrics
Review Article

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ABSTRACT

ABO antigens types are polymorphic traits that are inherited through generations .Differences in the expression of ABO antigens types can decrease or increase host susceptibility and vulnerability to many infections. Growing evidences provide that ABO types occupy a role in the pathogenesis of COVID-19 immunity and vulnerability , with group O humans are less likely to acquire the disease and blood group A conferring a higher susceptibility of acquiring COVID-19 infection and severe disease course and outcomes. In this review, the relation between the blood group and COVID-19 and its mechanisms will be discussed . These mechanisms could include the symbiotic link between the expression of blood groups and the maturation of the gastrointestinal microbiota. In addition, the anti-A antibodies inhibit the adhesion of COVID-19 protein-expressing cells to ACE2-expressing cell lines. Furthermore, individuals with blood group O are less likely to be in a hypercoagulable state. Further mechanisms will be discussed.

Keywords
ABO; COVID-19; microbiota; pathogenesis; hypercoagulable;antibodies

Introduction

The rapid and global spread of the coronavirus SARSCoV-2 greatly affects the healthcare worldwide. It is causing COVID-19 to affect some humans more than others, with a considerable numbers of patients experiencing only mild clinical pictures and other patients being hospitalized and may require mechanical ventilations. Considering the prioritization and identification of patients most at risk is a critical challenge. The pathogenesis of Corona virus severity and the associated respiratory compromise aren't fully understood , however, the higher morbidity and deaths are linked to the older age and the male sex . In addition, patients with underlying comorbid associations are more susceptible to develop severe clinical picture of COVID-19, including diabetes mellitus , hypertension,and cardiovascular disease (1). Biological factors which identify susceptibility and severity of COVID-19 aren't yet completely addressed . Previous studies determined that the ABO blood group is an influential and a considerable risk for some diseases such as obesity which exists when the child's weight for the height is above the mean by 3 standard deviations of the WHO Child Standards for growth or BMI (Body Mass index) is higher than 97^{th} centile for age. (2, 3). The ABO blood type can also enhance the vulnerability of acquiring COVID-19 and its severity. Preliminary reports have suggested a link between the vulnerability to COVID-19 infection and ABO blood groups.(4-6). Importantly, persons with blood group O type were observed to be less vulnerable to SARS-CoV-2 infection. The anti-A antibody, found in persons with blood group O or B, seems to antagonize the link between COVID-19 and the receptors for angiotensin converting enzyme 2 (ACE2), that is expressed by target cells of the host .(7). Provided that COVID-19 also binds to ACE2,(8,9), it is logic to consider and address that blood group types may also be possible determinants of susceptibility to COVID-19 infection. Multi-organs affection of SARS-CoV-2 has been reported. (10) These are consistent data indicating that COVID-19 has a multisystem affection which can include renal(11) and liver manifestations. (12) ,(13).In a study done by Hoiland et al, 2020 , it was demonstrated that critically ill patients with COVID-19 having blood group type A or AB are linked with increased risks for requiring artificial ventilations, Continuous Renal Replacement Therapy(CRRT), and prolonged stay in the intensive care unit hospital length stay compared with patients having blood groups B or O. Further researches are mandatory to identify the biological pathways underpinning these findings.(14).In a study done by

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Kibler, et al , 2020, It was found that patients with blood group A were more likely to develop the disease and yield unfavorable outcomes.(15).In a study done by **Muñiz-Diaz , et al, 2021** , it was determined that there was an association between the susceptibility to acquire the COVID-19 infection and the ABO type . Individuals with blood type A had a greater risk of acquiring COVID-19 and individuals with group O blood type had a lower susceptibility. (16).In another study done by **Fan et al ,2020**, it was found that females whose blood group type is A are more vulnerable to COVID-19.(17) .In a study done by **Zhao,et al ,2020,** it was found that the severity, incidence, and the deaths linked to COVID-19 were more common in the non-blood group O. While individuals with blood group O were more protected against acquiring COVID-19 (18). In a study done by **Solmaz and Araç ,2020** , it was found that blood group O can be a protective factor , and blood group A may be a risk for greater possibility to acquire the disease, but this does not affect the prognosis and is not linked to the number of deaths .(19).

1.Role of anti-A antibodies :

It was found that anti-A antibodies (e.g. present in O and B groups) specially inhibit the adhesion of COVID-19 protein-expressing cells to ACE2-expressing cell lines , thus preventing entering cells of the host via the angiotensin-converting enzyme 2 (ACE2) receptor, that is expressed in human organs . The higher susceptibility of blood group A and the lower one of blood group type O for COVID-19 infection might be as a result of the natural anti-blood group antibodies, especially anti-A antibody, in the blood. (20)

2.Viral Neutralization

Anti-A and/or anti-B antibodies (e.g. in group O humans) can attach the corresponding antigens on the viral envelopes leading to neutralization of the virus, subsequently, preventing infection of the target cell. (21)

3.Sialic acid-containing receptors distribution

Virus infectivity can be mediated through the attachment of the transmembrane glycoproteins spike to protein receptors which are specific and present on the surface of host cells . The virion releases out the spike which is as a homotrimer . Separately, each monomer has two subunits which are named S1 and S2, that are linked to the cell recognition and the membrane fusion, respectively. S1unit contains two domains named S1A and S1B. It is suggested that binding to sialic acid-containing glycoproteins, such as CD147, occurs via the former and the latter binds the ACE2 receptor. Researches findings yield that the ABO system greatly modulates the vulnerability and prognosis of COVID-19 infection .For example, type-A humans are more likely to get infected and complicated from a severe disease course. It is hypothesized that the link between the ABO system and the COVID-19 risk might be possibly due to the modification of the distribution for sialic acid receptors on the surface of the host cells that is triggered by ABO antigens via the interactions related to carbohydrates, that could increase or decrease the binding of the Spike protein of viruses to the host cell. (22)

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4.Microbiota

It was found thatBlautia microbiota were lower in the individuals with blood group A in comparison with the non-A-individuals, (O and B) and higher amount in individuals with blood group O. Blautia is anaerobic a gram-positive bacteria present in the gastrointestinal tract . It yields an anti-inflammatory role(23)

The gastrointestinal microbiome can affect the prognosis in COVID-19 patients due to its links with both the immune system and the respiratory system . Receptors for Angiotensin Converting Enzyme 2 (ACE2) are excessively exposed on the epithelial surface of gastrointestinal system (23). COVID-19 can interfere with the nutrient absorption by binding to ACE2 receptors disrupting the intestinal homeostasis , a condition known as dysbiosis. Dysbiosis can lead to gut leakage leading to systemic inflammation. In addition, dysbiosis can disrupt the integrity of the gut barrier, that might accelerate the viral dissemination (24).

5. ABO blood types and the Furin

Furin is an enzyme belonging to proprotein convertases group . Furin is consumed in the cleavage related activation of the viruses. Furin is shown to be a determinant of endothelial pathogenicity of SARS-CoV-2 .(25)

It was found that there is a negative relationship between the level of Furin-related proprotein convertases and the blood type O. Thus , Furin -being low in blood type O humans- can lead to a remarkable reduction of pathogenicity and the viral load in those with blood group type O (26).

6.Von Willebrand factor

Although the carbohydrate structures of ABO blood group are considered to be RBCs antigens, they are present on other cell types, including platelets and the endothelium .(27) .Furthermore, covalently-associated ABO determinants are present on plasma glycoproteins, including factor VIII (FVIII) and von Willebrand factor (VWF).Essentially , the ABO carbohydrates on VWF have been found to affect biological activity of it . To our knowledge , the levels of plasma VWF are found to be less (20–30%) in blood group O individuals than non-O ones (28).Owing to the fact that in individuals with group O, VWF has a markedly low plasma half-life compared to non-O VWF (10·0 compared to 25·5 h), the levels of VWF are low in blood group O individuals. Since FVIII is circulating in a complex with VWF, FVIII:C levels are markedly decreased in individuals with blood group O. In addition, ABO blood determinants on circulating VWF are found to modulate the susceptibility to ADAMTS13 proteolysis. Specifically, VWF in individuals with group O is more rapidly cleaved via ADAMTS13 in comparison to the non-O VWF. In the view of these data , ABO effects on the platelet biology and VWF/FVIII obviously have an essential role in addressing the low thrombosis risk noticed in blood group O individuals. (29).

Based on the link between Covid-19 susceptibility and ABO blood group type , it is essential to mention that elevated levels of VWF:Ag and FVIII:C have been found markedly in Covid-19 sever infection (30) .Since VWF is synthesized abundantly within the endothelial cells, these data provide a support for the hypothesis that severe Covid-19 disease is linked to the significant endothelial cells activation. Importantly , the ACE-2 receptor that helps the entry of Covid-19 is expressed on endothelial cells. (31) .Furthermore, ABO antigens are present on the surfaces of the endothelial cells. Further studies are required to address the relative importance

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related to plasma VWF/FVIII values and endothelial cells activation in the etiology and pathology of coagulopathy related Covid 19. However, acute endothelial cells secretion of the ultra-large VWF pathological multimers have been observed in the microvascular cerebral occlusion in children with severe *Plasmodium falciparum*. Similar to Covid-19, patients with blood group O are potentially less susceptible to acquire cerebral malaria, the pathological important hallmark of which is the microvascular occlusion.. (32), (33), (34)

7.Diabetes Mellitus

DM increases the complications and mortality related to COVID-19 (35). Current evidences demonstrate that individuals with DM seem more likely to acquire severe infection than those patients without DM due to COVID-19 (35). It hypothesized that hyperglycemia enhances the entry of the virus into the cells as ACE2 and COVID-19 need glucose for their function (36).
It was found that individuals havingO+ve blood group are less vulnerable while individuals with AB+ve blood type are more susceptible to develop type 2 DM. Based on these considerations , the risk of acquiring COVID-19 could be less likely in individuals with blood group O . (37)

Haemoglobin A1c

In a study done by Merzon ,et al 2020, using pre-infection glycemic control data, It was identified that HbA1c is a clear predictor of COVID-19 severity. (38)

Applied Implications or outcomes from this review

Primary outcomes :

1.As regards humans with blood group A, they should receive stricter and stronger infection control measures . Regarding blood group A COVID-19 patients, they should be planned for close monitoring . Additional prospective studies should be applied to address the link between ABO groups and COVID-19 . Subsequently , the protective role of blood group O could be more investigated .(39)

2.As regards blood group O and B , while preserving ABO match compatibility, blood group B and O donors from convalescent patients with COVID-19 could be directed for therapy, and their titers of anti-A isoagglutinin should be tested. Convalescent plasma manufacturing should be taken into consideration among the first responses during a pandemic while vaccines and antivirals are under trials (40)

Secondary outcomes :

1. As regards HBA1C, pre-infection stratification of the risks is important to efficiently manage the disease, successfully allocate resources, and reduce the social and economic burden .(38)

2.As regards patients with DM , clinicians should concentrate on the close monitoring of patients with diabetes and COVID-19, to prevent diabetic emergencies as diabetic ketoacidosis and hyperosmolar hyperglycemic state.(41)

3. As regards Microbiota , there is an evidence that probiotics can decrease the incidence and severity of diseases, supposing their promise in treating or preventing of COVID-19 infection .(42)

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