

ABO-Rh Blood Types and Clinical Consequences of COVID-19 Infection

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ABSTRACT

Aim and Background: Because of there is no sufficient evidence showing a relationship between blood types and severity of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, this study was planned to investigate the effects of ABO blood group on the clinical outcomes of SARS-CoV-2 infection. **Patients and Methods:** The data of the patients were examined retrospectively. The patients who were hospitalized in wards or intensive care unit, constituted the study group. The patients who presented to the hospital because of other causes and whose blood type examinations were performed, were included in the control group. **Results:** The study group consisted of 406 six patients were diagnosed with SARS-CoV-2 infection. Control group consisted of 38079 patients whose blood group was determined for any reason in the same period. The rate of Rh negativity was significantly higher in the patient group ($p = 0,01$). Hospitalization duration in intensive care was significantly longer in the blood type A and AB groups compared to the blood type O group ($p = 0,03$). **Conclusion:** Our results are in agreement with other studies suggesting that blood group O individuals are somewhat more resistant to clinically overt infection with SARS-CoV-2 than other blood groups. In addition, Rh negativity may also be an individual risk factor for SARS-CoV-2 infection.

KEYWORDS: Blood groups, COVID-19, outcome, SARS-CoV-2, severity

INTRODUCTION

Coronavirus disease 2019 (COVID-19) infection is a contagious disease caused by *Severe acute respiratory syndrome coronavirus 2* (SARS-CoV-2), which was defined in December 2019 for the first time in China. It may have a fatal prognosis. As the virus has a high level of contamination and asymptomatic individuals or individuals with mild symptoms are also contagious, it has spread rapidly throughout the world, and led to a global pandemic.^[1,2]

In October 15, 2021, there have been 239,437,517 confirmed cases of COVID-19, including 4,879,235

deaths, reported to the World Health Organization (WHO).^[3] While the disease is asymptomatic or manifested as upper respiratory tract infection with mild symptoms in the majority of these cases, hospitalization because of a clinical picture of viral pneumonia that may progress to acute respiratory failure, is required in a certain part. Need for intensive care develops due to

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causes such as severe pneumonia, respiratory distress syndrome, sepsis, septic shock, and a picture of multiple organ failure in about 5-10% of COVID-19 patients.^[4-6] Specifically, host factors have an important role in terms of this clinical variety. Although acquired comorbidities including age, cardiovascular disease, diabetes, lung diseases, obesity, and a history of smoking are probably associated with disease severity, it is thought that genetic factors are also involved.^[7-10]

Following discovery of the ABO blood group system in 1901 by Karl Landsteiner, studies supporting the relationship between the ABO blood group system and many diseases, such as cardiovascular diseases, infectious diseases, and cancer diseases, were reported.^[11-18] As blood groups are genetically determined characteristics with polymorphic expression between individuals and populations, they are being frequently used in epidemiological studies. The relationship of blood groups with infectious diseases is notable. Many blood groups are receptors for toxins, parasites, and bacteria, where they can facilitate infection or evade host clearance mechanisms. Blood groups can also serve as false receptors by preventing binding to target tissue. Finally, bacteria can stimulate antibodies against blood group antigens, including ABO. ABO antibodies may be considered a part of the natural immune system against some bacterial pathogens and enveloped viruses carrying ABO-active antigens. In addition, the carbohydrate portions of ABO blood groups are genetically inherited, and it has been proposed that there is a correlation between blood types and sensitivity against certain infections including SARS-CoV-2 virus.^[19-23]

Rapid global spread of the new coronavirus SARS-CoV-2 critically necessitated detection of individuals under risk and prioritization of these individuals forcing healthcare services and test sources. Studies related to the risk factors that influence the severity of COVID-19^[24-27] and studies that detail the characteristics rendering individuals susceptible to COVID-19 infection and investigate risk factors related to disease progression, are currently continuing to be the center of interest.^[28-31]

However, there is no sufficient data showing the relationship between ABO blood typing and severity of COVID-19 disease and further studies are needed in this area. Therefore, we aimed to investigate the effects of ABO blood group and Rh types on COVID-19 infection and clinical outcomes (infection status, intubation, and mortality) in this study.

MATERIAL AND METHODS

This study is a retrospective case-control study. The data of the patients, who were hospitalized between

March 11, 2020 and June 01, 2021 at Göztepe Prof. Dr. Süleyman Yalçın City Hospital because of COVID-19 infection, were obtained from the hospital's electronic medical records by way of data collection forms and examined retrospectively.

The patients who were hospitalized at wards or intensive care unit with a diagnosis of COVID-19 infection constituted the COVID-19 study group. The patients, who presented at the hospital in the same time period because of other causes and whose blood type examinations were performed, were included in the control group. The patients' demographic characteristics, comorbidities (cancer, obesity, coronary heart disease, chronic pulmonary disease, immune deficiency, diabetes mellitus), and clinical data (intubation, hospitalization period, mortality) were analyzed. The ABO blood group distribution of the COVID-19 patients were compared with the ABO and Rh blood group distribution of the control group.

In our hospital, the diagnosis of COVID-19 infection was made according to the results of real-time polymerase chain reaction (RT-PCR) tests performed on nasopharyngeal and oropharyngeal samples obtained using synthetic fiber swabs. ABO blood type of patients was determined by standard RBC typing performed for clinical purposes. Nucleic acid testing was performed according to the Technical Guidelines for SARS-CoV-2 Laboratory Testing.

ABO and Rh blood group test was performed using microplate method (forward and reverse grouping techniques). Neo Iris (Immucor medizinische Diagnostik GmbH, d-63322 Rödemark, Germany), is a fully automated analyzer for immunohematology testing in the blood bank. Among classical methods, microplate technology is a further step toward more sensitive and fast blood typing analysis with the feasibility of automation. In this technique, both antibodies in blood plasma and antigens on RBCs can be determined. Typical microplates consist of a large number of small tubes that contain a few μ L of reagents, which are treated against the blood samples. Following centrifugation and incubation, the subsequent agglutination can be examined by an automatic read out device. The foremost advantage of microplate technology is its fast response, low reagent volumes, and high throughput analysis.

Statistical analysis

The descriptive values belonging to the data obtained, were calculated as standard deviation (SD), number, and % frequencies depending on the type of the variable. The blood type distributions in the control group

and COVID-19 positive group were compared using Pearson's Chi-square test. The relationships between patient characteristics and blood type were evaluated using Pearson's Chi-square test or independent samples t-test. A *P* value of <0.05 was considered statistically significant, and SPSS (ver. 23) program was used for calculations.

This study was approved by Göztepe Prof. Dr. Süleyman Yalçın City Hospital Clinical Researches Ethics committee (Decision number: 2020/0475).

RESULTS

A total of 406 COVID patients (229 males; 56.4%) were included in the study. The mean age of the patients was 63,46 ± 17,43 years (7-97). The total number of patients hospitalized was 335 (82.5%) in the ward and 256 (63.1%) in the intensive care unit. Two hundred eighteen (85.2%) of the patients hospitalized in intensive care unit were intubated, whereas only 3 (2.0%) of

150 patients, who were not hospitalized in intensive care unit, were intubated. In addition, 187 (46.1%) patients died among all patients.

The blood type distributions in COVID-19 positive patients and in the control group are shown in Table 1. A significant difference was not found between the patient and control groups in terms of the distribution of blood types A, B, O, and AB (*P* = 0,070). When the distribution of Rh positivity and negativity was examined; however, it was found that the rate of Rh negativity was significantly higher in the patient group (*P* = 0,01).

The distribution of categorical demographic and clinical characteristics by blood type in the patient group is shown in Table 2. A significant difference was not found between the individuals with blood type A, B, O, and AB, and between Rh positive and Rh negative groups in terms of the demographic and clinical characteristics indicated in Table 2.

Descriptive data including rates of hospitalization in intensive care unit-hospitalization duration, rates of intubation and mortality rates are shown in Table 3. When Table 3 was examined, it was found that hospitalization duration in intensive care was significantly longer in the blood type A and AB groups compared to the blood type O group (*P* = 0,033). No other significant difference was found between the blood type A, B, O and AB groups. In addition, a significant difference was not found between Rh positive and

Table 1: Blood type distribution between groups

Blood type	COVID-19 positive patients, n (%) n: 406	Control group, n (%) n: 38079	χ^2	<i>P</i>
A	198 (48,8)	16389 (43,0)	7,06	0,070
B	67 (16,5)	6327 (16,6)		
O	114 (28,1)	12897 (33,9)		
AB	27 (6,7)	2466 (6,5)		
Rh positive	342 (84,2)	33651 (88,4)	6,66	0,010
Rh negative	64 (15,8)	4428 (11,6)		

Table 2: Relationship between blood type and clinical findings

Clinical Characteristics	Blood type				<i>P</i>	Rh		<i>P</i>
	A	B	O	AB		Positive	Negative	
<i>n</i>	198	67	114	27		342	64	
Age (year), Mean±SD	63,5±17	61,8±16	64,9±18	60,8±15	0,566	63,4±17	63,9±15	0,799
Male sex, n (%)	121 (61,1)	41 (61,2)	55 (48,2)	12 (44,4)	0,070	196 (57,3)	33 (51,6)	0,395
Fever, n (%)	68 (34,3)	27 (40,3)	47 (41,2)	13 (48,1)	0,400	130 (38,0)	39 (39,1)	0,874
Cough, n (%)	75 (37,9)	32 (47,8)	55 (48,2)	12 (44,4)	0,257	146 (42,7)	28 (43,8)	0,875
Sputum, n (%)	17 (8,6)	6 (9,0)	10 (8,8)	2 (7,4)	0,996	28 (8,2)	7 (10,9)	0,472
Respiratory distress, n (%)	148 (74,7)	47 (70,1)	81 (71,1)	18 (66,7)	0,738	251 (73,4)	43 (67,2)	0,308
Sore throat, n (%)	8 (4,0)	2 (3,0)	6 (5,3)	0 (0,0)	0,615	15 (4,4)	1 (1,6)	0,287
Muscle pain, n (%)	64 (32,3)	23 (34,3)	37 (32,5)	12 (44,4)	0,648	115 (33,6)	21 (32,8)	0,899
Headache, n (%)	7 (3,5)	2 (3,0)	7 (6,1)	0 (0,0)	0,421	14 (4,1)	2 (3,1)	0,715
Chest pain, n (%)	6 (3,0)	4 (6,0)	1 (0,9)	0 (0,0)	0,173	8 (2,3)	3 (4,7)	0,288
Diarrhea, n (%)	15 (7,6)	3 (4,5)	10 (8,8)	2 (7,4)	0,763	22 (6,4)	8 (12,5)	0,089
Comorbidity, n (%)	134 (67,7)	50 (74,6)	72 (63,2)	19 (70,4)	0,451	231 (67,5)	44 (68,9)	0,850
Diabetes, n (%)	68 (34,3)	16 (23,9)	28 (24,6)	10 (37,0)	0,157	99 (28,9)	23 (35,9)	0,263
Hypertension, n (%)	92 (46,5)	30 (44,8)	45 (39,5)	11 (40,7)	0,667	151 (44,2)	27 (42,2)	0,771
Heart disease, n (%)	46 (23,2)	19 (28,4)	20 (17,5)	4 (14,8)	0,273	76 (22,2)	13 (20,3)	0,735
Obesity, n (%)	1 (0,5)	0 (0,0)	1 (0,9)	0 (0,0)	0,847	1 (0,3)	1 (1,6)	0,183
Malign disease, n (%)	22 (11,1)	9 (13,4)	11 (9,6)	3 (11,1)	0,893	35 (10,2)	10 (15,6)	0,207
Chronic lung disease, n (%)	21 (10,6)	10 (13,4)	13 (11,4)	1 (3,7)	0,466	40 (11,7)	5 (7,8)	0,364

Table 3: Rates of hospitalization, intubation, and mortality rates

	Blood type				P	Rh		P
	A	B	O	AB		Positive	Negative	
Hospitalization rates in ICU, n (%)	130 (65,7)	42 (62,7)	66 (57,9)	18 (66,7)	0,56	220 (64,3)	36 (56,3)	0,21
Hospitalization days in ICU, mean±SD	10,2±10,6	8,5±11,1	6,9±9,45	11,5±11,7	0,03	9,1±10,3	9,0±11,7	0,96
Intubation, n (%)	113 (57,1)	36 (53,7)	58 (50,9)	14 (51,9)	0,74	190 (55,6)	31 (48,4)	0,29
Mortality, n (%)	98 (49,5)	30 (44,8)	51 (44,7)	8 (29,6)	0,26	162 (47,4)	25 (39,1)	0,22

negative groups in terms of rates of hospitalization in intensive care unit-hospitalization duration, rates of intubation, and mortality rates.

DISCUSSION

Four hundred eight COVID-19 patients, who were being followed up by our hospital, were included in this study. A significant difference was not found between the COVID-19 patients and the control group in terms of the frequencies of ABO blood groups. On the other hand, when the distribution of Rh positive and negativity is examined, Rh negativity rate was found to be significantly higher in patients.

Our result is in contrast with the findings of other studies in which an association between ABO blood type and susceptibility to infection was reported. Studies regarding the relationship between COVID-19 infection and blood groups have been conducted since the beginning of SARS-CoV-2 pandemic. In various studies, it has been proposed that the O blood group is observed with a lower frequency in patients with severe COVID-19 infection who need prolonged hospitalization, clinical course is more severe in individuals with blood group A and the blood group O may have a protective effect.^[22,23,32] However, Dzik *et al.*^[33] could not find a significant correlation between blood groups and COVID-19 in a review in which the distributions of ABO blood group were compared between 957 confirmed COVID-19 cases in the region of Boston during 2020 epidemic and 5840 control patients belonging to the same date in 2019. In the study of Negro *P et al.*,^[34] they evaluated the distribution of ABO and Rh blood groups in two populations of subjects exposed to the risk of infection tested for SARS-CoV-2. They found no difference in blood type distribution between SARS-CoV-2-infected or uninfected individuals. Similarly, we could not find a difference between COVID-19 patients and the control group in terms of the frequencies of ABO blood group in our study.

There are studies evaluating the relationship between blood groups and the clinical characteristics of COVID-19 infection (especially need for tracheal intubation, length of stay in intensive care unit, and mortality).^[22,23,35-38] Hoiland *et al.*^[36] reported that

among the patients, who were hospitalized in intensive care unit, the ones with blood group A or AB required mechanical ventilation and dialysis therapy with a higher rate compared to the ones with blood group O or B. Similarly, biomarkers of renal and hepatic dysfunction were found to be higher in the patients with blood group A or AB.^[36] In a multi-center retrospective review conducted in USA, a relationship could not be found between ABO blood group and intubation or mortality related to COVID-19 infection.^[38] Similarly, we could not find any correlation between ABO blood group and intubation or mortality related to COVID-19 infection in our study. In addition, ABO blood group and Rh type were not found to have an effect on the frequency of becoming infected with COVID-19 and on disease severity in our study. However, a significant correlation was found between the length of stay in intensive care unit and blood groups. It was concluded that prolonged length of stay in intensive care unit in individuals with blood group A and AB influenced clinical prognosis by prolonging hospitalization period.

The Rh blood type consists of more than 50 protein antigens, the most clinically relevant of which are D, C, c, E, and e. The RH locus encodes two genes *RHD* and *RHCE*. An individual's Rh type is largely determined by the presence or absence of the D antigen on erythrocytes, Rh+ or Rh-, respectively. The Rh antigens complex with associated glycoproteins on the red blood cell surface, but physiologic roles of RhD and RhE have yet to be elucidated. Rh (D) phenotypes (positive and negative Rh blood types) are associated with very few diseases compared to ABO.^[13] The Rh (Rhesus) blood group system is the most complex of known human blood group polymorphisms. Expression of their antigens is controlled by a two-component genetic system consisting of RH and RHAG locus encoding Rh30 polypeptides and Rh50 glycoprotein, respectively.^[39] West Nile virus infection is more common in Rh-negative individuals, a hypothesis posits that glycosylated structures expressed differently on the surface of erythrocytes will facilitate virus binding or serve as receptors/co-receptors through glycan-glycan or lectin-glycan interactions in a Velcro-like interaction.^[40] However, natural antibodies can block or opsonize the

entry of viral particles leading to complement-mediated neutralization.^[41] It has also recently been shown that natural antibodies can aid the formation of cytotoxic T cells against the pathogen.^[42] These additional protection mechanisms may have contributed to the protection of that individual's blood group during the COVID-19 outbreak. The association between Rh blood and SARS-CoV-2 positivity merits further investigation.

Unlike previous studies, in our study, the Rh (-) ratio was found to be significantly higher than the community ratio.^[43] Our study suggests that the Rh (+) blood group is protective and the Rh (-) blood group is predisposed to COVID-19 significantly.

With many of the abovementioned mechanisms, it is obvious that the virus infections show affinity to some blood groups or may be protective. Although the mechanism is unknown, this study suggests an association between Rh (D) negative blood groups and Covid-19 pathogenesis in terms of potential risk factors. Our study has several limitations. First, as with any chart review, data quality is dependent on completion of the medical record; a factor that is likely exacerbated in the context of the swell of patients which occurred during the pandemic. Secondly, given the size of our population and the unequal distribution of blood types across the overall study population, differences in the groups represented have the ability to cast a heavier weight on overall analysis and therefore conclusions. Finally, given the unequal representation of ABO and Rh phenotypes in the population, we recognize that a much larger study may be necessary to elucidate any significant difference beyond the tendencies observed. In conclusion, a significant difference could not be found between ABO blood groups in terms of the frequency of becoming infected or severe disease. However, a significant difference was observed between lengths of stay in intensive care unit and blood groups. Although blood groups were not found to have a direct correlation with intubation and mortality, it was thought that blood groups A and AB prolonged hospitalization period and indirectly influenced clinical prognosis.

We need further molecular studies to elucidate the relationship between blood groups and the disease. Larger prospective multi-center studies should be conducted to clarify the possible protective role of blood groups in terms of COVID-19 infection. Studies including carefully selected control groups, analyzes of additional data sets from all corners of the world and the contribution of both genetic and newly emerging acquired cofactors, will continue to improve our understanding on the relationship between COVID-19 and ABO blood group, if present.

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Conflicts of interest

There are no conflicts of interest.

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