ORIGINAL ARTICLE

Role of ABO Blood Groups in Susceptibility and Severity of COVID-19 in the Georgian Population

Levan Ratiani[1], Tamar V Sanikidze[2], George Ormotsadze[3], Elene Pachkoria[4], Giga Sordia[5]

Abstract

Aim and objective: The establishment of the potential role of the infected people's ABO blood type in the virus infectivity and aggressivity could clarify the aspects of the various susceptibility to virus and play a key role in assessing its spreading potential in the future. We studied the possible association of risk of coronavirus disease-2019 (COVID-19) infection and severe outcomes of disease with ABO blood groups and Rh factor in the Georgian population.

Materials and methods: The effect of blood type on the severity of infection in COVID-19 positive patients admitted to the First University Clinic of Tbilisi State University (Tbilisi, Georgia) from December 2020 to September 2021 was analyzed retrospectively. The odds ratio (OR) criterion was used to determine the influence of the blood group on the risk of COVID-19 infection and of severe course of the disease.

Results: The incidence of COVID-19 was 1.65-fold higher in the patients with blood group II(A), and average twice lower in patients with blood groups III(B) and IV(AB), compared with the ABO blood group distribution in healthy donors of the region. The percentage of patients transferring in ICU with I(O) and II(A) blood groups was enough high (42–40%), whereas in patients with III(B) and IV(AB) blood groups very low (12–6%). There were not revealed any statistically significant differences in the distribution of the patients with Rh+ and Rh− blood groups in healthy and COVID-19 infected individuals (including those transferred in the ICU).

Conclusion: The link between patients' ABO blood groups and receptivity to COVID-19 infection, progression and severity of the disease, has been detected. These results are relevant in terms of elucidating the mechanisms and risk factors of infecting and severity course of COVID-19 disease.

Keywords: AOB blood groups, COVID-19, Rhesus factor, Severity of disease.

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Introduction

Coronavirus disease-2019 (COVID-19) pandemic has led to over 100 million cases and 2 million deaths worldwide.[1] The rapid spread of the disease has inflicted immense strains on healthcare and testing resources.[2,3] Therefore, identifying high-risk groups of COVID-19 has significance in controlling the pandemic.

During the epidemic progression degree of COVID-19, contagiousness and lethality differs by geographical location. The spread of the virus showed important variability in different countries. It is especially difficult to understand if these patterns are the consequence of ethnical heterogeneity of the population or differences in climate's geographical characteristics (temperature and humidity), or are related to the comorbidities (hypertension, obesity), and age distribution. There are not determined biological biomarkers predicting the risk of being infected, severity or outcome of the disease.

The observed variability in sensitivity to COVID-19 and severity of the disease development has raised great interest in their environmental and genetic risk factors.

Blood types are associated as a risk factor in the development of many diseases, including venous and arterial thromboembolism.[4] Many previous researches suggested connection between blood group and infectious diseases. The widest range of studies reveal these associations with infectious diseases. Information and knowledge about previous viral infections could contribute to the understanding of the observed heterogeneity.[5] Blood groups were identified as factor determining susceptibility to various microorganisms such as bacteria, viruses, parasites, and fungi.[6]

The blood group antigens (ABO) found in erythrocytes and other tissues interact with microorganisms—they can be considered as part of the innate immune system against some bacterial pathogens and enveloped viruses.[7] It was shown that some of the infectious agents, like Helicobacter pylori, Vibrio cholera, hepatitis C virus, human immunodeficiency virus, SARS, are associated with human blood groups.[6] The ABO gene is highly polymorphic, and ABO blood groups have various geographical and ethnic distribution. Strong geographical ancestry dependence of blood groups could be one of the factors underlying the heterogenic spread of epidemics.

Several clinical studies show an association between ABO blood types and the risk of COVID-19 infection, although the data in this area are quite contradictory. According to early report from

[1,4,5]First University Clinic of Tbilisi State Medical University, Tbilisi, Georgia

[2]Department of Physics, Biophysics, Biomechanics, Informative Technologies, Tbilisi State Medical University, Tbilisi, Georgia

[3]Laboratory of Radiation Safety Problems, Beritashvili Center of Experimental Biomedicine, Tbilisi, Georgia

Corresponding Author: Tamar V Sanikidze, Department of Physics, Biophysics, Biomechanics, Informative Technologies, Tbilisi State Medical University, Tbilisi, Georgia, Phone: +778899000, e-mail: tsanikidze@tsmu.edu

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China, blood group A was associated with increased vulnerability and blood group O was associated with reduced vulnerability to SARS-CoV-2 infection. The same results were observed in the reports of Italy and Spain. In contrast, a Danish study implicated disease sensitivity but not severity. Observations from Boston, Massachusetts, and New York did not reveal any specific associations between the ABO blood group and disease.[8] The establishment of the role of the blood types in the susceptibility to Covid-19 infection is significant for understanding its molecular mechanisms and prevention of viral infections.

The establishment of the possible role of the infected people's ABO blood type in both virulence and aggressivity could explain the aspects of the various susceptibilities to virus and play a key role in evaluating its spreading potential in the future.

Hence, the aim of our study was to identify the possible association of risk of COVID-19 infection and its severity with ABO blood groups and Rh factor in the Georgian population.

Materials and Methods

To establish the role of an individual's ABO blood groups in the likelihood of infection with COVID-19 and the severity of the course of the disease, in this study, we compared the blood groups of patients with COVID-19 infection, who were admitted for hospitalization and healthy donors from the same region. The distribution of AB0 blood groups among patients with COVID-19 was compared with the literature data of the distribution of the ABO groups in the population of Georgia.[9,10]

Patients

Patients with COVID-19 were diagnosed with a positive result of the PCR test for SARS-CoV-2 RNA. A total of 4,043 patients with a positive (COVID-19 positive patients) and 520 patients with a negative (COVID-19 negative patients) test admitted to the First University Clinic from December 2020 to September 2021 were analyzed; the patients' ABO blood group information was also collected. From the COVID-19 positive patients, 493 were transferred to the Intensive Care Unit (ICU) (Tables 1 and 2).

Table 1: Distribution of COVID-19 negative, COVID-19 positive patient and COVID-19 positive patients with severe course of disease in ICU, admitted to First University Clinic of Tbilisi State University (December 01, 2020–August 31, 2021), according to ABO blood groups

	All groups	*COVID-19 negative*	*COVID-19 positive*	*COVID-19 positive ICU*
O(I)	2,060	240	1,820	208
A(II)	1,676	120	1,556	196
B(III)	565	100	465	60
AB(IV)	262	60	202	29
All groups	4,563	520	4,043	493

Table 2: Chances of COVID-19 infection, disease complication (transferred into ICU) in group II, III, and group IV patients compared with group I blood group patients

	OR for infection	*OR ratio for ICU*
A(II) vs O(I)	1.71; $p < 0.001$	1.89; $p < 0.001$
B(III) vs O(I)	0.67; $p = 0.00 < 1$	0.70; $p = 0.50$
AB(IV) vs O(I)	0.56; $p < 0.001$	0.56; $p = 0.02$

The retrospective case series study was performed. Patients were not directly involved in the plan design, conduction of the research procedures or the measurements. No patients were asked the written consent on participation in the study and clarification of the results.

Statistical Analysis

To study the impact of blood type on the risk of the COVID-19 infection and severe outcomes, the distribution of blood groups was compared between COVID-19 positive individuals and COVID-19 patients' sample who were admitted to the intensive care unit (ICU).

The odds ratio (OR) criterion was used to evaluate relationship between blood group and the risk of COVID-19 infection and the probability of the disease severity. In particular, the chances of infection and disease exacerbation in blood group II(A), III(B), IV(AB) patients were compared to the chance of infection and disease exacerbation in blood group I(O) patients. The null hypothesis (H0) was tested that in the II(A), III(B), and IV(AB) blood group patients the ratio of COVID-19 positive and COVID-19 negative patients did not differ from the similar ratio in the patients with the I(O) blood group:

$$OR_i = \frac{N_i^{pos}/N_i^{neg}}{N_I^{pos}/N_I^{neg}}$$

Test of significance—the *p*-value is calculated according to[11]

Results

According to the results of our studies, the frequency of distribution of AB0 blood groups among PCR-tested 4563 persons admitted to the First University Clinic of Tbilisi State Medical University was: I(O)—45%, II(A)—37%, III(B)—12%, IV(AB)—6% (Table 1). This distribution is very close to the literature data concerning the distribution by blood groups of the Georgian population [I(O)—46%, II(A)—37%, III(B)—12%, IV(AB)—5%].[9]

Assuming that the patients admitted to the First University Clinic of Tbilisi State Medical University are representative of the major population by ABO blood groups (i.e., reflect the distribution of the population of Georgia by ABO blood groups), and that blood type does not affect both the infection risk and the severity of the disease, it would be expected that the distribution of ABO blood groups in COVID-19 negative patients would be approximately the same as in a cohort of COVID-19 positive patients. However, the diagram presented in Figure 1 clearly shows that this pattern is not confirmed—if the percentage of COVID-19 negative and COVID-19 positive patients in the I(O) blood group is approximately the same (46–45% of tested representatives), the percentage of persons with II(A) blood group among COVID-19 positive patients is about 1,65-fold higher, and in the III(B) and IV(AB) blood groups—on average, almost twice less than the COVID-19 negative patients. Based on this data, it can be assumed that individuals of the II(A) blood group belong to the high-risk group in terms of COVID-19 infection, while patients of the third and fourth groups belong to the relatively low-risk group.

The statistical validity of the revealed regularity was checked using the odds ratio (OR) criterion [ratio of the event in one group versus the event in the other group; OR 1.0 indicates that there

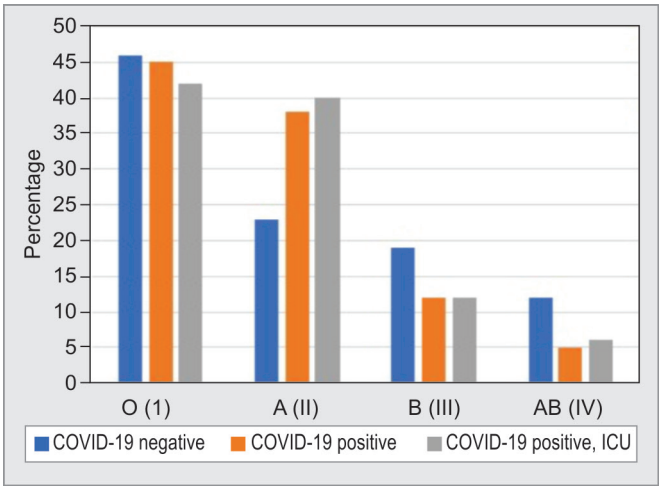

Fig. 1: Distribution of COVID-19 negative, COVID-19 positive, and COVID-19 positive patients transferred in the ICU, admitted to the First University Clinic of Tbilisi State University (December 01, 2020–August 31, 2021 period) by OAB blood groups

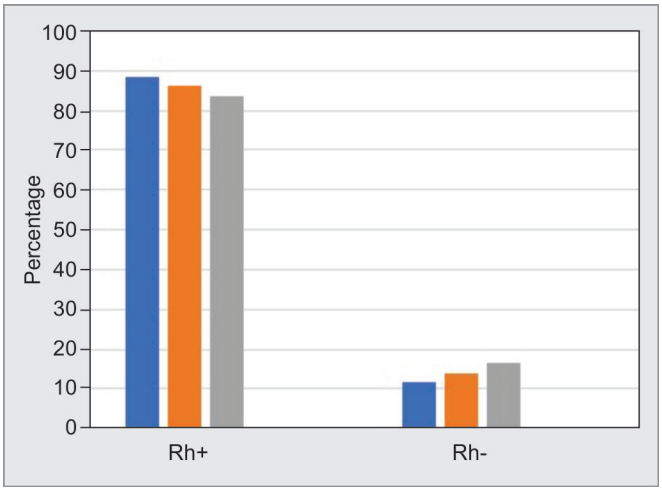

Fig. 2: Distribution of COVID-19 negative, COVID-19 positive, and COVID-19 positive patients transferred in the ICU, admitted to the First University Clinic of Tbilisi State University (December 01, 2020–August 31, 2021 period) by Rh-positive and Rh-negative

is no difference in risk (or odds) between the compared groups], which confirmed the high degree of reliability of the detected regularity (Table 2).

Analysis of the COVID-19 positive patients transferred in the ICU of the First University Clinic of Tbilisi State Medical University showed that the percentage of transferring patients with I(O) and II(A) blood groups was enough high (42–40%, respectively), whereas in patients with III(B) and IV(AB) blood groups—very low (12–6% of all COVID-19 positive representatives, respectively) (Table 1, Fig. 1). The statistical validity of the revealed regularity was checked using the OR criterion, which confirmed the high degree of reliability of the detected regularity (Table 2).

Analysis of the distribution of Rh-positive and Rh-negative blood groups between healthy and COVID-19 infected individuals (including those transferred in the ICU) who underwent PCR-test at First University Clinic did not reveal statistically significant differences in the infection rate and severity of the disease (transferring in the ICU) between the Rh groups (Fig. 2).

Discussion

Advanced age, comorbidities, history of past infections, gender, and abnormalities in some laboratory values are known as risk factors for morbidity and mortality in the COVID-19 infection development.[12–16] The pathogenesis and prognostic criterion of COVID-19 disease is not still fully known; furthermore, biological factors that determine susceptibility to COVID-19 and the severity of the disease outcome is yet to be fully understood.

The surface of red blood cells is coated with antigens (glycated proteins and lipids). The gene encoded glycosyltransferase is responsible for the transport of N-acetyl D-galactosamine [group II(A)] or D-galactose [group III(B)] and glycation of the corresponding groups on the erythrocytes' membrane. The presence of only A or B antigens on the membrane surface assigns erythrocyte to group II(A), or group III(B), respectively, the group I(O) phenotype results from the inactivation of the glycosyltransferase gene and the nonreduced ends of the corresponding groups;[17] the presence of both A and B antigens on the surface of the erythrocyte assigns it to group IV(AB). At the same time in blood plasma reciprocal antibodies are presented: group B antibody in the plasma of the I(A) blood group, group A antibody in the plasma of the III(B) blood group, both A and B antibodies—in the plasma of the I(O) blood group. On the surface of each erythrocytes' membrane in addition to blood groups, antigens (A, B, Rh+, Rh– and other) are located.

The presence of the antigens on the surface of the cell's membrane provides a further protein–protein interaction that supports vital functions, like signal transduction and protection. It was found that ABO polymorphism is associated with susceptibility to different microbial and virus infections. Supposedly protection against pathogens determined evolution of antigens' glycated group interactions.

The relationship between ABO blood groups and COVID-19 risk was evaluated,[18] but there is not enough evidence in this respect; correlation between blood types and mortality is not clear yet.

In our study, the link between receptivity to COVID-19 infection, progression, and severity of the disease, and patient's ABO blood type (Rh+, Rh–) has been investigated. We found that ABO blood groups are related to different risks for the COVID-19 infection. In our study, the prevalence of COVID-19 was highest in the patients with II(A) blood group, and significantly low—with the III(B) and IV(AB) blood groups (compared with the blood group distribution in healthy donors of the region). The percentage of patients transferring in ICU with I(O) and II(A) blood groups was enough high, whereas in patients with III(B) and IV(AB) blood groups—very low. The statistical validity of the revealed regularity was checked using the OR criterion, which confirmed the high degree of reliability of the detected regularities. Our results are in correlation with studies suggesting that individuals with II(A) blood group are somewhat less resistant to the COVID-19 infection than other blood groups.[18] There were not revealed any statistically significant differences in the distribution of the patients with Rh-positive and Rh-negative blood groups in healthy and COVID-19 infected individuals (including those transferred in the ICU). These results are relevant in terms of elucidating the mechanisms and risk factors of infecting and severity course of COVID-19 disease.

Scientific data indicate the relation of viral infection with various factors, such as Willebrand factor, anti-A immunoglobulin isotype,

and anti-A is hemagglutinin titers.[19] Controversially, increased tendency of II(A) blood group to infection may be due to the thromboembolic diseases are more common in blood group II(A) and therefore can increase the severity of the disease.[20]

It was established that human anti-A antibodies can inhibit interaction between SARS-CoV-2 S protein and membrane receptor ACE2 by blocking the interaction between angiotensin-converting enzyme-2-dependent cellular adhesion to angiotensin-converting enzyme-2-expressed on cells[21] and therefore, by this way may provide protection from the virus. Therefore, the absence of antibodies A in the plasma of II(A) blood group patients may cause their high susceptibility to infection.

Blood group II(A) and III(B) glycosyltransferases participate in glycosylation process in a large number of cell types, including epithelial cells, and are involved in shedding of the viral particles.[22] Recent genomic analyses revealed specific gene clusters (3p21.31) as associated markers in patients with COVID-19 and respiratory failure. Given the association to this specific ABO blood group locus, the authors consider that this may be one of the mechanisms for the engagement of ABO typing with COVID-19-related illness, although the complete mechanism is not yet fully understood.

Conclusion

The link between patients' ABO blood groups and receptivity to COVID-19 infection, progression, and severity of the disease has been detected. The high prevalence of COVID-19 was revealed in the patients with blood group II(A) and significantly low in patients with the blood groups III(B) and IV(AB) (compared to healthy donors of the region). The severity of disease was enough high in patients with I(O) and II(A) blood groups. These results are relevant in terms of explaining the mechanisms and risk factors of severe COVID-19 disease development.

Future studies in this field may help shed light on the molecular mechanism by which ABO polymorphism impacts susceptibility to SARS-CoV-1 infection and transmission, contribute to the development of prophylactic and therapeutic interventions for COVID-19 infection.

Orcid

Levan Ratiani https://orcid.org/0000-0002-2122-8915
Tamar V Sanikidze https://orcid.org/0000-0003-1618-5276
George Ormotsadze https://orcid.org/0000-0002-0283-0281
Elene Pachkoria https://orcid.org/0000-0002-6273-9455
Giga Sordia https://orcid.org/0000-0003-0873-9339

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