

# ABO blood grouping and COVID 19: Is there any correlation in susceptibility?

## INTRODUCTION

Currently, the Coronavirus emerging from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (COVID 19) virus in Wuhan, Hubei Province, China has been declared as a pandemic disease by World Health Organization and is spreading widely across the globe like wildfire. This began in Wuhan wet-market, China that deals with animal trade business of different kinds of horse bats, poultry, snakes, marmots. Recent reports have highlighted the role of zoonotic links, cross-species jumping and spillover conjuncture between animals and human transmission, before acquiring direct human-to-human contact.<sup>[1,2]</sup> Also known as (SARS-CoV-2, SARS2, 2019-nCoV), it is a newly emerging zoonotic agent that causes severe respiratory illness leading to pneumonia, multiorgan failure and cardiac arrest.<sup>[3,4]</sup>

ABO blood grouping, discovered in 1900 by Austin immunologist Karl Landsteiner to explain the phenomena of red blood cell (RBC) agglutination, is well-documented hypothesis. A recent study has documented the relationship between the ABO Blood Group and the COVID-19 susceptibility concluding that blood Group O individuals are at low risk and blood Group A are at high risk to COVID-19 infection.<sup>[5]</sup> This review uncovers the detailed mystery on the correlation of the ABO blood group and COVID 19, including the structure of coronavirus, pathogenesis and current scenario on preventive approaches.

## CORONAVIRUS AND ITS STRUCTURE

Is a spherical-shaped, enveloped, single-stranded RNA virus with helical symmetry belonging to the family that comes under the order “Nidovirales” (group of viruses that utilize a nested set of mRNAs for their replication). The subfamily is further classified into four genera (alpha, beta, gamma and delta coronaviruses). Among these, only 2 genera, i.e., alpha and beta coronavirus infect humans. These are designated as human CoV (HCoVs). HCoV-229E and HCoV-NL63 are examples of alpha coronavirus whereas HCoV-HKU1, HCoV-OC43, Middle East

respiratory syndrome CoV (MERS-CoV), the SARS-CoV, and SARS-CoV-2 are examples of beta coronavirus.<sup>[6-8]</sup> This family includes a total of seven viruses of which four produce mild respiratory illness, while the other three (SARSCoV-1, MERS and current SARS-CoV-2) are extremely dangerous, resulting in the current pandemic and huge rise in mortality rates.<sup>[7]</sup>

The name is derived from the Latin “corona” which means crown representing the spike proteins (peplomers) projecting over the virus envelope.<sup>[3]</sup> It also represents like a reminiscent of solar corona around the virus particles (virions) due to the surface covered by peplomers (spike proteins).<sup>[4]</sup> These spike proteins help in binding the virus receptors present in the body of bats, rodents, civets, cats, Malayan pangolins, camels, among other potentially competent hosts and humans.<sup>[9-11]</sup> Alterations in the spike proteins can lead to zoonotic spilling and cross over between different species. In addition, the genomic similarities between the SARS-COVID 2 have further confirmed its origin from the bats as the natural ancestral host.<sup>[12-16]</sup>

To detail the structure, the RNA genomes of the corona virus are considered to be the largest (27–32 kb) among the RNA viruses.<sup>[6]</sup> It has an enveloped membrane with 4–5 proteins attached over it. The beta family HCoV-HKU1, HCoV-OC43, MERS-CoV, SARS-CoV and SARS-CoV-2 is made up of four proteins that include SEMN-S for spike protein, E for envelope protein, M for membrane protein and N for nucleocapsid protein. The alpha family HCoV-OC43 and HCoV-HKU1 contains an extra HE protein along with the four proteins SEMN.<sup>[6]</sup>

## S protein

It is a 150 kDa protein, 23 N-linked highly glycosylated transmembrane protein called TMPRSS2, and makes the peculiar spike structure on the virus envelope. Its trimeric form is a class I fusion protein, that facilitates the receptor attachment. Further, its gets cleaved by a furin-like protease present in the host<sup>[6]</sup> into two functional domains, S1 and S2. S1 mainly helps in receptor binding, whereas S2 gives structural support by forming the stalk of S protein.<sup>[17-22]</sup>

### M protein

It is a 25–30 kDa protein with N-terminal ectodomain and a C-terminal endodomain. It is present as a dimer in virions in abundance and thus helps in maintaining the membrane curvature and gives shape for the virions. It also additionally helps in binding to the nucleocapsid.<sup>[23,24]</sup>

### E protein

It is an 8–12 kDa transmembrane protein with an N-terminal ectodomain and a C-terminal endodomain, found scarcely in the virion. It also has an ion channel activity (required for the pathogenesis of SARS-CoV and probably SARS-CoV-2) and plays a vital role in the virus assembly and release.<sup>[25,26]</sup>

### N protein

It constitutes the viral genome, i.e., nucleocapsid and has an N-terminal domain and a C-terminal domain. Each domain of the N protein can bind to RNA and is highly phosphorylated, thus increasing the affinity of the N protein for the viral RNA. The C-terminal domain of the N protein binds to the viral RNA and gives beads on a string structure forming a genomic packaging. The encapsulated viral genome produces viral particles by interacting with the M protein and nsp3, which is a component of replicase complex, facilitating the binding to the replicase-transcriptase complex.<sup>[27-31]</sup>

## PATHOGENESIS

### Mode of entry

The mode of entry of this virulent pathogen is through respiratory droplets, tears, body fluids, mucous membranes of the eyes, mouth, or nose of the infected person.<sup>[32]</sup> However, another mode of transmission via fecal-oral route of transmission has also been thought of, but the lack of recent studies with evidence of viral nucleic acid in the fecal samples of pneumonia patients could not prove the same.<sup>[33]</sup>

### Tropism

Once entered, the virus has tropism to type 2 pneumocytes and ciliated bronchial epithelial cells through angiotensin-converting enzyme 2 (ACE2) receptors and the immune cells like the dendritic cells and the macrophages.<sup>[34]</sup>

### Incubation period

The incubation period is about 2–14 days postinfection, and the virions survive in the air for about 2 h.<sup>[35-37]</sup>

### Clinical symptoms

It presents with a wide range of clinical manifestations such as cold, fever, fatigue, respiratory failure, pneumonia and cardiac arrest.<sup>[32]</sup>

### R-NAUGHT (Ro/reproduction number)

It is an indicator used to measure the contagiousness of infectious disease, i.e., how many people, from disease-free population, can be infected by one person with the disease. The significance of this lies in the importance of understanding virus biology and immunity. The estimated Ro of SARS-CoV2 is around 5.7.<sup>[37]</sup>

### High rate of susceptibility

The virus target mainly individuals with weak immunity such as the neonates, the older adults, and the ones with other chronic comorbidities.<sup>[38]</sup>

## ABO AND CORRELATION WITH COVID 19

ABO blood grouping discovered in 1900 by Austin immunologist Karl Landsteiner to explain the phenomena of RBC agglutination is well-documented hypothesis. Substantial evidence with experimental analysis supporting the proposition of ABO blood grouping are related to susceptibility and resistance to infections and infectious diseases.<sup>[39,40]</sup> Blood group antigens also represent polymorphic traits inherited among individuals and hence are frequent targets in epidemiological studies.<sup>[41]</sup> Being well equipped with receptors for antigens (bacteria, viruses, etc.), they facilitate colonization and thus play a role in innate immune system against bacterial pathogens or enveloped viruses that carry ABO active antigens. Association between ABO antibodies and bacteria has been documented. Check JH in 1971 and Boes M in 1988 hypothesized that IgM antibodies bind and fix complement on bacteria to facilitate phagocytosis, and this was further supported by evidence of *in-vitro* studies conducted using *Escherichia coli* O86 (a Group B active strain) inferred a ten-fold increase in the level of bacterial phagocytosis by neutrophils (10.9 versus 1.19 bacteria per cell).<sup>[42-44]</sup> Harris *et al.*<sup>[45]</sup> hypothesized that the blood group O are more prone for cholera (*Vibrio cholera* strains O1 El Tor and O139) than the nonblood group O individuals whereas Glass RI *et al.* inferred that the blood group B had a high prevalence of cholera and blood group O had low prevalence for the same.<sup>[45]</sup> The outbreak of gastrointestinal infections caused by *E. coli* O157 in Scotland in 1996 documented mortality rate of about 87.5% of patients in blood group O.<sup>[46]</sup> The pandemic spread of smallpox in Europe showed high susceptibility of blood group A individuals. The HIV-1 resistance mutation CCR532 in Europe with protection against smallpox and black death showed a combination of a selection of infectious diseases in different populations concluding the genetic drift and founder effects in small populations (resulting from migration patterns of early

humans). The genetic drift was linked to an active FUT2 (a secretor) that can express A, B, H and Leb, which was found to be inactivated in 20% of Europeans.<sup>[47-50]</sup> All the past studies, hence have shown the correlation between blood groups and genetic link of the susceptibility of infectious diseases.

Few genetic studies have also documented the correlation between COVID 19 and ABO, stating that the blood group A is at high risk and Blood group O being at low risk.<sup>[51]</sup>

- Zhao *et al.* in 2020 conducted a study in among 2173 patients with COVID-19 confirmed patients from three hospitals in Wuhan and Shenzhen, China. The authors correlated the patients' ABO blood group, and the results inferred that blood group A were associated with a higher risk when compared with non-A blood groups, whereas blood group O was associated with a lower risk for the infection compared with non-O blood groups.<sup>[51]</sup> However, this study had few limitations such as smaller sample size, multivariate analysis with demographic profiles due to the lack of information on sex, age, etc., among the controls and influence of systemic conditions on the multivariate analysis. Further studies should be conducted to prove this speculation<sup>[5]</sup>
- Yamamoto in 2020<sup>[41]</sup> assumptions were that at the S protein produced in A, B, AB blood group individuals with their antigens would produce their respective antibodies (as per Karl Landsteiner law of agglutination) that would block the interaction with S protein and ACE receptors
- Tanigawa *et al.* in 2020 reviewed the current literature and provided substantially updated analysis on COVID-19 and associated phenotypes. The authors aggregated human leukocyte antigen and ABO blood type frequencies among 337,579 cases across five populations in UK Biobank. The results inferred that there was significant and consistent risk reduction of blood group O which was in accordance to study conducted by Zhao *et al.* and further encouraged broad sharing of ABO blood type frequencies that are readily accessible across COVID-19 with mild, moderate, and severe/critical symptoms for robust inferences at <https://tinyurl.com/abo-covid19>.<sup>[52]</sup>

## DIAGNOSIS AND PREVENTIVE MEASURES

Diagnosis can be made by an epidemiologic survey on the history of travel/residence in the affected region or contact with affected persons 14 days before the onset of symptoms. The clinical symptoms, as mentioned in the pathophysiology (above text) can be asked for.

Bilateral ground-glass opacity that is an indicative of bilateral pneumonia in chest computed tomography image can be a diagnostic clue. Laboratory tests using reverse transcriptase-polymerase chain and serological screening with antibodies IgM and IgG can be done.<sup>[37]</sup>

Preventive measures such as social distancing, hand hygiene, home or hospital quarantine as well as restrictions on movement (lockdown) help in preventing the spread of the disease. Isolation and supportive therapy, including ventilatory support, are the mainstays of treatment of infected patients.<sup>[38]</sup>

## CONCLUSION

This review is a compilation of about the structure of coronavirus with basic epidemiology and pathophysiology. The main highlight is on its correlation with ABO blood grouping. Knowing the biological implications of the ABO blood group in this pandemic outbreak of COVID 19 can provide a platform for new therapeutic applications, thereby opening a gateway for research in this area.

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## Conflicts of interest

There are no conflicts of interest.

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