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The Possible Relationship Between ABO and Rhesus System Phenotypes and SARS-CoV-2 Infection

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ABSTRACT

Background: The relationship between blood Rhesus factor and SARS-CoV-2 viral infection has recently been revealed by several studies; however, the underlying mechanism is still unclear. An intriguing finding was the very low viral infection rate among blood Rhesus-negative people (notably O(I) and Rh-) and the high vulnerability in Rh-positive infected patients.

Objectives: The current study aimed to find a possible relationship between Rh blood groups and susceptibility to the SARS-CoV-2 viral infection. Based on the results of the comparison of ABO and Rh blood group phenotypes in uninfected (healthy) and post-infection individuals, we were able to identify SARS-CoV-2 susceptible or resistant phenotypes.

Methods: A total of 447 blood samples were examined, including 333 from SARS-CoV-2 post-infection patients and 114 from healthy controls within four months (from January 28, 2021, to April 30, 2021).

Results: The distribution of phenotypic categories for Rhesus positive (Rh+) and Rhesus negative (Rh-) individuals in the control and post-infection groups has been demonstrated to be identical. There was no correlation between the Rhesus factor and susceptibility to SARS-CoV-2 virus infection. However, there was a significant correlation between the combination of two variables (the Rh and ABO groups) and SARS-CoV-2 susceptibility. Particularly, the frequency of the O(I) and Rh- phenotypes was approximately 1.4 times lower in the post-infection period than in controls. In contrast, patients in the post-infection period exhibit the largest prevalence of the A(II)Rh+ phenotypic combination.

Conclusions: The SARS-CoV-2 infection susceptibility is low in people with the O(I)Rh- phenotype and high in individuals with the A(II)Rh+ phenotype.

Keywords: COVID-19; Rh blood group; SARS-CoV-2 viral infection.

BACKGROUND

Blood group antigens are carbohydrates or proteins attached to the surface of red blood cells (RBC). The AB0 blood group antigen chemically belongs to carbohydrates, and their formation requires a series of enzymatic reactions. Rh blood group-specific antigens are proteins.[1] Blood group antigens are evolutionary-established characteristics that determine the adaptation of human beings as biological species (Homo sapiens) to the surrounding environment.[2]

Blood group antigens are ancient biomarkers that have been established evolutionarily. There are several hypotheses describing the development of blood group antigens.[3] One of the most popular hypotheses is that the prototype blood group was AB(IV). A(II), B(III), and the last O(I) blood groups have been formed due to several allele-specific inherited mutations.[2]

The distribution of blood groups varies according to geographic regions and is the result of the so-called "genogeographic adaptation" of different types of ecosystems.[4,5] Numerous scientific publications show that ABO blood group antigens are associated with pandemics and infectious diseases such as the black plague, cholera, and measles.[1,5,6]

The pandemic SARS-CoV-2 is a respiratory virus that is spreading very easily with a high risk of severe complications, including death.[7,8]

Numerous medical and sociodemographic risk factors can affect the incidence of viral infections and are associated with both the onset and severity of COVID-19.[9-15]

Identifying additional risk factors is the most important step in prevention. The erythrocyte ABO and Rh blood groups may also play a potential role in the immunopathogenesis of the SARS-CoV-2 viral infection.[16] The majority of recent studies have revealed a higher proportion of blood group A(II) and a lower proportion of blood group O(I) among COVID-19 patients compared to healthy controls. However, group A patients have a higher incidence of major comorbidities, which is considered to be one of the contributors to COVID-19 complications.[17-19]

Despite evidence from several studies demonstrating a correlation between blood Rh factor and SARS-CoV-2 infection, the precise mechanism of this relationship is still

unclear. Rhesus-negative individuals (especially O(I) and Rh) showed a fairly low rate of infection.[20] The data from New York City suggest that the Rhesus-negative phenotype may also be protective.[21] Individuals with a Rh-positive but not a Rh-negative blood group are more vulnerable to the SARS-CoV-2 viral infection.[22] The current study aims to investigate the relationship between blood groups and SARS-CoV-2-infected patients.

METHODS

447 blood samples in total have been analyzed in the study period from January 28, 2021, to April 30, 2021. 2 ml of whole blood drawn from a peripheral vein in special test tubes of EDTA K3 served as the primary source of the sample after being assigned a special code for each sample.

The majority of the studied materials (n=333) belonged to SARS-CoV-2 post-infection individuals with (i) verified SARS-CoV-2 viral infection by a rapid (antigen/antibody) or PCR test and (ii) less than one month after the SARS-CoV-2 virus infection.

The control group (n=114) consisted of individuals who (i) were not infected with the SARS-CoV-2 virus during the collection of the study materials and (ii) were not vaccinated (the vaccination process in our country started on March 15, 2021). Written informed consent was received from all participants before study initiation. The protocol of the study was approved by the ethics committee of the school of medicine and health sciences at Batumi International University (BAU). The control group and the post-infection cohort had similar baseline data.

We used direct immuno-serological forward and reverse methods with anti-A, anti-B, anti-AB, anti-C, anti-c, anti-D, anti-E, and anti-e monoclonal antibodies for ABO and Rh blood typing (Bio-Rad, Cypress Diagnostics). The blood type procedures were carried out at the Immunogenetics Laboratory of Batumi Shota Rustaveli State University's (BSU, Batumi, Georgia) and the Microbiologic Laboratory of Batumi International University's (BAU, Batumi, Georgia).

The differences between the cohort of post-infection patients and the control group were assessed by the Chi-square (χ^2) analysis. A statistical significance was taken as a $p<0.05$.

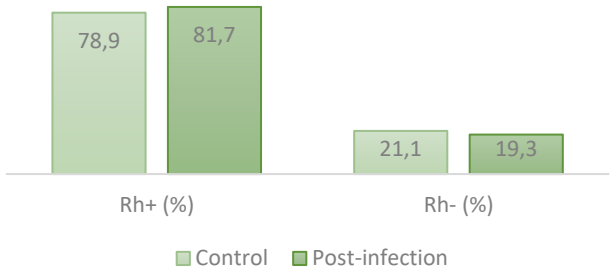
RESULTS

At the initial stage of our study, we checked the associations between the presence of Rhesus factors (Rhesus-positive and Rhesus-negative) and SARS-CoV-2 susceptibility.

As can be seen from Figure 1, the distribution of the mentioned phenotypes is almost identical in the control and post-infection groups.

The equal distribution of Rhesus phenotypes refuses a possible correlation between Rhesus factor and SARS-CoV-2 susceptibility (chi square is 0.2867, p-value is 592363, the results are not reliable $p<0.05$).

FIGURE 1. Phenotypic groups of the Rhesus system in the post-infection and control groups



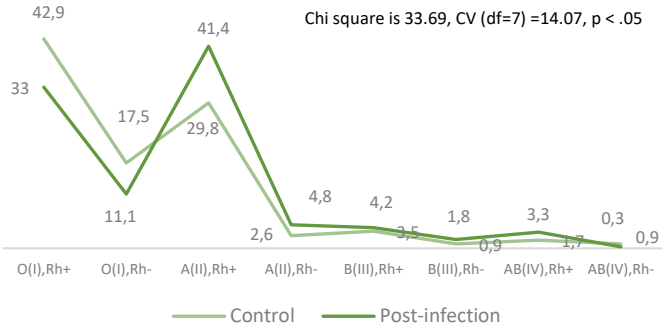
Abbreviations: Rh+, Rhesus-positive phenotype; Rh-, Rhesus-negative phenotype.

In the second stage of the current study, we evaluated the correlation between the phenotypic combinations of the Rhesus and ABO blood group systems and SARS-CoV-2 susceptibility.

Eight combinations (O(I)Rh-; O(I)Rh+; A(II)Rh-; A(II)Rh+; B(III)Rh-; B(III)Rh+; AB(IV)Rh-; and AB(IV)Rh+) of ABO and Rh systems were studied in post-infection and control groups.

Figure 2 depicts the distribution of the above-mentioned combinations in both groups.

FIGURE 2. ABO and Rh system combinations in the post-infection and control groups



Abbreviations: Rh+, Rhesus-positive phenotype; Rh-, Rhesus-negative phenotype.

There were only two statistically significant differences between the post-infection cohort and the control group: the high prevalence of the A(II)Rh- phenotype in the cohort of patients and the O(I)Rh+ phenotype in the control group (41.4% vs. 29.8% and 33% vs. 42.9%, respectively).

DISCUSSION

The majority of blood group antigens are found on red blood cells, thrombocytes, leukocytes, plasma proteins, and some epithelial tissues.[1]

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The Rhesus (Rh) blood group system is one of the most complex, polymorphic, and immunogenic systems of our body and consists of approximately 45 independent antigens.[23]

It is known that the ABO and Rh blood group systems are linked with infection, malignancy, and coagulation. Rhesus-negative subjects were reported to have more frequent allergic, digestive, cardiovascular, hematological, immune, mental health, and neurological problems.[24]

Several studies investigating possible relationships between blood types, SARS-CoV-2 susceptibility, and the severity of COVID-19 disease have been conducted during the past two years.

According to the results of the current study, Rh+ and Rh- phenotypes were equally distributed in the control and post-infection groups (chi-square is 0.2867, the p-value is 592363, and the results are not reliable $p<0.05$). Particularly in the control group, the prevalence rate of the Rh-positive phenotype was 78.9% and the Rh-negative phenotype was 21.1%, while in the post-infection group, the prevalence rates of the Rh+ and Rh- phenotypes were 81.7% and 18.8%, respectively. These results allowed us to conclude that there is no correlation between the Rhesus factor and SARS-CoV-2 susceptibility.

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In our previous work, we demonstrated an association between ABO blood types and SARS-CoV-2 infection.[25] Evaluating the relationship between combined ABO and Rhesus phenotypes and SARS-CoV-2 susceptibility, we found some statistically significant correlations. Particularly, the O(I)Rh-phenotypic group was presented at approximately 1.4 times lower frequency in post-infection individuals than the controls. This fact gives the O(I)Rh- group the status of a relatively resistant phenotype to the SARS-CoV-2 infection. On the other side, the prevalence of the A(II)Rh+ phenotypic combination was higher in the group of post-infection patients than in the controls. This indicates that this phenotype is more susceptible to SARS-CoV-2 virus infection.

Our findings are consistent with those of other authors. In a single-center, retrospective investigation, Rana and colleagues[26] hypothesized that blood groups O, AB, and Rh-negative are less likely to be infected with SARS-CoV-2 infection than blood groups A, B, and Rh+. The cited authors found no association between blood types and COVID-19 disease severity or mortality.

Zeits and co-authors suggested that blood type is important for the risk of infection, intubation, and death.[21] They predict that all three outcomes are less likely for Rh-negative individuals. A protective relationship between Rh-negative blood types and SARS-CoV-2 infection, intubation, and death was also suggested by them.

There are several hypotheses that explain why Rh-negative individuals are more resistant to viral infections. One of the most well-known is that those who are Rh-negative are more likely to develop a variety of cardiac and respiratory conditions, as well as some immunological and autoimmune disorders, like rheumatoid arthritis. According to the global population pattern, Rh-negative people may struggle with autoimmunity, may be more resistant to viral infections, and conversely, may be less resistant to illnesses of bacterial origin.[24]

There are alternative suggestions by several authors.[27] Laurys and coauthors didn't find any relationship between blood group and infection rate.

We think that larger sample sizes or meta-analyses are required to estimate these effects more clearly. We hope that our findings will be used in meta-analyses.

CONCLUSIONS

According to the findings of the present study, there was no correlation between the Rhesus blood group and SARS-CoV-2 susceptibility. On the other hand, the highest prevalence of the A(II)Rh+ and lowest O(I)Rh- phenotypic combinations are found among patients in the post-infection period. Due to this, the O(I)Rh- the group might be classified as relatively resistant to SARS-CoV-2 infection. On the other hand, SARS-CoV-2 virus infection is more likely to affect the O(I)Rh- phenotype.

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REFERENCES

1. Ewald, D.R., Sumner, S.C.J., 2016a. Blood type biochemistry and human disease. WIREs Syst. Biol. Med. 8, 517–535. https://doi.org/10.1002/wsbm.1355.
2. Farhud, D.D., Zafir Yeganeh, M., 2013. A Brief History of Human Blood Groups. Iran. J. Public Health 42, 1–6.
3. Ségurel, L., Gao, Z., Przeworski, M., 2013. Ancestry runs deeper than blood: The evolutionary history of ABO points to cryptic variations of functional importance. BioEssays 35, 862–867. https://doi.org/10.1002/bies.201300030.
4. Daniels, G., 1999. Functional aspects of red cell antigens. Blood Rev. 13, 14–35. https://doi.org/10.1016/S0268-960X(99)90020-6.
5. Cooling, L., 2015. Blood Groups in Infection and Host Susceptibility. Clin. Microbiol. Rev. 28, 801–870. https://doi.org/10.1128/CMR.00109-14.

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6. Liumbruno, G.M., Franchini, M., 2013. Beyond immunohaematology: the role of the ABO blood group in human diseases. Blood Transfus. https://doi.org/10.2450/2013.0152-13.
7. Stower, H., 2020. Spread of SARS-CoV-2. Nat. Med. 26, 465–465. https://doi.org/10.1038/s41591-020-0850-3.
8. Wu, Y.-C., Chen, C.-S., Chan, Y.-J., 2020. The outbreak of COVID-19: An overview. J. Chin. Med. Assoc. 83, 217–220. https://doi.org/10.1097/JCMA.0000000000000270.
9. Hu, S., Wang, W., Wang, Y., Litvinova, M., Luo, K., Ren, L., Sun, Q., Chen, Xinghui, Zeng, G., Li, J., Liang, L., Deng, Z., Zheng, W., Li, M., Yang, H., Guo, J., Wang, K., Chen, Xinhua, Liu, Z., Yan, H., Shi, H., Chen, Z., Zhou, Y., Sun, K., Vespignani, A., Viboud, C., Gao, L., Ajelli, M., Yu, H., 2021. Author Correction: Infectivity, susceptibility, and risk factors associated with SARS-CoV-2 transmission under intensive contact tracing in Hunan, China. Nat. Commun. 12, 2561. https://doi.org/10.1038/s41467-021-23108-w.
10. Vena, A., Berruti, M., Adessi, A., Blumetti, P., Brignole, M., Colognato, R., Gaggioli, G., Giacobbe, D.R., Bracci-Laudiero, L., Magnasco, L., Signori, A., Taramasso, L., Varelli, M., Vendola, N., Ball, L., Robba, C., Battaglini, D., Brunetti, I., Pelosi, P., Bassetti, M., 2020. Prevalence of Antibodies to SARS-CoV-2 in Italian Adults and Associated Risk Factors. J. Clin. Med. 9, 2780. https://doi.org/10.3390/jcm9092780.
11. Goldstein, E., Lipsitch, M., Cevik, M., 2021. On the Effect of Age on the Transmission of SARS-CoV-2 in Households, Schools, and the Community. J. Infect. Dis. 223, 362–369. https://doi.org/10.1093/infdis/jiaa691.
12. Mahallawi, W.H., Alsamiri, A.D., Dabbour, A.F., Alsaeedi, H., Al-Zalabani, A.H., 2021. Association of Viral Load in SARS-CoV-2 Patients with Age and Gender. Front. Med. 8, 608215. https://doi.org/10.3389/fmed.2021.608215.
13. Fadini, G.P., Morieri, M.L., Longato, E., Avogaro, A., 2020. Prevalence and impact of diabetes among people infected with SARS-CoV-2. J. Endocrinol. Invest. 43, 867–869. https://doi.org/10.1007/s40618-020-01236-2.
14. Schiffrin, E.L., Flack, J.M., Ito, S., Muntner, P., Webb, R.C., 2020. Hypertension and COVID-19. Am. J. Hypertens. 33, 373–374. https://doi.org/10.1093/ajh/hpaa057.
15. Zhou, F., Yu, T., Du, R., Fan, G., Liu, Y., Liu, Z., Xiang, J., Wang, Y., Song, B., Gu, X., Guan, L., Wei, Y., Li, H., Wu, X., Xu, J., Tu, S., Zhang, Y., Chen, H., Cao, B., 2020. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet 395, 1054–1062. https://doi.org/10.1016/S0140-6736(20)30566-3.
16. Zietz, M., Zucker, J., Tatonetti, N.P., 2020a. Testing the association between blood type and COVID-19 infection, intubation, and death (preprint). Infectious Diseases (except HIV/AIDS). https://doi.org/10.1101/2020.04.08.20058073.
17. Muñiz-Diaz, E., Llopis, J., Parra, R., Roig, I., Ferrer, G., Grifols, J., Millán, A., Ene, G., Ramiro, L., Maglio, L., García, N., Pinacho, A., Jaramillo, A., Peró, A., Artaza, G., Vallés, R., Sauleda, S., Puig, Ll., Contreras, E., 2021. Relationship between the ABO blood group and COVID-19 susceptibility, severity and mortality in two cohorts of patients. Blood Transfus. https://doi.org/10.2450/2020.0256-20.
18. Zhao, J., Yang, Y., Huang, H., Li, D., Gu, D., Lu, X., Zhang, Z., Liu, L., Liu, T., Liu, Y., He, Y., Sun, B., Wei, M., Yang, G., Wang, X., Zhang, L., Zhou, X., Xing, M., Wang, P.G., 2020. Relationship between the ABO Blood Group and the COVID-19 Susceptibility (preprint). Epidemiology. https://doi.org/10.1101/2020.03.11.20031096.
19. Golinelli, D., Boetto, E., Maietti, E., Fantini, M.P., 2020. The association between ABO blood group and SARS-CoV-2 infection: A meta-analysis. PLOS ONE 15, e0239508. https://doi.org/10.1371/journal.pone.0239508.
20. Ray, J.G., Schull, M.J., Vermeulen, M.J., Park, A.L., 2021. Association Between ABO and Rh Blood Groups and SARS-CoV-2 Infection or Severe COVID-19 Illness: A Population-Based Cohort Study. Ann. Intern. Med. 174, 308–315. https://doi.org/10.7326/M20-4511.
21. Zietz, M., Zucker, J., Tatonetti, N.P., 2020b. Associations between blood type and COVID-19 infection, intubation, and death. Nat. Commun. 11, 5761. https://doi.org/10.1038/s41467-020-19623-x.
22. Taha, S.A.H., Osman, M.E.M., Abdoelkarim, E.A.A., Holie, M.A.I., Elbasheir, M.M., Abuzeid, N.M.K., Al-Thobaiti, S.A., Fadul, S.B., Konozy, E.H.E., 2020. 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 New Infect. 38, 100763. https://doi.org/10.1016/j.nmni.2020.100763.
23. Avent, N.D., Reid, M.E., 2000. The Rh blood group system: a review. Blood 95, 375–387. https://doi.org/10.1182/blood.V95.2.375.
24. Flegr, J., Hoffmann, R., Dammann, M., 2015. Worse Health Status and Higher Incidence of Health Disorders in Rhesus Negative Subjects. PLOS ONE 10, e0141362. https://doi.org/10.1371/journal.pone.0141362.
25. Nagervadze, M., Tsintsadze, I., Akhvlediani, L., Koiava, T., Tskvitinidze, S., Khukhunaishvili, R., Koridze, M., 2021. ABO system combination with Rh, Kell and MN group in Georgian blood donors. Am. J. Blood Res. 11, 132–139.
26. Rana, R., Ranjan, V., Kumar, N., 2021. Association of ABO and Rh Blood Group in Susceptibility, Severity, and Mortality of Coronavirus Disease 2019: A Hospital-Based Study from Delhi, India. Front. Cell. Infect. Microbiol. 11, 767771. https://doi.org/10.3389/fcimb.2021.767771.
27. Laurys Boudin, Frédéric Janvier, Olivier Bylicki, Fabien Dutasta, 2020. ABO blood groups are not associated with risk of acquiring the SARS-CoV-2 infection in young adults. Haematologica 105, 2841–2843. https://doi.org/10.3324/haematol.2020.265066.

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