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Review

ABO phenotype and SARS-CoV-2 infection: Is there any correlation?

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A R T I C L E I N F O

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A B S T R A C T

COVID-19 is the currently evolving viral disease worldwide. It mainly targets the respiratory organs, tissues and causes illness. A plethora of studies has been performing to bring proper treatment and prevent people from the infection. Likewise, susceptibility to some infectious diseases has been associated with blood group phenotypes. The co-relationship of blood group with the occurrence of SARS-CoV-2 infection and death has been examined in numerous studies. This review explained the described studies regarding the correlation of blood group and the other essential factors with COVID-19.

1. Introduction

An outbreak of the report of respiratory distress and pneumonia with an indefinite origin in Wuhan city, Hubei a principal administrative division of China was first stated to the World Health Organisation (WHO) on 31 December 2019 (Hafeez et al., 2020; Wu et al., 2020). The Centers for Disease Control and Prevention (CDC) organized an investigation program and the cause of the illness was attributed to a novel virus, subsequently named the 2019 novel coronavirus in January 2020 (Cascella et al., 2020; Dawood et al., 2020). The WHO termed the new epidemic disease COVID-19, which stands for coronavirus disease 2019, and the associated virus is assigned as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in February 2020 (Guo et al., 2020). COVID-19 has been stated as a pandemic disease by the WHO in March 2020 (Hu et al., 2020; "Naming the coronavirus disease (COVID-19) and the virus that causes it,", 2021). Globally, over 40 million cases have been confirmed and one million deaths were reported to the WHO by October 2020 ("WHO Coronavirus Disease (COVID-19) Dashboard | WHO Coronavirus Disease (COVID-19) Dashboard,", 2021). Most individuals infected with SARS-CoV-2 will develop slight to moderate respirational sickness and improve without supplementary treatment. Elder individuals and persons' medical conditions such as cardiovascular diseases, diabetes mellitus, prolonged respiratory problems, and people with cancer are more susceptible to the illness. Signs like loss of taste or odor, nasal congestion, sore throat, conjunctivitis, headache, musculoskeletal pain, skin rashes and dizziness (Sheikhi et al., 2020). The most common indications of COVID-19 are dry cough, fatigue, fever, skin allergy and musculoskeletal pain (Ciotti and Minieri, 2020). Other symptoms that are fewer and may disturb very rarely to the patients include headache, conjunctivitis, nausea or vomiting, sore throat, diarrhea, chillness or giddiness ("Coronavirus disease (COVID-19),", 2021.; Larsen et al., 2020). The incubation period of the COVID-19 is projected to be amid 2 and 14 days. Several studies reported that the incubation period could be as long as 27 days (Chatterjee et al., 2020; "Coronavirus Incubation Period (COVID-19) - Worldometer,", 2021). Coronavirus are positive strand enveloped RNA contains the largest genome among all known RNA viruses, general size is 27 to 32 kb (Adnan et al., 2020). The structured viral genome contains a helical capsid shaped as a nucleocapsid protein (N) and additionally enclosed by an envelope (Astuti and Ysrafil, 2020). The envelope of the virus contains three major proteins: envelope protein (E), spike protein (S), and membrane protein (M) whereas E and M are playing its role in the virus assembly and viral entry will be taken care by S (Fig. 1) (Huang et al., 2020; Satarker and Nampoothiri, 2020a). Besides, certain coronaviruses also code hemagglutinin-esterase protein (HE) to form an envelope (Mousavizadeh and Ghasemi, 2020). In these structural proteins, spikes induce huge protrusions on the surface of the virus, giving coronavirus, a crown-like look, and hence the name corona means crown in Latin (Li, 2016).

The presence of ABO blood type antigens has been noticed in the red blood cells (RBCs) extracellular membrane. Furthermore, ABO antigens are also extremely expressed in the number of human cells and tissues,

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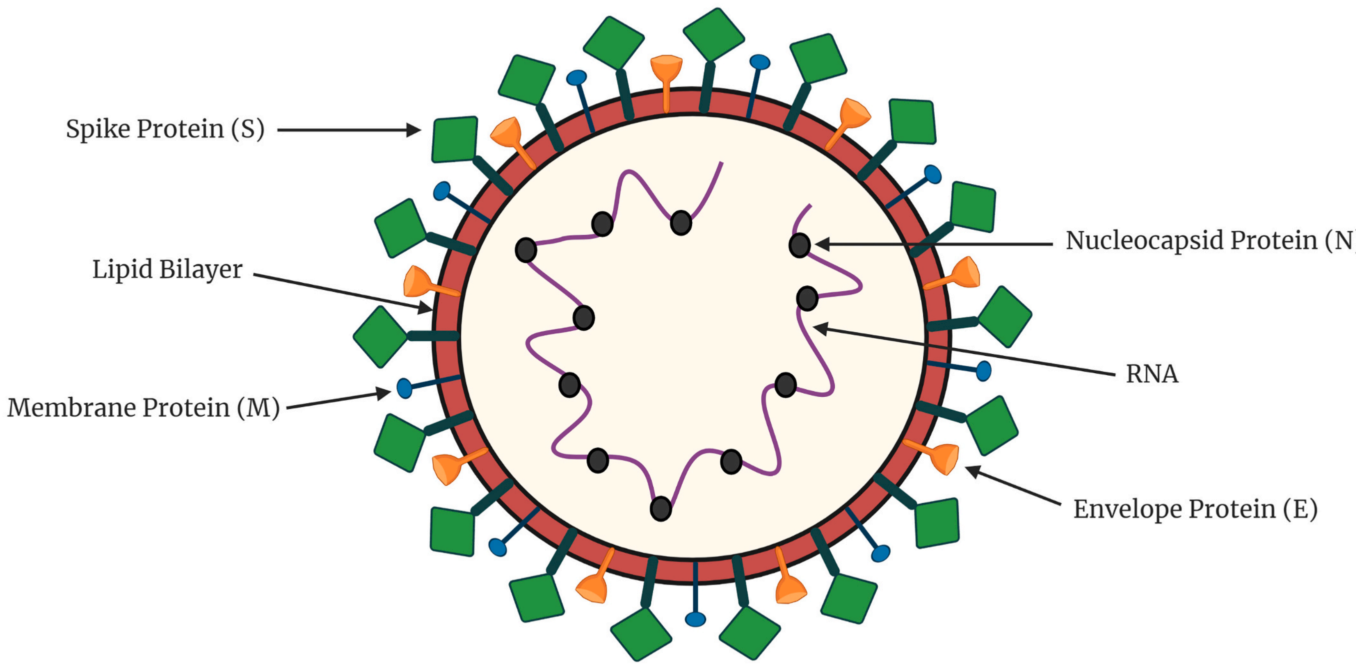

Fig. 1. Structure of Corona Virus.
Coronavirus is a positive-strand enveloped RNA that contains the largest genome among all known RNA viruses, general size is 27 to 32 kb. The viral genome of coronavirus contains a helical capsid shaped as a nucleocapsid protein (N) and additionally enclosed by an envelope. The envelope of the virus contains three major proteins: envelope protein (E), spike protein (S), and membrane protein (M) whereas E and M are playing their role in the virus assembly and viral entry will be taken care by S. The spikes induce huge protrusions on the surface of the virus, giving coronavirus, a crown-like look, and hence the name corona means crown in Latin.

Table 1
Different types of coronavirus and its target organ with examples.

S. No.	Types of coronavirus	Examples	Target Organ	Symptoms	References
1	Alphacoronavirus	Human coronavirus NL63	Respiratory system	Fever,Cough, Rhinorrhoea, Bronchiolitis	(Abdul-rasool and Fielding, 2010)
		Transmissible gastroenteritis coronavirus (TGEV)	Digestive system (small intestine)	Diarrhea, Vomiting, Dehydration	(Manuel et al., 2011)
		Porcine epidemic diarrhea virus (PEDV)	Gastro-Intestinal Tract	Acute diarrhea	(Jung et al., 2020)
		Porcine respiratory coronavirus (PRCV)	Respiratory system	Cold,Dyspnea,Tachypnea,Cough,Polypnea, Anorexia (Generally Asymptomatic)	(Brockmeier et al., 2008)
2	Betacoronavirus	(SARS-CoV)	Respiratory system	Fever, Myalgia, Malaise, Headache, Chills, Diarrhea, Dry cough, Shortness of breath,	(Gu and Korteweg, 2007)
		MERS-CoV	Respiratory system	Fever, Cough, Shortness of breath Chills, and Myalgia	(Ramadan and Shaib, 2019)
		Bat coronavirus HKU4	Unknown		(Yang et al., 2014)
		Mouse hepatitis coronavirus (MHV)	Mouse Brain, Intestine and Liver	Encephalomyelitis, Diarrhea, Hepatitis (Generally asymptomatic)	(Yokomori and Lai, 1992)
		Bovine coronavirus (BCoV)	Respiratory tracts and Intestines	Cough, Fever, Pneumonia, Rhinitis, Dyspnea, Diarrhea, Anorexia	(Saif, 2010)
		Human coronavirus OC43	Respiratory system	Fever, Cough, Upper respiratory tract infections	(Jean et al., 2013)
3	Gammacoronavirus	Avian infectious bronchitis coronavirus (IBV)	Respiratory tract, Kidney	Gasping, Sneezing, Tracheal rales, listlessness, profuse lacrimation, Nasal discharges, decreased egg production, wet droppings	(Bande et al., 2016)
4	Deltacoronavirus	Porcine delta coronavirus (PdCV)	GIT	Diarrhea, Gut lesion, Vomiting, Dehydration	(Boley et al., 2020)

The coronavirus can be categorized into 4 genera like alpha, beta, gamma, and delta coronavirus. In this, alpha and beta coronavirus affect mammalian species and mainly targets the respiratory and digestive system. Likewise, gammacoronavirus attack avian species and delta coronavirus target both species and mainly affects the kidney, respiratory, and gastrointestinal tract.

like epithelium, platelets, vascular endothelium and, neurons. Hence, the clinical importance of the ABO blood grouping drives beyond transfusion medicine, and some studies have indicated major participation in the progress of infections, cardiovascular diseases, and cancer (Liumbruno and Franchini, 2013). Since the detection of the ABO blood type, enormous concern regarding the possible roles of these blood types in infectious diseases. The ABO blood groups are common targets of epidemiological inquiries and they are genetically defined characters with identified polymorphic appearance among people (Cooling, 2015). This review reveals comprehensive research of the uncertainty concerning about the relationship between COVID-19 and ABO blood group including the scientific studies and the related hypothesis.

Fig. 2. Structure of SARS-CoV-2 chimeric receptor-binding domain complexed with its receptor human ACE2.
The human ACE2 is shown in sea green color. The SARS-CoV-2 chimeric receptor-binding domain is shown in brown color. Green and blue color indicate carbohydrate molecules.

2. Classes of coronavirus and its action on the host system

SARS-CoV-2 in the order Nidovirales belong to the family *Coronaviridae*. The coronavirus can be categorized into 4 genera like alpha, beta, gamma, and delta coronavirus. In this, alpha and beta coronavirus affect mammalian species. Likewise, gammacoronavirus attack avian species, and delta coronavirus target both species and cause the disease (Table 1) (Li, 2016; Unhale et al., 2020).

3. Molecular mechanism involved in the SARS-CoV-2 and ABO blood group

3.1. SARS-CoV-2 entry into the host cell

Usually, a coronavirus spike includes 3 segments that follows a large ectodomain, a single transmembrane anchor, and a short intracellular tail. The ectodomain involves mainly two subunits like receptor-binding subunit (S1) and membrane-fusion subunit (S2) (Walls et al., 2020). During virus entry into the host cell, S1 gets attach to the host cell surface receptor, and S2 fuses the membranes of the host cell and facilitating viral genomes to go into the host cells. Zinc peptidase angiotensin-converting enzyme 2 (ACE2) receptor gets recognized by the alphacoronavirus like HCoV-NL63 and the betacoronavirus (SARS-CoV) (Li, 2016; Satarker and Nampoothiri, 2020b). The novel coronavirus infects the host cell via receptor binding of virus spike glycoprotein to specifically protein receptors, particularly human membrane receptor ACE2 (PDB: 6VW1) (Fig. 2) and other transmembrane proteins, CD147 and TMPRESS2 on the host cell surface (Lan et al., 2020; Ulrich and Pillat, 2020). Spike is a homotrimer that arises from the virion, each of which comprises two subunits named S1 and S2, of which S1 is subdivided into S1A domain or N-terminal domain (NTD) and S1B domain or Receptor Binding Domain (RBD) (Walls et al., 2020). Angiotensin-converting enzyme 2 (ACE2) receptor is spread across the surface of a broad range of cell types associated with the central nervous system, upper airways and lungs, kidney, liver, heart, pancreas, and endothelial regions (Gheblawi et al., 2020). CD147 (also known as EMMPRIN) is found to serve as a co-receptor for the new coronavirus binding to host cells (Wang et al., 2020). Transmembrane Protease Serine Type 2 (TMPRSS2) has been described to facilitate cleavage of spike protein at two separate sites to cause SARS-CoV-1 and SARS-CoV-2 invasions (Fig. 3) (Glowacka et al., 2011).

3.2. Role of natural anti-A antibodies against SARS-CoV-2 infection

The SARS-CoV-2 attack the individuals with blood groups A, B, AB, and O possess anti-B, anti-A, none and anti-A or anti-B antibodies respectively. Therefore, these antibodies can respond to the respective antigens and inhibit, at least moderately, and seems to be only related to the early viral attack. For instance, SARS-CoV-2 viruses attacked group A people who may express A antigens and infect group A or AB individuals without such antigen-antibody reactions. However, infection in group B or O that possess anti-A antibodies slightly inhibits the entry of the virus into the host cell (Yamamoto et al., 2020). Enclosed viruses show ABO antigens on the virus surface and isoagglutinin act as neutralizing antibodies. Under this model of transmission from group O individuals and between individuals of the same group will always be maximal. High-titer isoagglutinin can avoid the transmission, while low-titer isoagglutinin could lead to minor disease preventions (Focosi, 2020). Anti-A, Anti-B and Anti-AB antibodies of the IgA class may be primarily responsible for the inhibition of SARS-CoV-2 infection, although natural antibodies of other classes like IgM and IgG may also function as a preventing agent. Also, restricting viral attachment to its receptor can be blocked by natural antibodies that lead to complement-mediated neutralization. Moreover, natural antibodies can also contribute to help the generation of cytotoxic-T cells against the pathogen (Yamamoto, 2020).

Adhesion cellular model was used to study the role of ABO blood group antibodies in inhibiting the interaction between viral spike protein and ACE2 receptor on the surface of the host cell. To co-express, the spike protein ectodomain and antigen-A at the cell surface, a C-terminally EGFP-tagged S protein were expressed in Chinese hamster ovary cells co-transfected with α-1,2-fucosyltransferase and A-transferase. It has been observed that the natural anti-A antibodies significantly inhibited the adhesion of S-protein to an ACE2 expressing cell line, revealed that these natural antibodies may prevent the attachment between the viral S protein and ACE2 receptor. Therefore, it was found to be inhibiting the virus from entry into the host cell (Fig. 4) (Guillon et al., 2008).

3.3. Role of ABO antigens in SARS-CoV-2 infection

The spike protein of SARS-CoV-2 binds to the ACE2 receptor for the host cell entry and the serine protease TMPRSS2 for spike protein priming. The coronavirus spike protein is comprised of two protein subunits like S1 and S2, which together carry N-linked as well as O-linked glycosylation sites. Studies revealed that the structure of glycan epitopes on ACE2 involved with viral binding and they have considered the terminal sialic acid linkages and glycosylation in the ACE2 receptor.

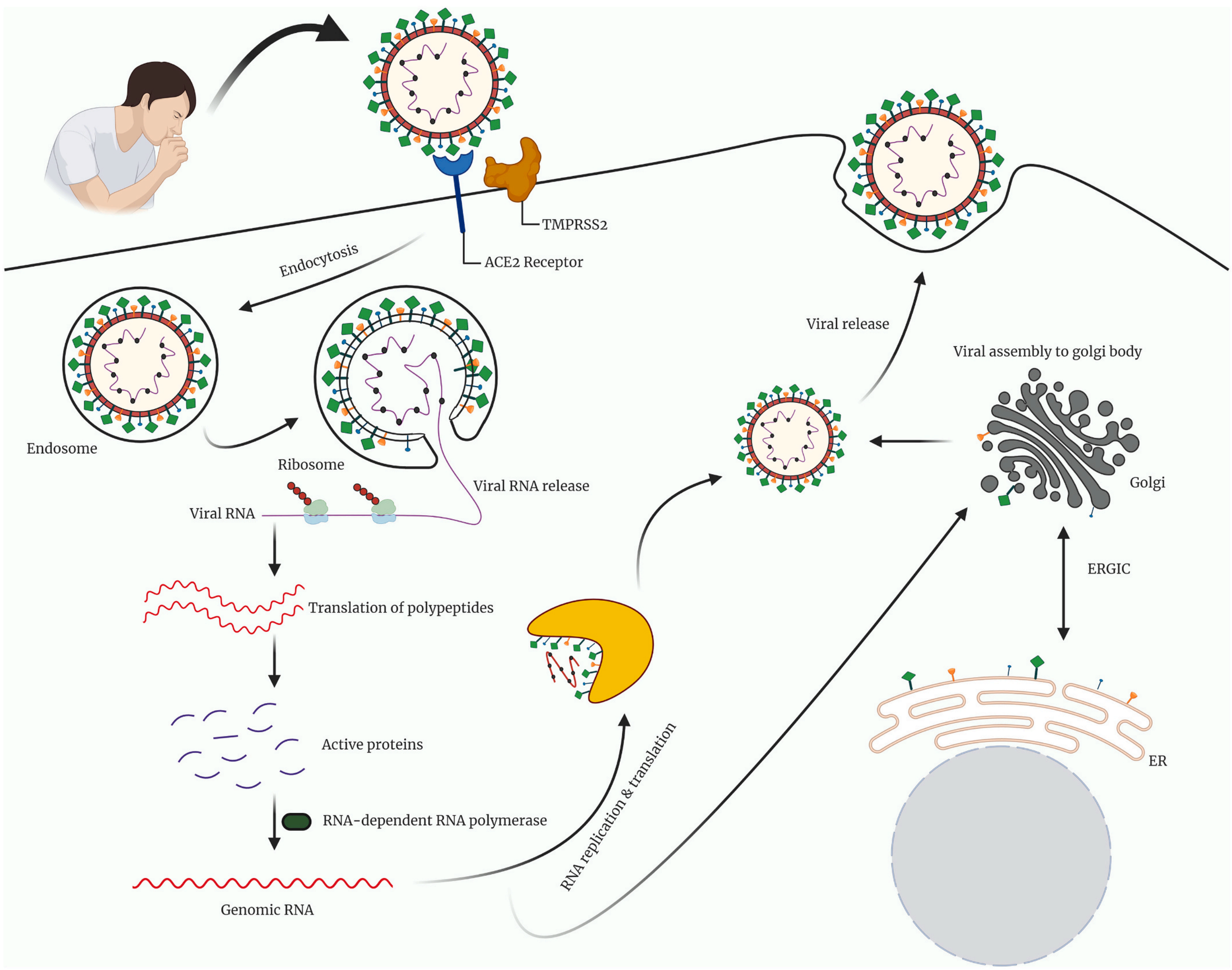

Fig. 3. Entry and life cycle of COVID-19.
The novel coronavirus infects the host cell via receptor binding of virus spike glycoprotein to a specific protein receptor, ACE2, facilitated by other transmembrane protein, TMPRESS2 on the host cell surface. Following entry by endocytosis, the viral genome in the form of single-stranded RNA is released from the uncoated virus, and then replicated and translated into active viral proteins by the host cell machinery. Then the viral components are assembled into a new virion in the golgi and release via vesicular exocytosis.

In this case, natural or monoclonal anti-histo-blood group antibodies could bind to spike glycans and prevents its interaction to host cell glycoprotein receptors (Shajahan et al., 2020). Another research work elucidated the relationship between the ABO blood system and SARS-CoV-2 infection and hypothesizes that the variation of sialic acid receptors on host cell surface induced by ABO antigens through carbohydrate-carbohydrate interactions (CCIs), which could trigger the virus spike protein attachment to the host cell receptor. Antigens associated with A, B, AB, and O blood cell phenotypes can modify the sialic acid-containing receptors in the host cell plasma membrane. Mostly antigen A, sometimes antigen B, and AB to a minor extent can trigger the establishment of sialoside clusters in target cells by cis CCIs. These CCIs could exploit the virus spike protein binding of the NTD and RBD domains to CD147 and ACE2 receptor (Silva-filho et al., 2020).

3.4. Role of VWF and factor VIII in COVID-19 risk

Blood clotting factor VIII (FVIII) and von Willebrand factor (VWF) are the major determinant of plasma levels in ABO histo-blood group. TheVWF is an essential glycoprotein playing important role in platelet adhesion, aggregation, and formation of fibrin by acting as an FVIII carrier and stabilizer. VWFs get synthesized in vascular endothelial cells and released into the plasma region. Likewise, around 10% are synthesized by bone marrow megakaryocytes and deposited primarily in the alpha granules of circulating platelets (Peyvandi et al., 2011). Liver sinusoidal cells and endothelial cells synthesize the clotting factor VIII throughout the body. The risk level of thrombosis and pulmonary embolism was higher with increased levels of coagulation factor VIII (Orlova et al., 2013). Compared to the non-O blood group, O blood group people have a significantly lower range of FVIII and VWF indicated that lower risk of thromboembolism (Donnell and Laffan, 2001). Factor VIII is stable only when bound with VWF. Therefore, the condition associated with venous thromboembolism was lower once theVWF followed by FVIII gets decreased (Federici, 2003). The severity of COVID-19 has been stated with a higher level of plasma von Willebrand factor antigen (VWF: Ag) and factor VIII procoagulant (F VIII: C) and associated with the endothelial activation (Escher et al., 2020). This endothelial activation stimulates the ACE2 receptor expression on endothelial cells. Hence, VWF serves as a potential marker to predict the endothelial activation expressing ACE2 receptor and multi-organ

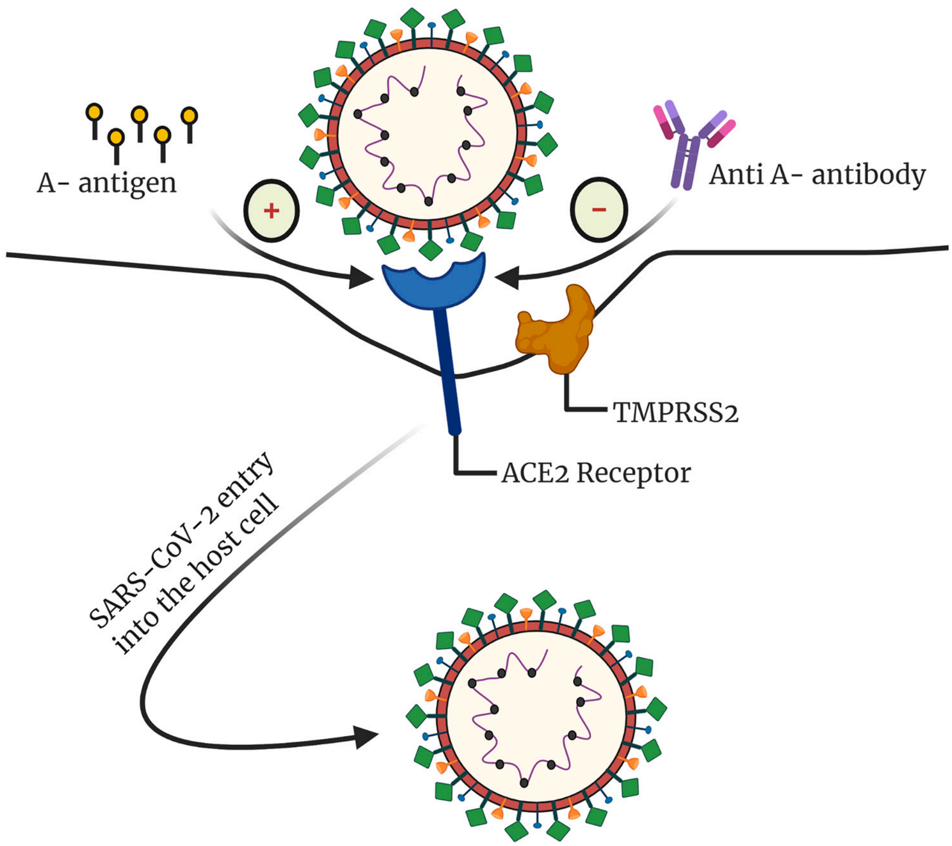

Fig. 4. Role of A- antigen & Anti-A antibody in SARS-CoV-2 infection.
During the virus entry into the host cell, the A-antigen may trigger the binding of viral spike protein to ACE2 host cell receptor through cis carbohydrate-carbohydrate interaction. In contrast, anti-A antibodies inhibit the interaction between viral spike protein and host cell ACE2 receptor via complement-mediated neutralization.

failure. This hypothesis supports FVIII and VWF in ABO(H) determinants also shows the association of COVID-19 vulnerability to the ABO blood group (Sullivan et al., 2020). Plasma VWF concentrations are related to clinical outcomes in acute lung injury and acute respiratory distress syndrome. COVID-19 may occasionally dispose of fatal venous arterial thromboembolism due to excessive inflammation, hypoxia, immobilization, and intravascular coagulation. Recently, the impact of clotting factor gained major attention in respiratory disorders rather than viral pneumonia. High incidence of thrombotic difficulties including pulmonary embolism has been detected in critically ill ICU patients (30% with COVID-19 against 1.3% without COVID-19). Blood flow is obstructed in the lungs producing trouble in breathing, and viruses including HIV, dengue, Ebola are susceptible to cause blood cell clumping. This pro-clotting activity seems to be more noticeable in patients diseased with SARS-CoV-2 (Fig. 5) (Yamamoto, 2020).

4. Scientific reports linked with the blood grouping and COVID-19 patients

In the meantime, the current attention of the ABO blood group is increased related to the infectious diseases. Differences in blood groups can alter the host's susceptibility to many diseases. Blood groups acting as a receptor or transporter for micro-organisms and supports for its entry into the host cell (Cooling, 2015). Numerous studies revealed the role of ABO alleles susceptibility to different types of pathogens. A cross-sectional case-control study was performed to explore the association between blood group and rotavirus gastroenteritis. The results suggested that blood group A was encountered more in gastroenteritis cases (43.3%) than blood group O (26.8%), signifying that blood group A may be a host-susceptibility factor for the rotavirus gastroenteritis (Elnady et al., 2017). The relationship between ABO blood group and hepatitis B virus (HBV) infection was determined by meta-analysis and results advised that blood group B was linked with a lesser risk of HBV infection and blood group O showed higher incidence in prevalent zones (Jing et al., 2020). The statistical examination was directed to study the association of blood group and chikungunya virus (CHIKV). It was observed that Rh+ individuals of the A and AB blood group infected more compared to Rh- counterparts. (Kumar et al., 2010).

The correlation between blood groups and the occurrence of COVID-19 has been examined in numerous studies. A retrospective study on COVID-19 disease was based on data from 105 countries and analyzed to assess the correlations between the ABO blood group and COVID-19. Results showed that people in the blood group A are at an increased risk of SARS-CoV-2 virus infection and COVID-19 disease severity. Blood groups B and O were less likely to be infected and the severity of infection progressed less severely (Alkout and Alkout, 2020). In China, 3 hospitals conducted another study to compare the impact of ABO blood group with 2173 covid-19 patients with healthy individuals in the respective areas. Results showed that A blood group association risk was higher in the development of COVID-19 compared to non-A blood groups, whereas blood group O was related with a lower risk compared to non-O blood groups (Zhao et al., 2020). A meta-analysis approach was used to predict the connection between ABO blood groups and the mortality condition of COVID-19 infection. This meta-analysis found that people with blood type A are at advanced risk with COVID-19, however, those with blood type O are at lesser risk (Pourali et al., 2020). A hospital-based case-control study was performed to assess the influence of the ABO blood group in COVID-19 susceptibility. This case-control includes a total of 105 COVID-19 cases with 103 normal controls. The study evaluated the link between the diseased cases with a

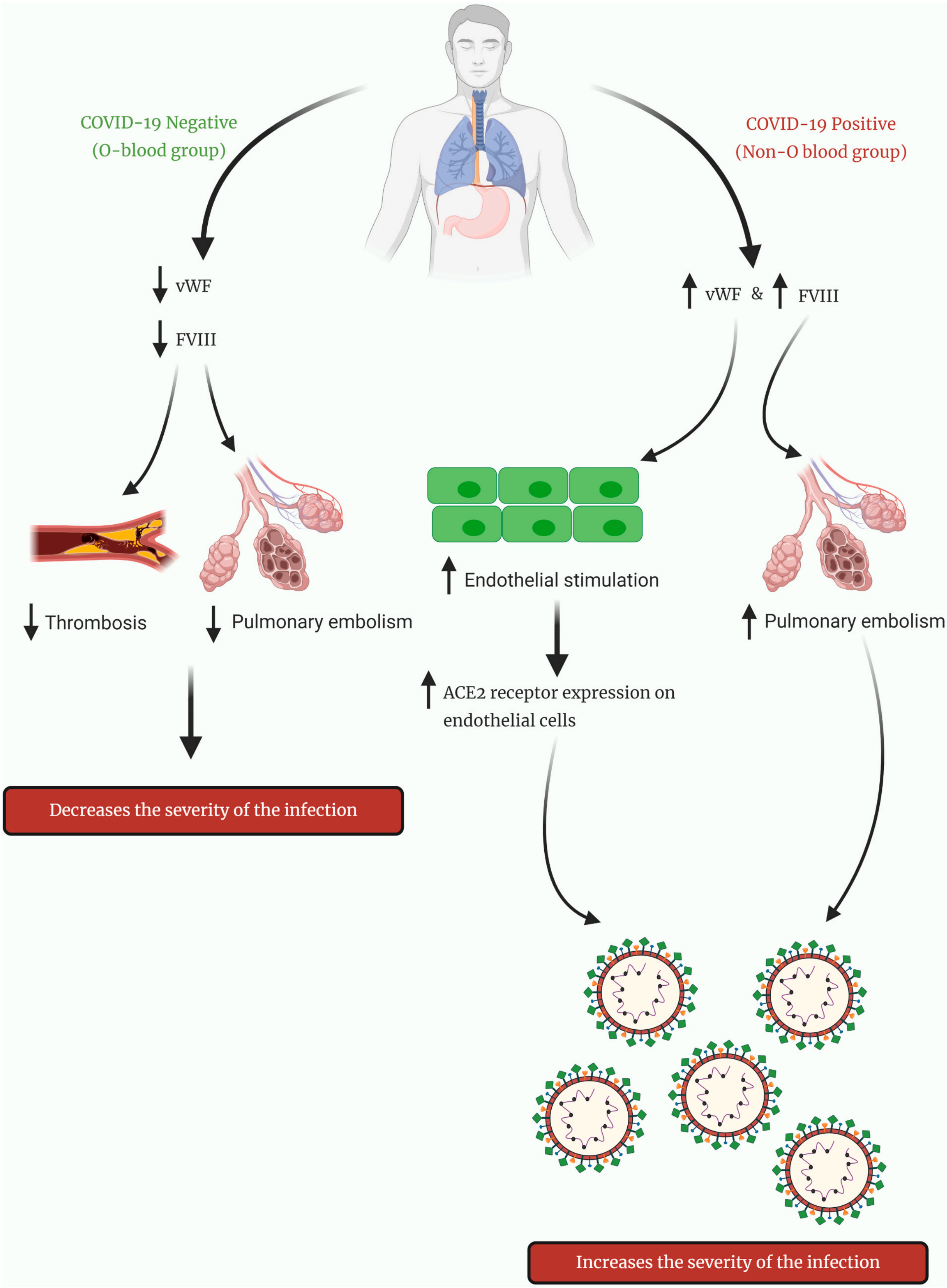

Fig. 5. Impact of vWF and FVIII in COVID-19.
The severity of COVID-19 has been stated with a higher level of plasma von Willebrand factor antigen (VWF: Ag) and factor VIII procoagulant (F VIII: C) and associated with the endothelial activation. This endothelial activation stimulates the ACE2 receptor expression on endothelial cells. Hence, VWF serves as a potential marker to predict the endothelial activation expressing ACE2 receptor and multi-organ failure. Compared to the non-O blood group, O blood group people have a significantly lower range of FVIII and VWF indicated a lower risk of thromboembolism.

control group by gender. By considering lymphopenia as a feature of COVID-19, the association between the ABO blood group and the lymphocyte count was measured in case samples. These findings deliver the epidemiological proof that females with blood type A are vulnerable to COVID-19 infection (Fan et al., 2020). A logistic regression analysis was used to clarify the hereditary relationship of ABO blood groups with the incidence of COVID-19 infection. ABO blood group was identified in 300 COVID-19 patients includes 159 under therapy, 104 recovered, 37 deceased, and 595 healthy blood donors. These findings revealed that group AB might be a biomarker for COVID-19, and group A may be connected with an augmented risk of death (Adhiah et al., 2020). An observational healthcare data were obtained from 14,112 individuals screened for SARS-CoV-2 for identified blood type to determine the correlation between ABO and Rh blood types with infection, intubation, and death. Infection prevalence among non-O groups was found to be marginally increased. The risk of intubation decreased for A and increased for B and AB relative to type O, whereas the chance of death increased for type AB and decreased for type A and type B. Rh-negative blood types have been estimated to have a protective effect for all three outcomes (Zietz et al., 2020). The correlation between ABO histo-blood group phenotypes and COVID-19 was examined in 397 confirmed cases of COVID-19 and 500 normal controls. This case-control study showed that ABO histo-blood phenotypes are associated with patients' vulnerability to infection. A rate of infection was higher among patients with the AB histo-blood group, whereas patients with the O histo-blood group had a lesser rate of infection. The Rh blood group phenotype was not statistically important in the determination of the patients susceptibility to COVID-19 (Abdollahi et al., 2020). From the above mentioned studies, it is advised that individuals with type A blood may be more sensitive to the follow-up of safety measures.

There are several studies also reporting no correlation between ABO blood group and COVID-19. A descriptive study was conducted to assess the relationship between blood groups and COVID-19 patients using data from 256 patients with COVID-19 patients. The mean age of the patients was 37, and the number of patients in need of intensive care was minimal. There was no distinction in symptoms, based on the blood type. (Cakir, 2020). A multi-institutional study was conducted across five hospitals, from March 6 to April 16, 2020, and included about 1289 patients tested positive for covid-19. Hospitalization, intubation, and mortality were assessed for determining the correlation of COVID-19 outcome with ABO blood type. From the 1289 COVID-19 patients, 440 (34.2%) were blood group A, 201 (15.6%) were blood group B, 61 (4.7%) were blood group AB, and 587 (45.5%) were O blood group. In this retrospective review, no association was noted between ABO blood group type with the risk of intubation or severity or death of covid-19 patients. B and AB blood type, as well as Rh + status, were related to higher probabilities gets infected and blood type O was connected with a lesser risk of testing positive (Latz et al., 2020). A hospital-based, retrospective study was intended to examine ABO, Kell, and Rh blood group phenotypes and their vulnerability to SARS-CoV-2 infection. Around, 132 established positive cases of COVID-19 were included in the study. In this research, it has been found that individuals with blood type A are more vulnerable to COVID-19 than to non-A types. Also, there was no noteworthy connection between the AB, B, and O blood groups with COVID-19 susceptibility. There was no interaction between Rh(D) antigen and the spread of SARS-CoV-2. Kell negative also appears to be extra vulnerable to SARS-CoV-2 infection (Bhandari et al., 2020).

5. Conclusion

From the scientific studies regarding the relation of COVID-19 risk to ABO blood group, it was observed that individuals with blood group O are fewer in SARS-CoV-2 infection related to non-O blood group individuals. The mechanism of protection conferred by blood group O is not known but several reports hypothesize that it may be mediated by natural anti-A antibodies (and less clearly anti-B-antibodies) or by the influence of plasma glycoproteins (FVIII and VWF). It was also observed that blood group A is related to increased odds of SARS-CoV-2 infection and with a greater risk of severe disease, which may be due to the role of A-antigen (less clearly B-antigen) in triggering the binding of viral spike protein with ACE2 host cell receptor. Further evidence is needed to affirm the correlation of SARS-CoV-2 infection vulnerability with the ABO blood group and with the epidemiological evidence of protection associated with blood group O against COVID-19.

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Author contributions

AM performed the literature review and contributed to the conceptualization of the review article. AM provided the concept for the diagrams and VB developed the figures. KSRP, AK and CKS reviewed and edited the final manuscript. All authors approved the final draft of the manuscript.

Declaration of Competing Interest

None.

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