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

Nazia Hasan Khan¹, Nusrat Mannan², Mohammad Saroare Zaman³, Arifa Akram⁴

¹United Hospital Limited, Dhaka, Bangladesh, ²Department of Microbiology, US-Bangla Medical College, Bangladesh ³Sheikh Hasina National Institute of Burn and Plastic Surgery, Dhaka, Bangladesh, ⁴Department of Virology, National Institute of Laboratory Medicine and Referral Center, Dhaka, Bangladesh.

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 interest¹. 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 outpourings². Rising evidence suggests that the ABO blood group may play a role in the immunopathogenesis of SARS-CoV-2 infection, with group O being protective and group A conferring risks of higher disease predisposition and severity³. 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)⁴.⁵. 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 consequences⁶.⁷.⁸.⁹.

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 system¹⁰. The progressive additions of carbohydrates to an oligosaccharide backbone resulted in formation of three antigens, including A, B, and H¹¹. 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 B¹². The ABH antigens which in reality
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.  

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 glycoprophingolipids, 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.  

**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. 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. 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. 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. Additionally, the efficacy of infectious disease related vaccines may be influenced by the distribution of blood groups in the target population.

**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. Expression of ACE2 on various human cell surfaces gives SARS-CoV-2 the capability to infect multiple tissues. 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.

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.

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.
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. 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. 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. A retrospective study at the First Hospital of Changsha in Changsha, Hunan, China, likewise showed that blood type A 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.

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. 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). 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).

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.

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. 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. 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.

Another retrospective study had comparable findings, but did not describe comorbidities. Another study defined a higher rate of infection in group AB patients and a lower rate in group O patients. 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. One probable reason for these varying results is that many such studies did not account for various confounders (e.g., age), including comorbidities. 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 numerosity 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. 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. 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. Another study stated significant associations between Rh (D) blood group status, group B, and SARS-CoV-2.

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
COVID-19 Severity and ABO Blood Types; Association and Molecular... Akram et al

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.

References

1. Shokri P, Golmohammadi S, Noori M, Nejadghaderi SA, Carson-Chahhoud K, Safiri S. The relationship between blood groups and risk of infection with SARS-CoV-2 or development of severe outcomes: A review. Reviews in medical virology. 2021 May 14.
2. Zhang Y, Garner R, Salehi S, La Rocca M, Duncan D. Association between ABO blood types and coronavirus disease 2019 (COVID-19), genetic associations, and underlying molecular mechanisms: a literature review of 23 studies. Annals of hematology. 2021 Mar;8;1-0.
3. Barnkob MB, Pottegård A, Støvring H, Haustrup TM, Homburg K, Larsen R, et al. Reduced prevalence of SARS-CoV-2 infection in ABO blood group O. Blood advances. 2020 Oct 27;4(20):4990-3.
4. Hoiland RL, Fergusson NA, Mitra AR, Griesdale DE, Devine DV, Stukas S, et al. The association of ABO blood group with indices of disease severity and multiorgan dysfunction in COVID-19. Blood advances. 2020 Oct 27;4(20):4981-9.
5. Focosi D. Anti-A isoheamagglutinin titers and SARS-CoV2 neutralization: implications for children and convalescent plasma selection. British journal of haematology. 2020 Aug 1.
6. Zimringer JC, Spitalnik SL. Pathobiology of transfusion reactions. Annual Review of Pathology: Mechanisms of disease. 2015 Jan 24;10:83-110.
7. Branch DR. Anti-A and anti-B: what are they and where do they come from?. Transfusion. 2015 Jul;55(S2):S74-9.
8. Mourant AE, Kopec AC, Domaniewska-Sobczak K. The Distribution of Human Blood Groups and Other Polymorphisms. London, Oxford University Press. 1976.
9. Estrada-Mena B, Estrada FJ, Ulloa-Arvizu R, Guido M, Méndez R, Coral R, et al. Blood group O alleles in Native Americans: implications in the peopling of the Americas. American journal of physical anthropology: The Official Publication of the American Association of Physical Anthropologists. 2010 May;142(1):85-94.
10. Clausen H, Hakomori SI. ABH and Related Histo-Blood Group Antigens; Immunochemoical Differences in Carrier Isotypes and Their Distribution. 1. Vox sanguinis. 1989 Jan;56(1):1-20.
11. Landsteiner K. Zur Kenntnis der antif ermentativen, lytischen und agglutinierenden Wirkungen des Blutserums und der Lymph e. Zentralblatt für Bakteriologie, Mikrobiologie und hygiene. 1900;27:357-62.
12. Daniels G. Human blood groups. John Wiley & Sons; 2008 Apr 15.
13. Holodick NE, Rodriguez-Zhurbenko N, Hernández AM. Defining natural antibodies. Frontiers in immunology. 2017 Jul 26;8:872.
14. Zouine S, Marnissi F, Otmami N, Othmani MB, Zaid N, Kojok K, et al. Expression of histo-blood group antigens in tumor and adjacent normal breast tissues as prognostic markers of breast carcinoma. Journal of breast cancer. 2020 Feb 1;23(1):69-79.
15. Cooling L. Blood groups in infection and host susceptibility. Clinical microbiology reviews. 2015 Jul;28(3):801-70.
16. Liao Y, Xue L, Gao J, Wu A, Kou X. ABO blood group- associated susceptibility to norovirus infection: a systematic review and meta-analysis. Infection, Genetics and evolution. 2020 Jul 1;81:104245.
17. Ruvoën-Clouet N, Belliot G, Le Pendu J. Noroviruses and histo-blood groups: the impact of common host genetic polymorphisms on virus transmission and evolution. Reviews in medical virology. 2013 Nov;23(6):355-66.
18. Lee B, Dickson DM, deCamp AC, Ross Colgate E, Diehl SA, Uddin MI, et al. Histo-blood group antigen phenotype determines susceptibility to genotype-specific rotavirus infections and impacts measures of rotavirus vaccine efficacy. The Journal of infectious diseases. 2018 Apr 11;217(9):1399-407.

19. Clemens JD, Sack DA, Harris JR, Chakraborty J, Khan MR, Huda S, et al. ABO blood groups and cholera: new observations on specificity of risk and modification of vaccine efficacy. The Journal of infectious diseases. 1989 Apr 1;159(4):770-3.

20. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor cell. 2020 Apr 16;181(2):271-80.

21. Kochi AN, Tagliari AP, Forleo GB, Fassini GM, Tondo C. Cardiac and arrhythmic complications in patients with COVID-19. Journal of cardiovascular electrophysiology. 2020 May;31(5):1003-8.

22. Wu SC, Arthur CM, Wang J, Verkerke H, Josephson CD, Kalman D, et al. The SARS-CoV-2 receptor-binding domain preferentially recognizes blood group A. Blood advances. 2021 Mar 9;5(5):1305.

23. Goel R, Bloch EM, Pirene F, Al-Riyami AZ, Crowe E, Dau L, et al. ABO blood group and COVID-19: a review on behalf of the ISBT COVID-19 working group. Vox sanguinis. 2021 Feb 12;13076.

24. de França ND, Poli MC, Ramos PG, Borsoi CS, Coellela R. Titers of ABO antibodies in group O blood donors. Revista brasileira de hematologia e hemoterapia. 2011;33:259-62.

25. Tendulkar AA, Jain PA, Velaye S. Antibody titers in Group O platelet donors. Asian journal of transfusion science. 2017 Jan;11(1):22.

26. Fan Q, Zhang W, Li B, Li DJ, Zhang J, Zhao F. Association between ABO blood group system and COVID-19 susceptibility in Wuhan. Frontiers in cellular and infection microbiology. 2020 Jul 21;10:404.

27. Golinelli D, Boetto E, Maietti E, Fantini MP. The association between ABO blood group and SARS-CoV-2 infection: A meta-analysis. PLOS One. 2020 Sep;15(9):e0239508

28. Wu BB, Gu DZ, Yu JN, Yang J, Shen WQ. Association between ABO blood groups and COVID-19 infection, severity and demise: A systematic review and meta-analysis. Infection. Genetics and evolution. 2020 Oct 1;84:104485.

29. Wu Y, Feng Z, Li P, Yu Q. Relationship between ABO blood group distribution and clinical characteristics in patients with COVID-19. Clinica chimica acta. 2020 Oct 1;509:220-3.

30. Zietz M, Zucker J, Tattonetti NP. Testing the association between blood type and COVID-19 infection, intubation, and death. Medrxiv. 2020 Jan 1;20058073

31. Pourali F, Afshari M, Alizadeh-Navaei R, Javidnia J, Moosazadeh M, Hessami A. Relationship between blood group and risk of infection and death in COVID-19: a live meta-analysis. New microbes and new infections. 2020 Sep 1;137:100743.

32. Abdollahi A, Mahmoudi-Aliabadi M, Mehtash V, Jafarzadeh B, Salehi M. The novel coronavirus SARS-CoV-2 vulnerability association with ABO/Rh blood types. Iran journal of pathology. 2020; 15:156-160

33. Solmaz İ, Arac S. ABO blood groups in COVID-19 patients; cross-sectional study. International journal of clinical practice. 2021 Apr;75(4):e13927.

34. Gallian P, Pastorino B, Morel P, Chiaroni J, Ninove L, de Lamballerie X. Lower prevalence of antibodies neutralizing SARS-CoV-2 in group O French blood donors. Antiviral research. 2020 Sep 1;181:104880.

35. Ray JG, Schull MJ, Vermeulen MJ, Park AL. Association between ABO and Rh blood groups and SARS-CoV-2 infection or severe COVID-19 illness: a population-based cohort study. Annals of internal medicine. 2021 Mar;174(3):308-15.

36. Gérard C, Maggipinto G, Minon JM. COVID-19 and ABO blood group: another viewpoint. British journal of haematology. 2020 Jul 1.

37. Zeng X, Fan H, Lu D, Huang F, Meng X, Li Z, et al. Association between ABO blood groups and clinical outcome of coronavirus disease 2019: Evidence from two cohorts. Medrxiv. 2020 Jan 1.

38. Wu Y, Feng Z, Li P, Yu Q. Relationship between ABO blood group distribution and clinical characteristics in patients with COVID-19. Clinica chimica acta. 2020 Oct 1;509:220-3.

39. Leaf RK, Al-Samkari H, Brenner SK, Gupta S, Leaf DE. ABO phenotype and death in critically ill patients with COVID-19. British journal of haematology. 2020 Aug 1.
COVID-19 Severity and ABO Blood Types; Association and Molecular...

40. Li J, Wang X, Chen J, Cai Y, Deng A, Yang M. Association between ABO blood groups and risk of SARS-CoV-2 pneumonia. British journal of haematology. 2020 Jul 1.

41. Latz CA, DeCarlo C, Boitano L. Blood type and outcomes in patients with COVID-19. Annals of Hematology. 2020 Jul;1-6

42. Patel EU, Bloch EM, Grabowski MK, Goel R, Lokhandwala PM, Brunker PA, et al. Sociodemographic and behavioral characteristics associated with blood donation in the United States: a population-based study. Transfusion. 2019 Sep; 59(9):2899-907.

43. Golding J, Northstone K, Miller LL, Davey Smith G, Pembrey M. Differences between blood donors and a population sample: implications for case–control studies. International journal of epidemiology. 2013 Aug 1;42(4):1145-56.

44. Stussi G, Huggel K, Lutz HU, Schanz U, Rieben R, Seebach JD. Isotype-specific detection of ABO blood group antibodies using a novel flow cytometric method. British journal of haematology. 2005 Sep;130(6):954-63.