

Examination of the Relationship between the ABO Blood Group and Susceptibility to SARS-CoV-2 Infection Risk

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Received: 16 Dec 2021; Accepted: 16 Jan 2022; Published: 20 Jan 2022

Citation: Chrysanthakopoulos NA. Examination of the Relationship between the ABO Blood Group and Susceptibility to SARS-CoV-2 Infection Risk. Insights Blood Disord. 2022; 1(1): 1-11.

ABSTRACT

The ABO blood group system has been linked with multiple infectious and non-infectious diseases and disorders such as, hepatitis B, dengue haemorrhagic fever, cancer, cardiovascular diseases, hematologic disorders, metabolic diseases, malaria, etc. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is the virus that causes COVID-19 (Coronavirus disease 2019), a respiratory infectious disease that has become a global pandemic. Several reports have investigated the role of ABO blood groups in susceptibility/resistance to various infectious Diseases, and have proposed that ABO blood group polymorphism may be linked with COVID-19 susceptibility and clinical outcomes, however, the results were questionable. It has been suggested that blood type O may have a protective role against COVID-19 infection, as blood group O individuals were found COVID-19 positive in lower levels. This could demonstrate that those individuals are less susceptible to infection, or are asymptomatic in higher proportions, or may be associated with a slightly lower risk for severe COVID-19 disease. It has been hypothesized that the mentioned association can be probably explained by the configuration of distribution of the sialic acid-containing receptors on host cell surfaces induced by ABO antigens through carbohydrate-carbohydrate interactions, that could maximize or minimize the SARS-CoV-2 virus spike protein (S) binding to the host cell. The classical viral entry through the ACE-2 receptors can be prevented by the anti-A antibodies that are produced from O and B blood group individuals. Experimental models based on cellular lines suggested a possible explanation for blood type configuration of infection showing that S protein/ACE-2-dependent adhesion to ACE 2-expressing cells was especially inhibited by natural or monoclonal human anti-A antibodies. Consequently, non-A blood groups individuals, mainly O, or B blood group, that produce anti-A antibodies, may have a lesser degree of susceptible to SARS-CoV-2 infection due to the inhibitory effects of anti-A antibodies. Therefore, it is possible that individuals with group A are more susceptible to SARS-CoV-2 infection and/or manifestation of a severe status.

Keywords

SARS-COV-2, ABO blood groups, COVID-19, Susceptibility.

Introduction

SARS-COV-2 virus is responsible for COVID-19 disease that has resulted in a global pandemic [1]. The SARS-COV2 virus has various consequences on the global population, mainly in older individuals with comorbidities such as cardiovascular disease, pulmonary diseases, diabetes mellitus, as those individuals are more susceptible to severe disease [2,3].

The significant morbidity and mortality of COVID-19 disease led the scientific interest to investigate possible elements that may render individuals more susceptible to COVID-19 disease and determining possible risk factors that are implicated in progression and severity of COVID-19 disease [4]. Many hypotheses based mainly on molecular level have been suggested for the varied susceptibility to COVID-19 disease and vulnerability to severe disease. One of those has been focused on the ACE-2 variable expression in the airway epithelia of the lung [5].

Risk factors are parameters related to an increased risk of infection or disease. Two types of risk factors have been determined, non-modifiable and modifiable [6]. Several risk factors for COVID-19 infection susceptibility and prognosis have been suggested, even though are still under investigation. Non-modified risk factors for COVID-19 infection are innate immune elements.

Current clinical research suggests that individual's age, gender and chronic disease are known risk factors in the susceptibility to COVID-19 disease [7]. Males and older individuals are more susceptible to infection and development of more severe disease [8,9]. However, no biological biomarkers have been revealed to predict the susceptibility to COVID-19 disease or that can interpret the variability in the disease course among different groups until now [10].

The human ABO blood group contains four blood types, A, B, AB, and O, is the most important blood group system in humans, and is localized on chromosome 9 (9q34.2). Blood group is an inherited, non-modifiable feature, and consequently a non-modifiable risk factor. The antigens present or absent on erythrocyte surfaces are responsible for A, B, AB, and O blood group individuals [11].

Landsteiner's ABO blood groups are carbohydrate epitopes, genetically inherited and are present on the surface of erythrocytes and other human cells. The antigenic determinatives of A, B and AB blood groups are trisaccharide components GalNAc α 1-3-(Fuc α 1,2)-Gal β - and Gal α 1-3-(Fuc α 1,2)-Gal β -, and of O blood group antigen is Fuc α 1,2-Gal β -. As mentioned blood groups are genetically inherited, however, various environmental factors can possibly influence which blood groups will be transported more frequently to the next generation. Previous researches have suggested an association between ABO blood groups and a wide spectrum of diseases, including cardiovascular disease, several types of cancer, and susceptibility to certain infections, such as SARS-CoV-2 [12-19].

Moreover, the host susceptibility to many infections/diseases can be increased or decreased by differences in expression of blood group antigen. Many blood group antigens assist intracellular uptake, signal transduction, or cell adhesion through the membrane micro domains organization and modify the innate immune response to infection [20].

The susceptibility to viral/bacterial infection has been found to be associated with ABO blood groups. Such viruses/bacteria that show a clear ABO blood group susceptibility are *Norovirus* [21], Hepatitis B [14,19,22], Influenza [23], *H. Pylori* [24], *P. Falciparum* [25], and *N. Gonorrhoeae* [26]. More specifically, it has been shown that the blood group O might significantly decrease the risk of Hepatitis B [27], Rotavirus gastroenteritis was significantly more dominant among individuals with blood group A and less dominant among those with blood group B [28]. It has also been observed that blood group A malaria patients had an increased risk of anemia than those with B, AB and O phenotypes

[29]. Among individuals infected with *Dengue virus*, was revealed that those with AB blood group were at an increased risk of developing dengue haemorrhagic fever compared to those with A, B or O blood groups [30]. Moreover, a meta-analysis suggested that individuals with blood group O appeared to be more susceptible to *Noro-virus* infection, whereas those with non-O blood groups might not influence susceptibility to this infection [31].

Given that SARS-CoV-2 is a completely new virus it remains not fully known whether the ABO blood groups influence the susceptibility to COVID-19 infection. However, previous reports have suggested an association between ABO blood groups and host susceptibility to infectious respiratory viruses, such as SARS-CoV [10,12,13,15,32-43], MERS-COV[44], AH1N1 [45], and influenza [46]. Nevertheless, other studies found no associations between ABO blood groups and susceptibility to COVID-19 infection [47-51]. However, there have been controversial outcomes due to possible confounder effects. To be more specific, it has been shown that non-O blood group individuals had a higher risk of being infected [12,13,52-57], whereas blood group O individuals were less possible to become infected with SARS-CoV-2 [15].

Previous cross-sectional and meta-analysis reports showed that SARS-CoV-2 positive individuals were more possible to have blood group A [35], or had a higher risk of being infected [42,57], or may have greater susceptibility to the disease [10,12,15,53,58,59], or a higher probability of SARS-CoV-2 infection [10,34,35], or a higher prevalence of infection amongst individuals with blood type A [37,43,60]. However, similar researches [39,48], failed to confirm this association. Zhao et al. [12], Padhi et al. [41] and Latz et al. [39], recorded a higher risk of COVID-19 infection with blood type AB, and Aljanobi et al. [61] and Abdollahi et al. [62] found that AB blood group individuals had a higher susceptibility to COVID-19 infection. In contrast, similar studies showed a lower risk associated with blood group AB [13,63].

A few reports recorded that blood group B was associated with a higher risk of SARS-CoV-2 infection [43,65], however other studies did not confirm such a finding [12,64]. Blood group O patients showed a decreased risk for acquiring COVID-19 infection compared to individuals with non-O blood group [12,13,36,37,42,55-57,59]. Moreover, similar researches recorded a lower prevalence of infection amongst blood type O individuals [35,39,40,43,65], or had lower susceptibility to COVID-19 infection [15,61,67], or had a decreased probability of COVID-19 infection [10]. Moreover, a protective role against SARS-CoV-2 infection among blood group O individuals has been also suggested [10,12,13,39,43,53,59]. The aim of the current review was to research the possible association between the ABO blood groups and susceptibility to SARS-CoV-2 infection.

ABO blood system as a non-modifiable risk factor of SARS-CoV-2 infection

The ABO blood group system is widely used in clinical practice, consisted of A and B antigens and their corresponding antibodies.

A and B antigens are coded by a gene localized on chromosome 9q34.1-34.2., it contains A, B and O alleles and four phenotypes, A, B, O, and AB have been identified [11]. Histo-blood group antigens (HBGAs) are complex carbohydrate molecules that consist of specific oligosaccharide sequences expressed on the surface of erythrocyte membranes, and are also highly expressed on a wide number of human cells and tissues, such as digestive and respiratory tracts epithelia, and on endothelial cells underlying blood vessels which also are able to compose ABH carbohydrate epitopes, vascular endothelia, platelets, and neurons [16,68].

It has been suggested that HBGAs regulate the spreading of pathogens through the action of natural antibodies and the proteins of the complement system. Differences in blood group antigen expression are able to enhance or reduce host susceptibility to various pathogen infections. ABO blood groups play a crucial role in infection by acting as receptors and/or co-receptors for viruses, bacteria, and parasites [17,22].

As already mentioned, many blood group antigens assist intracellular uptake, signal transduction, or cell adhesion through the membrane micro domains organization and modify the innate immune response to infection [20].

The possible role of ABO blood group in viral and bacterial infections, and the relation between ABO blood groups and infectious and non-infectious diseases has been widely investigated. Additionally, ABO blood group system has been used as a genetic marker in the human genome, obtained by a polymorphic glycosyl-transferase encoded by two prevalent active and a recessive inactive alleles [69].

Pathway responsible for the entry of the SARS-CoV-2 virus into the cell

SARS-CoV-2 belongs to the B beta coronavirus family and is responsible for the human severe acute respiratory syndrome [70]. It consists of two important viral proteins, the nucleocapsid and the spike (S) proteins. S proteins are large trans-membrane heavily N-glycosylated proteins that are responsible for the association with a cell surface receptor as the S protein mediates SARS-CoV-2 entry into the host cells [71,72].

The main host cell receptor of SARS-CoV-2 is Angiotensin II-converting enzyme 2 (ACE2) as it plays a critical role in the entry of the virus into the cell to cause the final infection [73-75]. The virus entry into the host cell through the ACE2 protein as mentioned, a multi-functional protein that represents the SARS-CoV binding domain. A complex signaling pathway is responsible for the entry of the virus into the cell as ACE2 binds to the S protein that protrudes from the viral envelope [76] and, after the subsequent ACE2-viral S protein complex cleavage by cathepsin L [77], the virus enters the cell by receptor-mediated process of endocytosis [78]. It has been recorded the similarity of SARS-CoV-2 mechanism of entry of virus into host cells, exploiting the structural similarity of SARS-CoV-1 and SARS-CoV-2, ACE1 and ACE2

receptors [79,80]. The ACE1 and the ACE2 a recently discovered homologue, are two antagonist enzymes of the RAS signaling pathway that act and offset each other [79,81]. The principal role of ACE1 is the conversion of angiotensin I to angiotensin II, a peptide that is responsible for inflammation, proliferation, fibrosis and constriction of blood vessels. An increased ACE2/ACE1 ratio provides protection against endothelial and vascular dysfunctions [82]. SARS-CoV-2 entry into the host cells requires the SARS-CoV receptor ACE2 and a specific trans-membrane serine protease 2 (TMPRSS2) for the S protein priming [79,80]. A moderate expression of ACE2 characterizes the upper respiratory tract and this should limit the virus receptiveness [83].

The host-virus fusion process is dominated by amino acids and the most crucial molecular step is the mobilization of the viral serine molecule, which is carried out by the host TMPRSS2 [84,85]. This hydrophilic amino acid is involved in SARS-CoV-2 pathogenesis and it has been suggested that the binding between virus and host's cell occurs through O-glycosylation [85]. The serine-rich repeat proteins (SRRPs) have emerged as an important group of cell surface adhesins found in a growing number of bacteria are involved in the adhesion of different bacteria [86] to host cell carbohydrates through O-glycosylation, have not yet been detected for the viral infections pathogenesis, however it is possible that such a mechanism might occur in SARS-CoV infections pathogenesis. It is certain that a more particular interaction between host and virus takes place. N- and O-glycosylation may occur in this complex pathogenic pathway and among multiple biological processes dominated by the pathogen's amino acid serine [87].

The proposed theory of a viral invasion, initiated by the mobilization of the serine molecule from the viral S protein and completed by the generation of a genetically undefined, hybrid A-like/Tn host-pathogen molecular bridge, does not question the ACE2 receptor protein determined functions [88,89].

The pathogenesis of a viral infection cannot be compared with the pathogenesis of a non-viral one, however it has been suggested that SARS-CoV-2 invades the human cell by producing an intermediate hybrid O-glycan. The virus uses the host cell's machinery in order to survive by exploiting the A-like/Tn formation after release of serine molecules as it is not possible outside its host [89].

ABO blood group system relation with infection of SARS-CoV-2

Age, gender [90] and ABO blood groups [42] are the only known demographic or clinical risk factors that affect the susceptibility to SARS-CoV-2 infection and the subsequent severity of COVID-19 disease. Especially, an increased host susceptibility connected with specific risk and predisposing factors in the host has been documented for various infectious diseases [15,17,22,32]. Additionally, the contribution of those risk factors is extremely high that it could cover any genetic effect on susceptibility to COVID-19 that would be more easily visible in the less severely infected patients. This could be the reason why one Genome-Wide

Association Study (GWAS) failed to disclose a point of association between COVID-19 disease and the ABO locus [91].

Previous and recent investigations have recorded an association of infectivity of various pathogenic microorganisms with specific blood groups [17], however it still remains unknown the exact mechanism that explains the association between ABO blood groups and viral infection [19]. It has been shown that genetic susceptibility to *Norovirus* is to a great degree dependent on the presence of HBGAs, specifically those corresponding to the ABO, secretor, and Lewis phenotypes [92]. Similarly, an HBGA genetic background has been found to be associated with *Rotavirus* susceptibility [93]. The clinical significance of HBGAs could be attributed to their expression on the surface of human erythrocytes and many human tissues [94].

Ellinghaus et al. [42] observed that the ABO blood group polymorphism was related with 2002-2003 SARS-CoV infection, however it has been questioned whether this increased susceptibility is also present for SARS-CoV-2 infection. The investigators in the mentioned genomic study recognized a 3p21.31 gene cluster as a genetic susceptibility locus in COVID-19 patients with respiratory failure and mentioned a possible involvement of the ABO blood group system.

Despite the fact the SARS-CoV-2 infection exact mechanism is still under investigation and the relation with ABO antigens is one of the hypotheses, it is apparent that a robust basis exists for such a hypothesis and needs further research. Several investigators have proposed possible molecular mechanisms underlying the specific ABO blood groups susceptibility to COVID-19 infection [95-98]. The mentioned molecular mechanisms can be, in general, divided into two essential groups, those influencing the SARS-CoV-2 infection and transmission risk, and those affecting COVID-19 disease severity. Although the suggested mechanism for such an association has been explained by the ACE2 receptor expression that may have an impact on susceptibility to COVID-19 infection, the overall relationship with ABO blood group seems to be impossible [10].

The exact mechanism of ABO blood group in COVID-19 infection has not been yet clarified, however some hypotheses have been proposed based on conclusions drawn by previous investigations. ABO blood group is a specific antigen type on erythrocyte membrane, but blood group antigens are expressed in airway and alveolar epithelial cells and in body fluids [99]. It has been supposed that through binding receptor-mediated affinity, genetic susceptibility of blood group glycoproteins can function, especially as an invasion mechanism. Cooling et al. [17] and Mackenzie et al. [100] demonstrated that blood group antigens were valid receptors for some infectious bacteria.

The beginning of SARS-CoV-2 infection is hypothesized to implicate the S protein attachment to ACE2 receptor [32,84]. However, it still remains unknown whether the ACE2 expression

level differs among individuals with different blood groups and whether individuals with blood type A have a higher ACE2 expression levels. Consequently, further investigations are needed to explore the exact mechanisms.

The difference in the suitability to COVID-19 infection could be explained by the differences in the ABO antigens. Dai [96] showed that SARS-COV-2 S protein imitates the blood group's antigen at a rate 80 %, in a previous virus that caused SARS in 2003.

Previous epidemiological studies have examined the relation between ABO phenotypes and COVID-19 infection risk, and only a few failed to reveal a significant association [48,91,101-103]. Moreover, the absence of an association between ABO blood groups and susceptibility to SARS-CoV-2 infection was also reported in another study [48], which suggested that ethnicity may have resulted in biased outcomes.

Silva-Filho et al. [104] proposed that the association between ABO blood group and susceptibility to COVID-19 infection and progression could be attributed to diverse distribution of sialic acid-containing receptors on host cells' surfaces. The mentioned distribution is regulated by ABO antigens through carbohydrate-carbohydrate interactions (CCIs), which could maximize or minimize the virus S protein binding ability to host cell's surface receptors. Viral entry is promoted by interaction of two subunits, S1 and S2. S1 specifically contributes to viral binding to host cell surface receptors through two domains, S1A corresponding to the N-terminal region, that interacts with sialic-acid containing glycoproteins and glycolipids, and S1B corresponding to the receptor-binding domain, which binds to ACE2 receptors. SARS-CoV-2 entry into a host cell is facilitated by ACE2 receptor, as mentioned [105].

ABH antigens are present on the erythrocyte membrane, platelets, lymphocytes, arterial and venular capillary endothelium [106]. Antigen A predominantly, and antigens B and AB, are responsible for carbohydrate accumulation, whereas antigen H that characterizes O blood group, is not involved in the induction of carbohydrate promotion. Additional carbohydrate accumulation promotes CCIs, maximizing the interaction, cell recognition, and aggregation. Increased inter-action raises the possibility of SARS-CoV-2 successfully binding to host cells through specific binding of S protein domains to ACE2 and CD147, a trans-membrane protein that may also promote the infectious process through viral anchoring to host cells [104].

ABO blood groups, SARS-CoV-2 infection susceptibility, and possible Mechanisms

The first statistical research examined the association between ABO blood groups and SARS-CoV-2 infection, suggested that blood group A individuals had a significantly increased risk of acquiring SARS-CoV-2 infection, whereas blood group O individuals had a significantly reduced risk compared to non-O blood groups [12]. Similar studies and meta-analyses researches confirmed the

decreased risk of acquiring SARS-CoV-2 infection for individuals with blood group O or recorded that they were protected against COVID-19 disease [10,12,13,39,62,64,107], or recorded an increased risk for non-O blood groups individuals, most often blood group A [35,36, 63,108-110]. Other reports revealed that blood group O individuals had decreased susceptibility to SARS-CoV-2 infection [15], whereas those with type A made them more vulnerable [12]. Gerard et al. [64] based on data published by Zhao et al. [12] from Wuhan, focused on the status of anti-A antibodies, found that individuals with blood type-B and O, were less probably to have COVID-19, or suggested that blood group O and B may be protective against COVID-19.

On the contrary, Zietz et al. [13] and Latz et al. [39] reported that group B individuals were more susceptible to be SARS-CoV-2 positive, and in a systematic review and meta-analysis Kabrah et al. [111] demonstrated that studies carried out in the United States, Saudi Arabia, Iraq, and China, blood group O individuals were at higher risk for COVID-19 disease, whereas other studies from France, Sweden, Turkey, and Cyprus recorded that blood group A individuals were at higher risk for COVID-19 disease. The same report showed that blood group AB individuals had lower risk of acquiring SARS-CoV-2 infection. This finding was confirmed by a study carried out in Bahrain [63].

The blood group AB synthesis permits the strongest contact with a pathogen and molecularly prevents any isoagglutinin activity, making AB blood group the least protected and the smallest among the ABO blood groups. On the contrary, individuals with blood group O, that are susceptible to other infections have survived all infectious diseases in an immunological balance with many pathogens and remain the largest blood group worldwide [112]. Those individuals rarely become infected by severe diseases classified as blood group A/ B-related infections. They maintain anti-A/Tn cross-reactive and anti-B complement-dependent is agglutinin activities, affected by the polyreactive, non-immune IgM, which is considered as the crucial point of innate immunity and the first line of defense. In this hypothetical pathogenesis model the contact between host and pathogen is initiated by formation of a *trans*-species, developmental A-like/Tn O-glycan, which plays a critical role in the evolution of species, in the human is replaced by ABO phenotypic epitopes and is controlled by its molecularly and functionally connected innate immunity [112].

SARS-CoV-2 binds to the carbohydrates that determine the ABO blood groups, which are considerably expressed in respiratory tract mucous membrane [88,113]. Consequently, AB blood group has the most contact and blood group O the least with the pathogen [88]. Moreover, it has been supposed that blood group A was considered to have more attachment molecules on the vascular wall by protecting P-selectin and intercellular cell adhesion molecule-1(ICAM-1) from cleavage which increases adhesion and inflammation and can cause more severe COVID-19 disease [96].

Arend [114] reported that blood group A individuals susceptibility to infections with *Plasmodium Falciparum*, that is responsible for

malaria tropica, is similar to SARS-CoV-2 infection, and given the fact that the ABO (H) phenotype development is molecularly associated with the humoral innate immunity development, it could be hypothesized that the viral and the non-viral pathogenesis could be induced through a hybrid, developmental classical A-like/Tn O-glycan. It has been proposed that SARS-CoV-2 infection is initiated a functional host-pathogen molecular bridge by constructing an intermediate and genetically undefined, serologically A-like/Tn structure, that must be differentiated from the blood group A-specific epitope. This is encoded by the ABO gene A-allele located on chromosome 9q34, which, together with the B-allele, defines the risk of acquiring life-threatening diseases in non-O blood groups individuals [114].

SARS-COV enters cells through the ACE2 receptors found in almost all cells of human organs [115]. The ability of natural antibodies to protect against certain viral infection could be related to the ability of anti-A and anti-B natural antibodies that are found in blood group O individuals to recognize A and B antigens on virus glycoproteins [32]. The absence of anti-A and anti-B natural antibodies in those individuals has been reported to restrict the SARS-COV-2 binding with ABO carbohydrates and ACE2 receptors [109].

A previous study by Guillon et al. [32] regarding SARSCoV-1 outbreak in Hongkong in 2003 recorded that blood group O(H) was associated with a low infection risk, whereas the interaction between S protein and host cell receptor was inhibited by natural and monoclonal anti-A anti bodies *in vitro*.

The SARS-CoV-2 S protein requires ACE-2 receptor to infect a cell, as already mentioned [32]. The interaction between S protein-ACE2 receptor is blocked in the presence of anti-A antibodies [32], which could be an explanation for the protective role of blood group O against COVID-19 infection and mortality. ABO antibodies contribute to the modifications of the interaction between the SARS-CoV-2 S protein and ACE-2 receptor according to previous experimental investigations. Guillon et al. [32] investigated whether ABO antibodies could stop the interaction between the SARS-CoV receptor and ACE2. The authors hypothesized that the virions S protein produced by individuals with A or B blood groups could be covered with A or B carbohydrates epitopes, respectively. Natural anti-A or anti-B antibodies from blood group O, A, and B could bind these epitopes on the viral particles S protein, and consequently adhesion of S protein and ACE2 receptor can be inhibited and prevent its interaction with the ACE2 protein receptors in the host cell membrane, thereby preventing infection.

The protection accorded by blood group O has been attributed to circulating anti-A antibodies [32,116] of the IgG type which could interfere with the virus-cell adhesion procedure [32]. Similarly, anti-B antibodies from group O is often IgG and more powerful against the virus in contrast to the anti-B antibodies from group A or B which are mostly IgM [64,117]. The same conclusions were obtained when the association of ABO blood group with susceptibility to COVID-19 was analyzed from the perspective of ABO antibodies instead of ABO blood group antigens.

As in transfusion [43], the dominant principles of this process could be that SARS-CoV-2 viruses produced in individuals with blood group A are able to express A antigens and infect individuals from blood groups A and AB without such antigen-antibody reactions. However, SARS-CoV-2 infection in individuals with B or O blood groups who have anti-A antibodies may provide some degree of protection. In a similar way, SARS-CoV-2 viruses that express B anti-gens are able to infect B or AB individuals. However, SARS-CoV-2 infection in individuals with blood group A or O having anti-B antibodies may be somehow restricted. Blood group O individuals would have helped the most by possessing defenses, anti-A and anti-B anti-bodies, against SARS-CoV-2 viruses expressing A or B antigens. This hypothesis was resulted from an experimental model in which Chinese hamster ovary cells were generated to express on cell surface S proteins transferring A glycan antigens [32]. The adhesion of those ovary cells to Vero E6 cells expressing ACE2 was especially inhibited by a mouse monoclonal anti-A antibody or human natural anti-A antibodies. The study assessed a substantial reduction in the infective ability of the virus because of ABO polymorphism.

Zhao et al. [12], observed that blood groups B and O individuals, and with anti-A antibodies in serum had significantly a lower rate in the COVID-19 group than those without anti-A antibodies regardless the blood group [64]. Moreover, after comparison of the hypothesized protective effect of anti-A antibodies from blood group O and from blood group B, it was recorded that O blood group individuals were under-represented, whereas those from blood group B, on the contrary, were over-represented, which means that anti-A antibodies from blood group O were more protective than anti-A antibodies from blood group B. This last finding was attributed to the fact that the predominant immunoglobulin isotype of anti-B/anti-A antibodies in the serum of blood groups A and B individuals was IgM isotype, whereas for those with blood group O was IgG, as previously mentioned [116]. It is apparent that the proper function of this defense mechanism against SARS-CoV-2 infection requires a strong immune system and adequate antibody production.

Blood group O individuals have a lower ACE level, whereas those with blood group A have a positive association with ACE efficiency [118]. ACE activates angiotensin and the lower level of this enzyme can decrease the risk of hypertension [119] which is a COVID-19 risk factor [120]. The mentioned mechanism has been suggested for developing more severe COVID-19 disease in blood group A individuals and less severe disease in blood group O ones [118]. ACE2 receptor can weaken inflammatory response and redox stress and also can offset the ACE effect [118, 21].

Blood group O individuals have higher interleukin-6 (IL-6) levels [12] than non-type O individuals [115]. IL-6 is a pro-inflammatory cytokine, produced by many different cells including macrophages, dendritic cells, T-and B-cells, endothelial cells, astrocytes, microglia, and neurons, and plays a crucial role in cell defense in the acute inflammation phase [122], especially

in moderating the inflammation reaction, consequently, the high level of IL-6 in individuals with O blood type could explain their lesser probabilities of developing severe COVID-19 disease and even death. However, previous researches recorded that IL-6 is associated with COVID-19 severity, as it can be ingredient of a cytokine storm [122-124]. IL-6 could play a dual role, a protective role with its implication in lung repair responses and aggravate its role in COVID-19 infection [125].

It should be noticed that the degree of protection against SARS-CoV-2 infection may depends on ABO anti-bodies titer, secretor status, and incidence of blood group O in the population [17, 126]. All of the mentioned mechanisms need to be investigated further.

Recent reports have proposed that host trans membrane protease serine subtype 2 (TMPRSS 2) may play a significant role in ABO blood group configuration of SARS-CoV-2 infection [80,87]. TMPRSS 2 protease is coded by a gene localized on chromosome 21q22.3 [127], and has been found to be substantial for S protein priming and sequent infection of SARS-CoV [80]. However, it has not been confirmed whether SARS-CoV and SARS-CoV-2 share similar genomic sequences for the TMPRSS 2 protease. Moreover, viral serine proteolysis by TMPRSS 2 protease may permit serine mobilization, a critical molecule of mucin O-glycan that has been found to be critical for SARS-CoV-2 infection [80].

Arend [87], in an effort to explain why blood group A individuals are at risk whereas blood group O individuals are protected from SARS-CoV-2 infection, suggested that A, B, and AB blood groups have up-regulated IgM activity, whereas O group has down-regulated IgM activity due to glycosylation. The A, B, and AB blood groups are thus favorable targets because they contain A/B phenotypic-determining enzymes that promote greater viral molecular contact, whereas O blood group does not contain these enzymes and only binds the virus through hybrid H-type antigen creation. Additionally, IgM down-regulation in the blood group O leads to downstream anti-A and anti-B is agglutinin activity, hallmarks of innate immune activity. The individual risk of SARS-CoV-2 infection cannot be predicted based on an individual's ABO blood group alone because various risk factors exist and also blood group O is no longer regarded a genetic entity [128-130]. Nevertheless, SARS- CoV-2 infection can be regarded as an evolutionary eclectic disease, conducting to the present global distribution with regard to human blood groups O, A, B, and AB, which according to Springer et al. [131] established over millions of years mainly in connection with ABO blood group-related life-threatening diseases, such as malaria [114,132-134].

It is apparent that the possible implication of ABO blood groups in the COVID-19 susceptibility and generally in its dynamics does not mean that ABO blood groups are monadic and determining factors influencing the COVID-19 epidemic. Other factors, such as population age, previous diseases, effectiveness of the health care system and socioeconomic status, also have serious impacts on this epidemic.

Moreover, the outcomes of the current research should be interpreted with great carefulness since some limitations exist, attributed to secondary limitations of the reports analyzed. The main drawback is the significant heterogeneity of those studies that depends on the study design, the methods of outcome estimation, and the possible differences in the study population. Another drawback is the effect of potential confounders such as gender, age, presence of vascular, cardiovascular, pulmonary diseases, and diabetes mellitus, that could not be eliminated, which may result in deviations in study conclusions because those factors may affect the vulnerability, susceptibility and the severity of COVID-19 disease. Finally, the current review was limited to English and Chinese language, which may have led to exclusion of reports in other languages that are appropriate, potentially leading to selection biases.

Conclusion

The data presented above indicated that in the majority of the articles analyzed, ABO blood groups affect the SARS-CoV-2 infection risk and several reports additionally indicated that blood group O, appears to have a protective role in comparison to non-O groups. It was also recorded that blood group O and B individuals had a lower risk of acquiring SARS-CoV-2 infection.

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