Global Journal of Medicine & Public Health

Blood groups and Covid-19 infection still an enigma-A Literature Review

Sarbjeet khurana[1] ,Anshu gupta[2]*

ABSTRACT

SARS-CoV-2 or COVID-19 disease caused by coronavirus was first reported in Wuhan, China in December 2019and,by March 2020 it turned into a pandemic by spreading to more than 200 countries globally. SARS-CoV-2 has a dynamic clinical progression with significant risk of mortality. [1,2]

The scientific fraternity is always in search for the new metabolic or biological markers of the diseases so that the risk of infection for a particular disease is predicted [11,12]. Recent accumulated evidence suggests that blood type (ABO) may affect the risk and severity of COVID-19infection[10]. There is a reported association between blood group A and an increased risk of SARS-CoV-2 infection, whereas group O was associated with a decreased risk in Chinese population. [6, 9, 10, 23,32, 33, 34, 35]

A meta-analysis study found that the COVID-19 infection rate was highest for blood group A and lowest for AB. Overall, the ABO blood group's vulnerability to COVID-19 infection was statistically significant (pooled p -value<0.001). [5]A population-based study from Canada reported the association between group O and severe COVID-19. The adjusted relative risk (aRR) for SARS-CoV-2 infection was higher for blood group AB than blood group A (1.15, CI 1.03-1.28) and B (1.21, CI 1.13-1.29) and slightly lower than type O (0.95, CI 0.91-1.01). [40]There are diverse results between the regions and countries. Therefore, it is necessary to conduct multi-centric prospective studies in different countries to authenticate blood groups as a predisposing risk factor and/ or a factor determining the severity of COVID-19.

Key-words: Blood groups, COVID-19 infection, COVID-19 severity

GJMEDPH 2023; Vol. 12, issue 6 | OPEN ACCESS

1*Corresponding author: Sarbjeet khurana ,Associate Professor & HOD Department of Epidemiology, IHBAS**; 2.**Anshu gupta ,Associate Professor, Department of Pathology & In-charge Emergency lab, IHBAS

Conflict of Interest—none | Funding-None

INTRODUCTION

1. From Coronavirus and COVID-19 to a Pandemic

In 2002,the first severe acute respiratory syndrome (SARS) outbreak occurred followed by SARS-CoV-2 which resulted in the 2019 coronavirus (CoV) disease .(COVID-19)is caused by an envelope, single- stranded, positive-sense RNA beta-coronavirus[1]and share79% genetic similarity with the SARS virus. SARS-CoV-2 was first reported in Wuhan, China in December 2019 and by March 2020 it turned into a pandemic by spreading to more than 200 countries. [2]From thereon, countries have experienced at least two waves of infections leading to significant morbidity and mortality rates which is being monitored at the global level by WHO. Several variants of SARS-CoV-2 have been encountered and classified as alpha, beta, gamma, delta and omicron. [3]The incubation period of novel coronavirus ranges between 3–7 days but usually varies from 1–14 days. Affected individuals remain contagious during the incubation period with disease transmission through respiratory droplets, aerosols, and direct contact. The asymptomatic cases of infection are also known to be a major source of infection. [4,5]The disease is diagnosed and confirmed by real-time reverse transcription-polymerase chain reaction (RRT-PCR) test. [5]

COVID-19 is clinically characterized by symptoms as fever, dry cough, dyspnea, fatigue, myalgia, sore throat, shortness of breath, a normal or decreased white blood cell count, dysgeusia and anosmia, and evidence of pneumonia on medical imaging. In severe conditions there is acute respiratory distress syndrome, septic shock, multi organ failure and even death. [4-6]Respiratory tract dysfunction is characterized by accumulation of fluid in alveoli, a hyper-inflammatory process called "cytokine storm". When multiple organs are affected, it is multi organ tropism of SARS-CoV.[7,8]

SARS-CoV-2 has a dynamic clinical progression with significant risk of mortality. High SARS CoV-2 susceptibility, severity and mortality is associated with old age, male sex, diabetes, hypertension, smoking, chronic respiratory disease and cardiovascular disease.[9,10]There is continuous search for biological biomarkers along with environmental and genetic risk factors that can predict the risk of infection. [11,12]Recent accumulated evidence suggests that blood type (ABO) may affect the risk and severity of COVID-19.[10]

2. ABO Blood Group and association with disease phenotypes

Human blood group antigens are expressed on the surface of human red blood cells (RBCs) along with other cells and tissues, including platelets, epithelia, vascular endothelial and neurons [4]. The Landsteiner's ABO blood group system involves the A and B antigens and their matching antibodies. The antigen-encoding gene located on chromosome 9, consists of the A, B, and O alleles yielding four blood groups A, B, O, and AB.[6]These genetic phenotypes follow Mendelian pattern of inheritance [4]and exhibit inter-individual and inter-ethnic polymorphic expression. Globally, blood type "O" is found to be the most common blood group, but regional variations have also been reported. [13]

The ABO blood groups are carbohydrate epitopes with the antigenic determinants of A and B blood types.[14]While the A and B proteins possess glycosyl transferase activity that catalyze conversion of H antigen into A or B antigen, the O group lacks this enzymatic activity due to a frameshift mutation induced a deletion in the gene. [15]

Previous studies have implicated ABO blood group in several human diseases, such as cardiovascular diseases , diabetes mellitus, cancer along with some infectious diseases. [4,16,17,18,19]As blood group antigens can facilitate intracellular uptake, cell recognition,[20]and cell adhesion, they may play a role in innate immune response to infections, tumor formation, metastasis and prognosis [4,21,22]. ABO antibodies have also been shown to be a part of the innate immune system against some microorganisms. The human blood group antigens can play an important role in infections by serving as receptors and/or co- receptors for parasites, bacteria and enveloped viruses modulating immune and inflammatory responses and influencing disease severity and susceptibility. [4,6,23]

Blood groups have been associated with SARS-CoV-1, rotavirus, noroviruses, dengue virus, hepatitis B virus, Norwalk virus, P. falciparum, H. Pylori and N. gonorrhoeae.[6,10]Blood group O was found to significantly reduce the risk of hepatitis B, but increase the risk of coronavirus infection in a recent meta-analysis study.

ISSN# 2277-9604

[4,24]Rotavirus gastroenteritis susceptibility was shown to be higher in children with blood group A and AB than those with blood group O [25]and B [26]. Degarege et al. observed higher risk of anemia in malaria patients with blood group A than O and B phenotypes.[27]AB blood group has 2.5 times higher risk of developing dengue hemorrhagic fever in comparison with other blood groups.[28]Blood groups A and D were found to be associated with poor prognosis and outcomes after West Nile virus infection.[29]Blood group A is associated with higher risk of acute respiratory distress syndrome in trauma and sepsis patients.[30]Lebiush et al. reported a higher seroconversion to a titre of > 20 in A and B blood groups carriers infected with influenza A (H1N1) [31].

3. Summary of Evidence: Association of ABO blood groups to Covid-19

Several studies were done on association of ABO blood groups with covid-19 susceptibility, severity and treatment outcome since the beginning of the pandemic. First study in the Chinese population reported association of blood group A with an increased risk of SARS-CoV-2 infection, whereas group O was associated with a decreased risk [32]. Similar results were observed in several studies from different countries including USA[10,23], Turkey [33], China [6], Sudan [9], Spain [34]and Brazil [35]. Interestingly, ABO blood group was also found to be associated with SARS-CoV infection risk in previous study by Cheng et al. [36]

A meta-analysis study by Kabrah et al found that the COVID-19 infection rate varies increasingly in people with blood group: A >O >B >AB suggesting highest risk for blood group A and lowest for AB [5]. The studies conducted in China, United States, Saudi Arabia, and Iraq reported increased risk for COVID-19 infection in individuals with O blood group. Further, individuals with AB blood group were found to be at a decreased risk for COVID-19 while blood group A carriers were at increased risk in studies from Sweden, Turkey, France, and Cyprus. The author suggested variability in included studies due to different regions, races, sample sizes, and ABO blood group distribution in Covid-19 positive participants [5]. However, findings in other meta-analysis studies indicated a protective effect of blood group O and poor outcome for group A compared to others. Subsequent research didn't find association between AB group and Covid-19 infection probably due to the non-consideration of country specific distribution patterns.[1,2,5,37]In addition, higher risk of infection was reported for individuals with blood group B instead of A in a meta-analysis by Almadhi et al. [12]Interestingly, a genome-wide association study (GWAS) also reported enrichment in blood group A and depletion in blood group O genotypes in COVID-19 patients as compared to blood donors as reference. [38]Hernández Cordero et al. found that a COVID-19 locus was associated with ABO gene expression in lungs as well as blood tissues, and ABO plasma protein levels in blood .The increased plasma levels were associated with an increased risk and severity of COVID-19infection.[15]

Several factors such as rhesus (Rh)-factor, gender and race were found to influence the strength of ABO blood group association with Covid-19 risk of infection. Individuals with Rh-positive blood types were reported to be at a higher risk [2,10,39]while those with Rh negative were protected from SARS-CoV- 2 infection and severity of infection, particularly in the O-negative carriers. The adjusted relative risk (aRR) for SARS-CoV-2 infection was higher with blood type AB than with type A (1.15, CI 1.03 to 1.28) and B (1.21, CI 1.13 to 1.29) and slightly lower with type O (0.95 ,CI, 0.91 to 1.01). [40]Females with blood group A were reported to be more vulnerable to COVID-19 as compared to men. Further, females transmit COVID-19 differently than men.[41]Previously, ethnic groups have been shown to differ in their prevalence of blood groups and blood antigens.[5]Among critically ill white patients, blood type A were found to be over-represented while patients with blood type O were under-represented.[23]

In contrast to most previously published reports, Dzik et al. [42]and Szymanski et al. [13]found no association between blood group and COVID-19 infections. Compared to O blood group, A blood group was not found to be associated with increased viral positivity by Anderson et al. [11] Further, although Al-Youha et al. observed an increased risk of SARSCoV-2 in blood group A and lowest risk in blood group O, no association was found between severe COVID-19 and ABO blood group in a unique population from Kuwait.[43]Recently published study suggests that perhaps the relationship lies in the levels of antibodies rather than the type of antibodies themselves, where COVID-19 patients were found to have significantly lower levels than asymptomatic controls.[15]There is no published analysis yet of the relationship between antibodies and severity of outcome.[12]No association between

SARS-CoV-2 infection rates with blood group A or RhD group was found.[43]

These findings highlight that a considerable amount of heterogeneity exists among the included studies in different meta-analysis studies influencing the final outcome. The severity at presentation, accessibility to the treatment facilities, residential living situation, and ethnicity are correlated to confound the association between ABO group and outcomes. The choice of a reference population in these studies varied, some studies used blood donors, others a COVID-19 (negative) subgroup or a historical population for comparison.[2]

4. ABO blood group and Covid-19: Underlying Mechanism

The exact underlying mechanism by which the ABO protein modulates COVID-19 risk is still unclear and several theories have been hypothesized. SARS-CoV infects several types of human cells mainly pneumocytes, enterocytes, kidney distal tubular epithelium cells, and all these cells are known to synthesize ABH antigens.[44]

The presence of N-acetyl galactosamine sugar moiety is considered as the target of coronaviruses for binding through spike (S) transmembrane N-glycosylated proteins which facilitate SARS-CoV-2 entry into the human host by binding to angiotensin-converting enzyme 2 (ACE2) receptor.[4]The blood group A cell differs from O cells in the presence of sugar with the former having an extra sugar whereas absence of sugar on O cells. [39]Further, presence of circulating anti-A antibodies has also been linked to decreased susceptibility by altering the viral-cell adhesion mechanism. It was observed that individuals with anti-A antibodies in serum (i.e. blood groups B and O) were significantly under-represented among COVID-19 positive groups than those lacking anti-A antibodies, whereas no significant difference was found in case of circulating anti-B antibodies. Additionally, anti-A antibodies from O blood group was found to be more protective than anti-A antibodies from blood group B. These observations are substantiated by the fact that serum from individuals with A and B blood groups have IgM as the predominant immunoglobulin isotype of anti-B/anti-A antibodies, while O blood group serum have IgG .[32]The blood group O is considered to have the protective effect due to the presence of the ancestral immunoglobulin IgM and its anti-glycan isoagglutinin activities.[39]

In an in vitro study, Guillon et al. observed that anti-A antibodies can inhibit or even block the interaction between the SARS-CoV 2 and its receptor-ACE2, hereby providing protection. Moreover, anti-A antibodies can inhibit or block spike-mediated adhesion only when the S-expressing cells express the A glycosyl transferase. [45]If the S protein of an A, B, or AB group individual carries respective glycan antigens, it is possible that binding of the respective antibodies can block the interaction between S protein and ACE2, thereby offering complete or incomplete protection. [39]

Besides ACE2, transmembrane proteins CD147 and transmembrane serine protease 2 (TMPRSS2) have also been identified to play an important role in the SARS-CoV2 infection process. SARS-CoV2 spike protein is a homotrimer with each monomer containing S1 subunit related to cell recognition and S2 subunit related to membrane fusion. S1 subunit contains S1A (or NTD) domain that binds to sialic acid-containing glycoproteins, such as CD147 and S1B (or RBD) domain that binds to ACE2 receptor. SARS-CoV2 S protein contains clusters of glycosylation sites in the receptor-22 binding motif. [7,44].

Silva-Filho et al. suggested that modulation of sialic acid-containing cellular receptors distribution on the host cell surface induced by ABO blood group antigens through carbohydrate-carbohydrate interactions (CCIs) could alter the spike protein binding to the host cell. The authors hypothesized that antigen A followed by antigens B and AB can facilitate sialoside clusters formation increasing the odds of viral NTD and RBD domain binding to CD147, known as basigin or EMMPRIN, and ACE2 receptors, respectively, through avidity and multivalency.[7]

Besides coronavirus, blood group A has been previously associated with the development of acute respiratory distress syndrome (ARDS) after major trauma and severe sepsis.[46]However, the association between ABO blood group and SARS-CoV2 severity appears to be more complicated due to the involvement of specific anti-A titers, the immunoglobulin isotype of anti-A antibodies, and ABO group differences in von Willebrand factor (VWF)[8]. Some traits are specifically associated with particular blood types. For instance, individuals with blood type O present lower plasma levels of VWF and coagulation factor VIII compared to non-O blood type carriers due to altered glycosyl transferase activity and increased clearance of VWF

[35] , and therefore have lower rates of venous thrombosis and cardiovascular diseases. Thus, patients with blood type O are less prone to develop COVID-19 related consequences such as pulmonary microvascular thrombosis and endothelial dysfunction. [23]People with blood group O have higher interleukin 6 (IL-6) levels which is a proinflammatory cytokine which plays a prime role during the active phase. However, studies showed that IL-6 is associated with COVID-19 severity, as it can be part of a cytokine storm. IL-6 could both play a protective role with its involvement in lung repair responses and exacerbate its role in COVID-19 infection.[1]These observations provide further support to the notion that blood type O may incur protection against SARS-CoV 2 infection.[43]In contrast, blood type A was considered to cause more severe COVID-19 disease by facilitating attachment of molecules on the vasculature by preventing P-selectin and intercellular cell adhesion molecule 1 (ICAM-1) cleavage resulting in increased adhesion and inflammation.[1]

The first genome-wide association study (GWAS) on SARS-CoV 2 comprising a European cohort (Italian and Spanish), one of the two genome-wide significant genetic variant was rs657152 at the ABO gene locus.[47]However, Al-Youha et al. suggested that ethnicity could alter the association between ABO blood group and COVID-19 infection risk. For instance, blood group secretor status, an autosomal dominant trait, is modulated by the fucosyl transferase 2 (FUT2) genes independent of ABO genotype. Further, only 22% of South Asians have been shown to bear the secretor phenotype as compared to 80% Caucasians. The ABO blood type distribution showed ethnic variability, to some extent due to selective genetic pressure caused by malarial infection.[43]The protein-decreasing rs505922 (T) was found to be in high Linkage disequilibrium (LD) (r ~ 1) with the blood group O rs8176719 genotype suggesting lower ABO protein level to be the reason for protective effect of blood group O . Finally, the protein-increasing rs505922 (C) was found to be a risk variant for venous thromboembolism (VTE).[15,48].

5. ABO blood group and covid-19: Effect on clinical outcome

Several studies have found significant association of ABO blood group with not only risk of COVID-19 infection, but also with poor prognosis/outcome following the infection [2]. Studies indicated that different blood types might influence clinical manifestations of patients with COVID-19. For instance, Wu et al. found that symptoms mainly fever, cough, dyspnea, sore throat, chest pain, distress, and fatigue were related to ABO blood type distribution [6]. The frequency of four blood types- A, B, O and AB was found to be 40%, 23%, 29% and 8% respectively among people who succumbed to COVID-19 infection. Although the odds ratio of fatality for AB blood type was non-significant, it was substantial [1]. The mortality risk in COVID-19 individuals in blood group A was much higher than in individuals in blood group O (OR: 1.75, 95% CI: 1.22–2.51) TO [34]. Further, Leaf et al. observed an increased proportion of COVID-19 patients in critical conditions with blood group A, but this association was limited to Caucasians ethnicity only [23]. Zietz et al. compiled data of 14,112 SARS-CoV-2 positive subjects at a hospital to assess the association between ABO and infection, intubation, and death. The authors observed increased prevalence of infection among non-O blood types. They reported decreased risk of intubation among blood type A and increased risk among AB and B blood types, compared with O blood type along with increased risk of mortality risk for type AB and decreased for blood types A and B. They also found that Rh-negative blood group imparts protective effect for all three outcomes [10]. Blood type A blood was found to be associated with the significantly increased cause-specific hazard of mortality among SARS-CoV 2 patients compared to blood type O and blood type B [13]. The meta-analysis by Liu et al. reported that blood type A was associated with a significantly increased risk of mortality due to COVID-19 infection [2]. Also, blood group A patients have been reported to have more severe disease according to the scores of the Sequential Organ Failure Assessment (SOFA) and Simplified Acute Physiologic Score 3 (SAPS 3). [35]These findings substantiate the previous data suggesting that blood type may influence the outcome after COVID-19 infection. Hoiland et al. demonstrated that blood type A or AB was associated with higher mechanical ventilation, and continuous renal replacement therapy (CRRT) requirement along with prolonged ICU stay compared with blood types O or B among COVID-19 patients. The association remained significant after adjusting for age, gender, and comorbid conditions. Although no difference in inflammatory cytokines levels was observed with blood type A or AB vs O or B, increased levels of Aspartate transaminase (AST), alanine transaminase (ALT), and peak serum creatinine were found in patients with blood type A or AB suggesting multi-organ protective effect exerted by the anti-A antibody. The higher fibrin D-dimers was reported in patients with blood types A or AB compared with

blood types O or B. As patients with blood type O are known to have reduced levels of factor VIII and von Willebrand factor, explaining protective effect against the manifestation of pulmonary vasculopathy and coagulopathy among COVID-19 patients [8].

A blood group–specific genomic analysis comprising Italian and Spanish cohorts demonstrated a genome wide significant association between genetic variant rs657152 at the ABO locus with severe COVID-19 cohort with respiratory failure requiring mechanical ventilation. Further, sub-group analysis showed that individuals with blood group A were at a higher risk as compared to group O who were protected. The FUT2 rs601338 G>A variant was found to protect against the severe COVID-19 infection with no mechanical ventilation requirement and ICU admission specifically in blood type carriers.[38,46]However, Dzik et al. compared the ABO blood type distribution between COVID-19 survivors and related fatality, and found no association between ABO locus polymorphism and COVID-19 casualty [42]. The data from the Covid-19 Host Genetics Initiative (The COVID-19 Host Genetics Initiative, 2020) indicates that the ABO locus is the most significant region for COVID-19 infection rate yet had no association with severity of disease when hospitalized and non-hospitalized patients were compared. Consistent with this, disease severity was not found to be associated in data reported from at-home COVID-19 genetics tests conducted by 23andMe and Ancestry DNA [49].

Among COVID-19 patients, the prevalence of mortality was found to be significantly higher in blood type A than B and AB blood types. However, country specific distribution of blood types with A being the most common blood type and AB the least prevalent in countries such as China and the United States could have potentially affected their results. Several other factors mainly gender, age, diabetes, asthma and other medical conditions were also found to be involved in mortality rates due to COVID-19 [1].

Several studies failed to find any statistically significant association between blood type and mortality or hospitalization, or intubation or ICU admission due to COVID-19 in their studies [1,2,10]. In a large study from Kuwait comprising 3,730,027 healthy control individuals, significant differences were not observed in severe clinical outcomes or fatality among the blood groups as compared to COVID-19 patients [43]. Similarly, in a retrospective observational study from Bahrain, no association was observed by Almadhi et al. between blood group and the risk of a COVID-19 severity requiring ICU admission [12]. Al-Youha et al. also showed no association of COVID-19 infection with severe clinical outcomes including intubation, ICU admission and mortality. Al-Youha et al. proposed that the scale of the detrimental effect of blood group A on COVID-19 fatal outcomes can only be detected in cohorts recruiting critically ill patients.[43]Similarly, Latz et al., who conducted hospital-based retrospective study using shared registry records from United States found no association between blood type and risk of intubation or fatality in COVID-19 patients.[50]In another study involving 323 Saudi adults with COVID-19 (108 patients who died and 215 controls who recovered) showed that older age and type 2 diabetes were the main independent predictors of mortality with no significant association between any ABO blood type and mortality risk.[51]Another study amongst patients with COVID- 19 from Turkey also failed to find any significant association between the clinical severe outcomes and the blood types.[33]In another large study from Turkey, Dal et al. used age-gender-comorbidity matched cohort to examine the association between blood types and COVID-19 outcome. The authors found no significant difference regarding the hospitalization rate and ICU admission, mechanical ventilation (MV) support, duration of hospital and ICU stay, and case fatality ratio (CFR) between blood type O and non-O blood types. Blood group A was reportedly associated with an increased ICU admission rate compared to other blood groups. Additionally, no difference was observed related to the hospital and ICU admission rate, MV support, and CFR when Rh-ve patients were compared to Rh+ patients. The authors also revealed that ABO blood types and Rh groups failed to show any impact on the COVID-19 progression and CFR [44].

Ray et al in a population-based study from Canada observed lower risk of severe COVID-19 with group O .[40]Elinghaus et al comprising ICU population from Italy and Spain observed that patients with blood group A had increased respiratory failure risk.[38]Li et al observed that blood group A was associated with higher risk of hospitalization in a Chinese cohort.[52]

CONCLUSIONS

The various studies included in the review suggest probable role of ABO blood groups in COVID-19 infection caused by SARS-COV-2. Patients with

blood group A were at increased risk for COVID-19 infection whereas patients with blood group O had reduced risk and blood groups B and AB did not show any significant association with COVID-19 infection. Gender wise, females with blood group A were reported to be more susceptible to COVID-19 infection as compared to males. Rh-positive individuals were at higher risk [2,10,39] while Rh negative individuals were protected from SARS-CoV- 2 infection and severity of infection, particularly in the O-negative carriers. [40] As far as severity is concerned, individuals with blood type O presented lower plasma levels of VWF and coagulation factor VIII due to altered glycosyl transferase activity and increased clearance of VWF [35].Therefore, they had lower rates of Covid -19 complications such as venous thrombosis and cardiovascular disease whereas blood type A was considered to cause more severe COVID-19 disease by facilitating attachment of molecules on the vasculature resulting in increased adhesion and inflammation.

[1]Some studies found that the mortality rate in COVID-19 patients with blood group A was reported to be significantly higher than that of patients with blood group O whereas several studies failed to find any significant association between blood type and mortality or hospitalization, intubation or ICU admission due to COVID-19.The methodological issues which restricted the projection of these studies for drawing major conclusions are mainly that these studies are retrospective, most with smaller sample size, diverse results apparently due to geographical variations, genetic diversity or chance factor. In future, more prospective studies preferably multi-centric studies with larger sample size might give us conclusive evidence whether the blood group is a risk factor predisposing to COVID-19 or a factor determining severe course of illness.

REFERENCES

1. 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;37:100743. Epub 2020/08/25. doi: 10.1016/j.nmni.2020.100743. PubMed PMID: 32837730; PubMed Central PMCID: PMC7418722.
2. Liu N, Zhang T, Ma L, Zhang H, Wang H, Wei W, et al. The impact of ABO blood group on COVID-19 infection risk and mortality: A systematic review and meta-analysis. Blood reviews. 2021;48:100785. Epub 2020/12/15. doi: 10.1016/j.blre.2020.100785. PubMed PMID: 33309392; PubMed Central PMCID: PMC7834371.
3. https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/.
4. 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;10:404. Epub 2020/08/15. doi: 10.3389/fcimb.2020.00404. PubMed PMID: 32793517; PubMed Central PMCID: PMC7385064.
5. Kabrah SM, Kabrah AM, Flemban AF, Abuzer A. Systematic review and meta-analysis of the susceptibility of ABO blood group to COVID-19 infection. Transfusion and apheresis science : official journal of the World Apheresis Association : official journal of the European Society for Hemapheresis. 2021;60(4):103169. Epub 2021/05/29. doi: 10.1016/j.transci.2021.103169. PubMed PMID: 34045120; PubMed Central PMCID: PMC8139534.
6. Wu Y, Feng Z, Li P, Yu Q. Relationship between ABO blood group distribution and clinical characteristics in patients with COVID-19. Clin Chim Acta. 2020;509:220-3. Epub 2020/06/21. doi: 10.1016/j.cca.2020.06.026. PubMed PMID: 32562665; PubMed Central PMCID: PMC7832938.
7. Silva-Filho JC, Melo CGF, Oliveira JL. The influence of ABO blood groups on COVID-19 susceptibility and severity: A molecular hypothesis based on carbohydrate-carbohydrate interactions. Med Hypotheses. 2020;144:110155. Epub 2020/12/02. doi: 10.1016/j.mehy.2020.110155. PubMed PMID: 33254482; PubMed Central PMCID: PMC7395945.
8. Hoiland RL, Fergusson NA, Mitra AR, Griesdale DEG, 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;4(20):4981-9. Epub 2020/10/16. doi: 10.1182/bloodadvances.2020002623. PubMed PMID: 33057633; PubMed Central PMCID: PMC7594392 interests.
9. Taha SAH, Osman MEM, Abdelkarim EAA, Holi MAI, Elbasheir MM, Abuzeid NMK, et al. Individuals with a Rh-positive but not Rh-negative blood group are more vulnerable to SARS- CoV-2 infection: demographics and trend study on COVID-19 cases in Sudan. New microbes and new infections. 2020;38:100763. Epub 2020/09/29. doi: 10.1016/j.nmni.2020.100763. PubMed PMID: 32983543; PubMed Central PMCID: PMC7505818.
10. Zietz M, Zucker J, Tatonetti NP. Associations between blood type and COVID-19 infection, intubation, and death. Nature communications. 2020;11(1):5761. Epub 2020/11/15. doi: 10.1038/s41467-020-19623-x. PubMed PMID: 33188185; PubMed Central PMCID: PMC7666188.
11. Anderson JL, May HT, Knight S, Bair TL, Muhlestein JB, Knowlton KU, et al. Association of Sociodemographic Factors and Blood Group Type With Risk of COVID-19 in a US Population. JAMA network open. 2021;4(4):e217429. Epub 2021/04/06. doi: 10.1001/jamanetworkopen.2021.7429. PubMed PMID: 33818622; PubMed Central PMCID: PMC8022215 endowment from Dell Loy Hansen Heart Foundation Heart Institute during the conduct of the study. Dr Horne reported receiving grants from Intermountain Research and Medical Foundation, AstraZeneca, and PCORnet; nonfinancial support in the form of in-kind donations from GlaxoSmithKline and CareCentra; serving on an advisory board for LabMe.ai; and licensing of intellectual property from Alluceo and CareCentra outside the submitted work. No other disclosures were reported.
12. Almadhi MA, Abdulrahman A, Alawadhi A, Rabaan AA, Atkin S, AlQahtani M. The effect of ABO blood group and antibody class on the risk of COVID-19 infection and severity of clinical outcomes. Sci Rep. 2021;11(1):5745. Epub 2021/03/13. doi: 10.1038/s41598-021-84810-9. PubMed PMID: 33707451; PubMed Central PMCID: PMC7952683.
13. Szymanski J, Mohrmann L, Carter J, Nelson R, Chekuri S, Assa A, et al. ABO blood type association with SARS-CoV-2 infection mortality: A single-center population in New York City. Transfusion. 2021;61(4):1064-70. Epub 2021/03/06. doi: 10.1111/trf.16339. PubMed PMID: 33665881; PubMed Central PMCID: PMC8014690.
14. Zhao J, Yang Y, Huang H, Li D, Gu D, Lu X, et al. Relationship Between the ABO Blood Group and the Coronavirus Disease 2019 (COVID-19) Susceptibility. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2021;73(2):328-31. Epub 2020/08/05. doi: 10.1093/cid/ciaa1150. PubMed PMID: 32750119; PubMed Central PMCID: PMC7454371.
15. Hernández Cordero AI, Li X, Milne S, Yang CX, Bossé Y, Joubert P, et al. Multi-omics highlights ABO plasma protein as a causal risk factor for COVID-19. Human genetics. 2021;140(6):969-79. Epub 2021/02/20. doi: 10.1007/s00439-021-02264-5. PubMed PMID: 33604698; PubMed Central PMCID: PMC7892327 submitted work. W.T. reports fees to institutions from Roche-Ventana, AbbVie, Merck-Sharp-Dohme and Bristol-Myers-Squibb, outside the submitted work. M.v.d.B. reports research grants paid to Institution from AstraZeneca, Novartis, outside the submitted work. D.D.S. reports research funding from AstraZeneca and received honoraria for speaking engagements from Boehringer Ingelheim and AstraZeneca over the past 36 months, outside of the submitted work.
16. Dentali F, Sironi AP, Ageno W, Turato S, Bonfanti C, Frattini F, et al. Non-O blood type is the commonest genetic risk factor for VTE: results from a meta-analysis of the literature. Seminars in thrombosis and hemostasis. 2012;38(5):535-48. Epub 2012/06/29. doi: 10.1055/s-0032-1315758. PubMed PMID: 22740183.
17. Kamil M, Al-Jamal HA, Yusoff NM. Association of ABO blood groups with diabetes mellitus. The Libyan journal of medicine. 2010;5. Epub 2010/01/01. doi: 10.3402/ljm.v5i0.4847. PubMed PMID: 21483592; PubMed Central PMCID: PMC3071167.

18. Stakisaitis D, Juknevičienė M, Ulys A, Valiuniene D, Stanislovaitiene D, Sepetiene R, et al. ABO blood group polymorphism has an impact on prostate, kidney and bladder cancer in association with longevity. Oncology letters. 2018;16(1):1321-31. Epub 2018/08/01. doi: 10.3892/ol.2018.8749. PubMed PMID: 30061952; PubMed Central PMCID: PMC6063046.
19. Etemadi A, Kamangar F, Islami F, Poustchi H, Pourshams A, Brennan P, et al. Mortality and cancer in relation to ABO blood group phenotypes in the Golestan Cohort Study. BMC medicine. 2015;13:8. Epub 2015/01/17. doi: 10.1186/s12916-014-0237-8. PubMed PMID: 25592833; PubMed Central PMCID: PMC4295491.
20. Gralinski LE, Menachery VD. Return of the Coronavirus: 2019-nCoV. Viruses. 2020;12(2). Epub 2020/01/30. doi: 10.3390/v12020135. PubMed PMID: 31991541; PubMed Central PMCID: PMC7077245.
21. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270-3. Epub 2020/02/06. doi: 10.1038/s41586-020-2012-7. PubMed PMID: 32015507; PubMed Central PMCID: PMC7095418.
22. Weisbrod AB, Nilubol N, Weinstein LS, Simonds WF, Libutti SK, Jensen RT, et al. Association of type-O blood with neuroendocrine tumors in multiple endocrine neoplasia type 1. The Journal of clinical endocrinology and metabolism. 2013;98(1):E109-14. Epub 2012/10/25. doi: 10.1210/jc.2012-2781. PubMed PMID: 23093487; PubMed Central PMCID: PMC3537107.
23. 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;190(4):e204-e8. Epub 2020/07/02. doi: 10.1111/bjh.16984. PubMed PMID: 32609874; PubMed Central PMCID: PMC7361419.
24. Mohammadali F, Pourfathollah A. Association of ABO and Rh Blood Groups to Blood-Borne Infections among Blood Donors in Tehran-Iran. Iranian journal of public health. 2014;43(7):981-
9. Epub 2015/04/25. PubMed PMID: 25909065; PubMed Central PMCID: PMC4401062.
25. Perez-Ortin R, Villa-Vicente S, Carmona-Vicente N, Santiso-Bellon C, Rodriguez-Diaz J, Buesa J. Histo-Blood Group Antigens in Children with Symptomatic Rotavirus Infection. Viruses. 2019;11(4). Epub 2019/04/13. doi: 10.3390/v11040339. PubMed PMID: 30974776; PubMed Central PMCID: PMC6520971.
26. Elnady HG, Abdel Samie OM, Saleh MT, Sherif LS, Abdalmoneam N, Kholousi NM, et al. ABO blood grouping in Egyptian children with rotavirus gastroenteritis. Przegląd gastroenterologiczny. 2017;12(3):175-80. Epub 2017/11/11. doi: 10.5114/pg.2017.70469. PubMed PMID: 29123577; PubMed Central PMCID: PMC5672705.
27. Degarege A, Legesse M, Medhin G, Animut A, Erko B. Malaria and related outcomes in patients with intestinal helminths: a cross-sectional study. BMC infectious diseases. 2012;12:291. Epub 2012/11/10. doi: 10.1186/1471-2334-12-291. PubMed PMID: 23136960; PubMed Central PMCID: PMC3519704.
28. Murugananthan K, Subramanian S, Kumanan T, Owens L, Ketheesan N, Noordeen F. Blood group AB is associated with severe forms of dengue virus infection. Virusdisease. 2018;29(1):103-5. Epub 2018/04/03. doi: 10.1007/s13337-018-0426-8. PubMed PMID: 29607366; PubMed Central PMCID: PMC5877852.
29. Khaidarova Z, Bravo MD, Kamel HT, Custer BS, Busch MP, Lanteri MC. Blood group A and D negativity are associated with symptomatic West Nile virus infection. Transfusion. 2016;56(7):1699-706. Epub 2016/05/18. doi: 10.1111/trf.13622. PubMed PMID: 27189860; PubMed Central PMCID: PMC4938756.
30. Reilly JP, Meyer NJ, Shashaty MGS, Feng R, Lanken PN, Gallop R, et al. ABO blood type A is associated with increased risk of ARDS in whites following both major trauma and severe sepsis. Chest. 2014;145(4):753-61. Epub 2014/01/05. doi: 10.1378/chest.13-1962. PubMed PMID: 24385226; PubMed Central PMCID: PMC3971970.
31. Lebiush M, Rannon L, Kark JD. The relationship between epidemic influenza (A(H1N1) and ABO blood group. The Journal of hygiene. 1981;87(1):139-46. Epub 1981/08/01. doi: 10.1017/s002217240006931x. PubMed PMID: 7252135; PubMed Central PMCID: PMC2134079.
32. Gérard C, Maggipinto G, Minion JM. COVID-19 and ABO blood group: another viewpoint. British journal of haematology. 2020;190(2):e93-e4. Epub 2020/05/27. doi: 10.1111/bjh.16884. PubMed PMID: 32453863; PubMed Central PMCID: PMC7283642.
33. Göker H, Aladağ Karakulak E, Demiroğlu H, Ayaz Ceylan Ç M, Büyükaşik Y, Inkaya A, et al. The effects of blood group types on the risk of COVID-19 infection and its clinical outcome. Turkish journal of medical sciences. 2020;50(4):679-83. Epub 2020/06/05. doi: 10.3906/sag-2005-395. PubMed PMID: 32496734; PubMed Central PMCID: PMC7379446.
34. Muñiz-Diaz E, Llopis J, Parra R, Roig I, Ferrer G, Grifols J, et al. Relationship between the ABO blood group and COVID-19 susceptibility, severity and mortality in two cohorts of patients. Blood transfusion = Trasfusione del sangue. 2021;19(1):54-63. Epub 2020/11/17. doi: 10.2450/2020.0256-20. PubMed PMID: 33196417; PubMed Central PMCID: PMC7850930.
35. Garibaldi PMM, Oliveira LC, da Fonseca BA, Auxiliadora-Martins M, Miranda CH, Almado CEL, et al. Histo-blood group A is a risk factor for severe COVID-19. Transfusion medicine (Oxford, England). 2021. Epub 2021/06/05. doi: 10.1111/tme.12796. PubMed PMID: 34085363; PubMed Central PMCID: PMC8242674.
36. Cheng Y, Cheng G, Chui CH, Lau FY, Chan PK, Ng MH, et al. ABO blood group and susceptibility to severe acute respiratory syndrome. JAMA. 2005;293(12):1450-1. Epub 2005/03/24. doi: 10.1001/jama.293.12.1450-c. PubMed PMID: 15784866.
37. 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;15(9):e0239508. Epub 2020/09/19. doi: 10.1371/journal.pone.0239508. PubMed PMID: 32946531; PubMed Central PMCID: PMC7500631.
38. Ellinghaus D, Degenhardt F, Bujanda L, Buti M, Albillos A, Invernizzi P, et al. Genomewide Association Study of Severe Covid-19 with Respiratory Failure. N Engl J Med. 2020;383(16):1522-34. Epub 2020/06/20. doi: 10.1056/NEJMoa2020283. PubMed PMID: 32558485; PubMed Central PMCID: PMC7315890.
39. Zaidi FZ, Zaidi ARZ, Abdullah SM, Zaidi SZA. COVID-19 and the ABO blood group connection. Transfusion and apheresis

science : official journal of the World Apheresis Association : official journal of the European Society for Haemapheresis. 2020;59(5):102838. Epub 2020/06/10. doi: 10.1016/j.transci.2020.102838. PubMed PMID: 32513613; PubMed Central PMCID: PMC7834841.

40. 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;174(3):308-15. Epub 2020/11/24. doi: 10.7326/M20-4511. PubMed PMID: 33226859; PubMed Central PMCID: PMC7711653.
41. Xiong J, Lipsitz O, Nasri F, Lui LMW, Gill H, Phan L, et al. Impact of COVID-19 pandemic on mental health in the general population: A systematic review. Journal of affective disorders. 2020;277:55-64. Epub 2020/08/18. doi: 10.1016/j.jad.2020.08.001. PubMed PMID: 32799105; PubMed Central PMCID: PMC7413844.
42. Dzik S, Eliason K, Morris EB, Kaufman RM, North CM. COVID-19 and ABO blood groups. Transfusion. 2020;60(8):1883-4. Epub 2020/06/21. doi: 10.1111/trf.15946. PubMed PMID: 32562280; PubMed Central PMCID: PMC7323215.
43. Al-Youha SA, Alduaij W, Al-Serri A, Almazeedi SM, Al-Haddad M, Jamal MH, et al. The impact of ABO blood groups on clinical outcomes and susceptibility to COVID-19: A retrospective study in an unselected population. Transfusion. 2021;61(5):1631-41. Epub 2021/03/09. doi: 10.1111/trf.16365. PubMed PMID: 33682150; PubMed Central PMCID: PMC8250670.
44. Dal MS, Ata N, Altuntaş F, Başçı S, Yiğenoğlu TN, Korkmaz S, et al. COVID-19 clinical course and blood groups: Turkish population-based study. Turkish journal of medical sciences. 2021;51(4):1659-64. Epub 2021/05/07. doi: 10.3906/sag-2101-321. PubMed PMID: 33957720.
45. Guillon P, Clement M, Sebille V, Rivain JG, Chou CF, Ruben-Clouet N, et al. Inhibition of the interaction between the SARS-CoV spike protein and its cellular receptor by anti-histo-blood group antibodies. Glycobiology. 2008;18(12):1085-93. Epub 2008/09/27. doi: 10.1093/glycob/cwn093. PubMed PMID: 18818423; PubMed Central PMCID: PMC7108609.
46. Valenti L, Villa S, Baselli G, Temporiti R, Bandera A, Scudeller L, et al. Association of ABO blood group and secretor phenotype with severe COVID-19. Transfusion. 2020;60(12):3067-70. Epub 2020/10/04. doi: 10.1111/trf.16130. PubMed PMID: 33009662; PubMed Central PMCID: PMC7675339.
47. Wang M, Gao J, Liu J, Zhao X, Lei Y. Genomic Association vs. Serological Determination of ABO Blood Types in a Chinese Cohort, with Application in Mendelian Randomization. Genes. 2021;12(7). Epub 2021/07/03. doi: 10.3390/genes12070959. PubMed PMID: 34202464; PubMed Central PMCID: PMC8306414.
48. Tregouet DA, Heath S, Saut N, Biron-Andreani C, Schved JF, Pernod G, et al. Common susceptibility alleles are unlikely to contribute as strongly as the FV and ABO loci to VTE risk: results from a GWAS approach. Blood. 2009;113(21):5298-303. Epub 2009/03/13. doi: 10.1182/blood-2008-11-190389. PubMed PMID: 19278955.
49. Ellis PJI. Modeling suggests ABO histo-incompatibility may substantially reduce SARS-CoV-2 transmission. Epidemics. 2021;35:100446. Epub 2021/03/12. doi: 10.1016/j.epidem.2021.100446. PubMed PMID: 33706041; PubMed Central PMCID: PMC7919530.
50. Latz CA, DeCarlo C, Boitano L, Png CYM, Patell R, Conrad MF, et al. Blood type and outcomes in patients with COVID-19. Annals of hematology. 2020;99(9):2113-8. Epub 2020/07/14. doi: 10.1007/s00277-020-04169-1. PubMed PMID: 32656591; PubMed Central PMCID: PMC7354354.
51. Badedi M, Makrami A, Alnami A. Co-morbidity and blood group type risk in coronavirus disease 2019 patients: A case-control study. Journal of infection and public health. 2021;14(4):550-4.Epub 2021/03/24. doi: 10.1016/j.jiph.2020.12.035. PubMed PMID: 33756193; PubMed Central PMCID: PMC7833201.
52. 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;190(1):24-7. Epub 2020/05/08. doi: 10.1111/bjh.16797. PubMed PMID: 32379894; PubMed Central PMCID: PMC7267665.