

ABO blood groups as determinants to patient outcomes in SARS-CoV-2

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ABSTRACT**Background**

Blood group antigens are present on the red blood cell surface. O, A, and B are the major blood groups. A, B, AB, and A1 are the antigens. An ample amount of research supports the close association of blood groups with diseases. A new school of thought and finding seems to be indicating that certain blood groups are more susceptible to the COVID-19 infection in comparison to others. Current evidence suggests that SARS-CoV-2 positive cases are more prevalent in individuals with blood group A as compared to those with blood group O. This finding, however, was only relevant for the Rh (+ve) positive blood types. Genetic association reveals that the ABO blood group locus and a chromosome 3 gene cluster are associated with severe acute respiratory syndrome in coronavirus (SARS-CoV-2) respiratory failure patients. This was found in an Italian-Spanish genome-wide association analysis. Various associations between the patients' blood groups when comparing the data with that of physiologically healthy individuals from the same geographical region helped to get a clear comparative picture. Associations that were cross-replicating in nature were determined at chromosome 3p21.31 and chromosome 9q34. The association at chromosome 9q34 was identified at the ABO blood group locus. The difference in the susceptibility could be correlated to the circulating anti-A antibodies, which inhibit or interfere with the virus-cell adhesion process

Conclusion

It is evident that the research conducted to date is supportive and does suggest that humans of the Blood group O are less likely to be infected in the COVID-19 pandemic as when compared to other blood groups. The SARS-CoV-2 situation is evolving rapidly, discoveries and anomalies are being reported daily. Therefore, it is advised that more definitive and consolidatory research is to be conducted to further elucidate the underlying mechanism of action for the protection in blood group O.

Keywords

A positive, Blood group, COVID-19, O positive, SARS-CoV-2, infection

Background

Blood Groups

The word "blood group" refers to the antigens present on the red blood cell (RBC) surface. Human blood groups are genetically determined and passed from parents to descendants. "Blood type" refers to a specific pattern of antigen-antibody reaction within a specified setting. The understanding of blood groups has evolved to include hazards linked to transfusion reactions and specific RBC surface antigen diseases. The International Blood Transfusion Society lists 33 blood group structures containing more than 300 antigens, which have been cloned and sequenced. Among the 33 systems, ABO remains as the mainstay for transfusion medicine for everyone over the age of six months, as they contain clinically significant anti-A and anti-B [1]. Austrian Scientist Karl Landsteiner was the pioneer of the ABO blood group system in 1900 [2]. O, A, and B types are the major blood groups. A, B, AB, and A1 are the antigens. Due to the different frequency of different ABO blood types among various populations, the ABO blood groups appear to be important during our evolution. This suggests that there is always a selection advantage for a specific blood type (e.g., resistance to an infectious disease). Although their clinical significance is well known, the physiological role of antigens in the ABO blood group remains a mystery. The second most crucial antigen in blood transfusions is the rhesus-system [3]. Currently, 50 identified blood type antigens are included in the Rh system, five of which are significant. An individual's RBC surface may or may not contain Rh or D-antigen; accordingly, Rh-positive (D-antigen present) or Rh-negative (D-antigen absent) blood group is indicated [4].

Blood groups and association with diseases

ABO antigens are expressed in several human tissues and cells, including epithelium, sensory neurons, platelets, and vascular endothelium. It is also simultaneously expressed as a surface molecule [5, 6]. It is, therefore, no wonder that the clinical relevance of an ABO blood group now reaches beyond the conventional frontiers of immunohematological understanding, where the pathogenesis of a wide variety of human diseases, primarily cancers and infectious, cardiovascular disorders are involved. Non-O blood group reveals that the risk of venous thrombosis is roughly doubled [7]. Non-O blood groups are plasma-related to FVIII and VWF and are approximately 25 percent higher than the O blood group subjects [8]. The risk of overall mortality in non-O blood groups is comparatively higher from cardiovascular disease when compared to individuals with the non-O blood groups [9, 10]. Individuals with blood group O are susceptible to stomach ulcers, and gastric cancer is predominant in blood group A. In comparison with blood group O, participants with blood group A, AB, or B are vulnerable to develop

pancreatic cancer [11]. O blood group individuals have a selective advantage against severe malaria [12].

Reduced resetting of *Plasmodium falciparum* isolates from group O is reported by Rowe et al. in contrast to other blood groups [13]. The ABO phenotype relates to the severity of a number of infectious diseases. The severity of Cholera infection (*Vibrio cholerae* strains O1 El Tor and O139) is most prominent amongst the O blood group [13, 14]. Outbreaks of gastrointestinal infections by *Escherichia coli* O157 in Scotland in 1996, was more aggravated in the O phenotype. The highest mortality was recorded (87.5%) amongst those individuals with the O phenotype [15].

COVID-19 pandemic and association with blood group

Coronavirus or (COVID-19) surfaced in the city of Wuhan located in China, at the end of 2019. This virus rapidly spread and caused the current global pandemic [16]. Health systems are under unprecedented pressure and are experiencing death counts in the hundreds of thousands [17]. As of today, the 27th of June 2020, the current global cases stand at a staggering 9,653,048 confirmed cases and a total of 491,128 deaths [18]. Numerous risk factors for COVID-19 have been reported. An increase in the patient's age has become synonymous with a rise in the risk of developing complications and has demonstrated higher death rates. Various studies have concluded that the male gender is more at risk and show more severe complications [19, 20]. Various comorbidities such as, inflammatory bowel disease (IBD) [21], pre-existing kidney disease [22], and diabetes mellitus [23] are documented risk factors. A new school of thought and finding is indicative that certain blood groups are more susceptible to the COVID-19 infection in comparison to others.

A study conducted by Zietz et al., in the New York-Presbyterian (NYP) group of facilities discovered that Blood group A was associated with increased odds of testing positive for COVID-19 (OR 1.338, 95% CI [1.072-1.672], $p=0.009$), while O blood groups were associated with decreased odds of testing positive (OR 0.804, 95% CI [0.654-0.987], $p=0.036$) [24]. This report follows previous research on SARS-CoV-2 by Cheng et al. The Authors documented substantially lower associations of blood group O among SARS patients when compared with non-O blood groups (OR, 0.18; 95% CI [0.04-0.81]). Although patients with blood group B exhibited chances of infection; it was however statistically insignificant (OR: 1.46) [25]. AB blood groups are to be associated with decreased odds of testing positive (OR 0.561, 95% CI [0.315-0.969], $p=0.033$). Ellinghaus et al. reported that patients with blood type A have a higher risk than other blood groups (OR, 1.45; 95% CI, 1.20-1.75; $P=1.48 \times 10^{-4}$) and for blood group O when compared with the other blood groups (OR, 0.65; 95% CI, 0.53-0.79; $P=1.06 \times 10^{-5}$) [26]. Considering the Rhesus antigen,

significant associations were only found in Rh-positive blood groups, but no relation between blood group and intubation or death was evident. A+ and O+ individuals were significantly associated. A lack of data available for negative Rh blood groups is currently a shortfall [24]. The Authors reported a significant odd decrease in odds for AB blood groups. Data produced by a meta-analysis from Wuhan and Shenzhen suggests that there is a new significant COVID-19 odds increase for B blood groups as when compared to the general population [24, 27].

Findings of Zietz et al. are further supported by Ellinghaus et al. on the ABO blood group locus and a chromosome 3 gene cluster associated with SARS-CoV-2 respiratory failure in an Italian-Spanish genome-wide association analysis. In this study, SARS-CoV-2 positive patients were included and underwent an analysis of their genomes for various associations. One thousand two hundred fifty-five controls were selected from Italy to undergo the same genome analysis. The total SNPs single-nucleotide polymorphisms detected were 8,582,968. Associations that were cross-replicating in nature were determined at chromosome 3p21.31 and chromosome 9q34.

The association at chromosome 9q34 was identified at the ABO blood group locus. After further investigation, it was shown that blood group A positive individuals were at an increased risk to the infection. [24, 26] Ellinghaus et al. reported that two loci have a strong association with Covid-19-induced respiratory failure with genome-wide significance: the rs11385942 insertion-deletion GA or G variant at locus 3p21.31 (OR for the GA allele, 1.77; 95% CI, 1.48-2.11; $P=1.15 \times 10^{-10}$) and the rs657152 A or C SNP at locus 9q34.2 (OR for the A allele, 1.32; 95% CI, 1.20-1.47; $P=4.95 \times 10^{-8}$) [26]. Zhao et al. also reported that 2173 COVID-19 positive patients showed that members of blood group A were at an increased risk of acquiring the virus. More research must be undertaken in order to further understand the reason behind this phenomenon [27]. Göker et al. reported that blood group A was (57%) higher amongst the COVID-19 patients followed by the blood group O (24.8%), the author added that clinical outcomes were not affected by the blood groups of the patients [28].

Postulated Mechanism

The coronavirus' diameter ranges between 65-125 nm [29]. It is an enveloped virus that has a single-stranded positive-sense RNA nucleic acid. This positive-sense RNA nucleic acid measures 26-32 kilobases. It is the virus with the largest known genome [30]. The virus has an outer layer of Spike glycoprotein molecules; these are implicated in the attachment of the virus to the host cells. This spike glycoprotein molecule layer also facilitates the fusion of the virus to the host cells', cell membrane. However, it was found that the spike glycoprotein shows more sequence variation than any other structural protein within the coronavirus species [29]. Research conducted

by Guillon et al., on the SARS-CoV spike protein in 2008, forms the basis of the mechanism by which various Blood groups could be more at risk to the family of SARS-CoV viruses. A model of cellular adhesion is proposed, whereby the antibodies of the ABO blood group could decrease the interactions between the virus and the receptor. COVID-19 can replicate in cells that contain blood group type antigens. Once released from an infected patient, the virus is coated with the particular blood group antigens of the infected patient. If the patient with the type A blood group would infect another healthy human with blood group O blood, the blood group O individual will have natural antibodies to the antigen on the virus. This does not hold true if the human being infected is also of blood group A as no antibodies will be present [31, 32].

Past research has shown the association regarding occurrence and mortality in cardiovascular disorders amongst O blood group and non-O variants in venous thrombosis, FVIII and VWF etc. [7, 9, 10]. In COVID-19, it was observed that the micro thrombosis developed in pulmonary vascular beds led to a serious consequence in acute respiratory syndrome; therefore, the use of prophylactic anticoagulants was included in the guidelines when cardiovascular disorders are involved. The non-O blood group reveals that the risk of venous thrombosis is roughly doubled [7]. Non-O blood groups are plasma-related to FVIII and VWF and are approximately 25 percent higher chance than O blood group subjects [8]. The risk of overall mortality in non-O blood groups is comparatively higher from cardiovascular disease as when compared with to the non-O blood groups [9, 10].

Conclusion

It is evident that the research conducted to date is supportive and does suggest that humans of the Blood group O are less likely to be infected than other blood groups. The SARS-CoV-2 situation is evolving rapidly, and discoveries and anomalies are being reported daily. Therefore, it is advised that more definitive and consolidatory research at the molecular level needs to be conducted before the blood groups of certain patients can be added to the list of risk factors associated with SARS-CoV-2. Prospective larger multicenter studies may be beneficial in this context to further elucidate the underlying mechanism of action for the protection in blood group O.

Abbreviations

Severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2), Coronavirus disease (COVID-19), World Health Organization (WHO)

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Authors' contribution

- a. Study planning: IB
- b. Manuscript writing: JR, IB, BR
- c. Manuscript revision: BR, IB
- d. Final approval: JR, IB, BR, BS, AL
- e. Agreement to be accountable for all aspects of the work: JR, IB, BR, BS, AL

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