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ARAŞTIRMA / RESEARCH

Relationship between COVID-19 infection and ABO and Rh blood group systems

COVID-19 enfeksiyonu ile ABO ve Rh kan grubu sistemlerinin ilişkisi

Tuba Damar Çakırca[1], Tayibe Bal[2]

[1]Department of Infectious Diseases and Clinical Microbiology, Şanlıurfa Training and Research Hospital, Şanlıurfa, Turkey
[2]Department of Infectious Diseases and Clinical Microbiology, Mustafa Kemal University School of Medicine, Hatay, Turkey

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Abstract

Purpose: The aim of this study was to determine whether there is a relationship between COVID-19 infection and ABO and Rh blood groups.
Materials and Methods: 1360 patients with positive SARS-CoV-2 RNA test between April 2020 and March 2022 and 80219 healthy controls whose blood groups were determined before March 2020 were included in this study. Patients were classified according to disease severity as mild, moderate, severe and critical.
Results: Patient and control groups were matched in terms of age and gender using case-control matched method. 1360 patients and 1161 controls were included in the analysis. Of the patients, 42.1% (n=572) had mild, 41.5% (n=564) moderate, 13.8% (n=187) severe and 2.7% (n=37) critical course of infection. It was observed that patients with blood group A were 1.33 times more at risk (OR: 1.33, 95%Cl: 1.12-1.56) for the development of COVID-19 infection compared to patients with other blood groups. No relationship was found between ABO and Rh blood groups and severe-critical COVID-19 disease, need for intensive care and mortality. However, when patients are divided into two groups as mild and non-mild (moderate, severe, critical); the frequency of having O and B blood groups was found to be significantly higher in non-mild cases than in mild cases ((53.3% and 46.7%), (64.5% and 35.5%, respectively).
Conclusion: In our study, while A blood group was found to be at risk for the development of COVID-19 infection, no relationship was found between Rh blood groups and susceptibility to the disease. In addition, the rate of O and B blood groups was found to be higher in patients who did not have mild disease.

Keywords: COVID-19, ABO blood group, Rh blood group

Öz

Amaç: Bu yazıda COVID-19 enfeksiyonu ile ABO ve Rh kan grupları arasında ilişki olup olmadığının belirlenmesi amaçlandı.
Gereç ve Yöntem: Çalışma kapsamında Nisan 2020-Mart 2022 tarihleri arasında SARS-CoV-2 RNA testi pozitif saptanmış 1360 hasta ile Mart 2020 tarihinden önce kan grubu tayini yapılmış 80219 sağlıklı kontrolün verisi kullanıldı. Hastalar hastalık şiddetine göre hafif, orta, ağır ve kritik olarak sınıflandırıldı.
Bulgular: Hasta ve kontrol grubu yaş ve cinsiyet açısından vaka-kontrol eşleştirmesi yapılarak 1360 hasta ve 1161 kontrol analizlere dahil edildi. Hastaların %42.1 (n=572)'i hafif, %41.5 (n=564)'i orta, %13.8 (n=187)'i ağır, %2.7 (n=37)'si ise kritik seyirliydi. A kan grubuna sahip olguların diğer kan gruplarına sahip olgulara göre COVID-19 enfeksiyonu gelişimi açısından 1.33 kat (OR: 1.33, %95Cl: 1.12-1.56) daha riskli olduğu görüldü. ABO ve Rh kan grupları ile COVID-19 hastalığının ağır-kritik geçirilmesi, yoğun bakım ihtiyacı ve mortalitesi arasında ilişki saptanmadı. Ancak hastalar hafif ve hafif olmayan (orta, ağır, kritik) olarak iki gruba ayrıldığında; hafif olmayan olguların hafif olgulara göre O ve B kan grubuna sahip olma sıklıkları anlamlı olarak daha yüksek bulundu (sırasıyla (%53.3 ve %46.7), (%64.5 ve %35.5).
Sonuç: Çalışmamızda A kan grubu COVID-19 enfeksiyonu gelişimi açısından riskli olarak bulunurken, Rh kan grupları ile hastalığa yatkınlık arasında ilişki saptanmadı. Ek olarak hastalığı hafif geçirmeyen olgularda O ve B kan grubu oranı daha yüksek bulunmuştur.

Anahtar kelimeler: COVID-19, ABO kan grubu, Rh kan grubu

Yazışma Adresi/Address for Correspondence: Dr. Tuba Damar Çakırca, Department of Infectious Diseases and Clinical Microbiology, Şanlıurfa Training and Research Hospital, Şanlıurfa, Turkey, E-mail: dr.tubadamar@gmail.com
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INTRODUCTION

COVID-19 (coronavirus disease 2019) infection which caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) first emerged in China at the end of 2019 and spread to all over the world. According to WHO (World Health Organization) data by the May 6, 2022; 513,384,685 people have been infected and 6,246,828 individuals have died because of this illness[1]. There are still no effective and reliable treatment options against this infection which has been a part of our lifes for more than two years. Therefore, it is crucial to identify individuals who are prone to disease and their risk factors, and early assessing the severity of disease in order to reduce mortality and morbidity. Manifold parameters and risk factors that predict the severity of COVID-19 disease were defined in the literature[2-5]. It was suggested that there may be a relationship between blood types and SARS-CoV-2 infection based on the prior experience with SARS-CoV-1[6]. However, conflicting results have been reported to date. Numerous studies and meta-analyses showed that, people with blood group A have a high[7-9] risk of contracting COVID-19 disease, people with blood group O have a lower[10,11] risk of infection, and people with non-O blood group[12] and people with blood group A[13] have the course of disease more severely. On the other hand, several research reported that there is no connection between COVID-19 infection and blood types[14,16]. In the light of this information, whether there is a relationship between COVID-19 infection and blood groups seems to be an issue that needs to be clarified.

The aim of this study is to determine whether there is an association between ABO and Rh blood group types and vulnerability to COVID-19 infection and/or disease severity in individuals with COVID-19 infection. We hypothesized that blood groups may affect the severity and course of disease in COVID-19 infection.

MATERIALS AND METHODS

This retrospective, cross-sectional, single-center, case-control study was conducted in Şanlıurfa Training and Research Hospital between April 2020 and March 2022. The ethical permission was obtained from the the Scientific Research Platform of the Turkish Ministry of Health and Harran University School of Medicine Ethics Committee Commission (HRU.22/07/15).

Study population

The inclusion criterias of this study were considered as follows; inpatients who have SARS-CoV-2 RNA positivity in nasopharyngeal swab samples, over the age of 18 years olds and patients whose blood type was accesible in the hospital database. The exclusion criterias of this study were considered as follows; outpatients, patients who suspected with COVID-19 infection but have a negative SARS-CoV-2 RNA test results, pediatric patients (<18 years olds) or patients whose blood type was unavailable in the hospital database.

Between April 2020 and March 2022 time period, 4474 patients whose SARS-CoV-2 RNA test results were positive were hospitalized in the Şanlıurfa Training and Research Hospital. 1360 patients who met all of the inclusion criteria enrolled in the study. Age, gender, disease severity, and blood types of patients were obtained retrospectively from the hospital database system and patient archive files.

The data of 80219 healthy individuals over the age of 18 whose blood group was determined between January 2018 and March 2020 in Şanlıurfa Training and Research Hospital Blood Center were used as the control group. Due to the differences in gender and age distribution between patient and control groups, case-control matched method was used. Finally 1161 cases included in the study as control group.

Clinical classification of COVID-19 patients

The patients were categorized based on disease severity as mild, moderate, severe, or critical[17]:

1. Mild cases: mild clinical symptoms without signs of pneumonia on imaging
2. Moderate cases: fever and respiratory symptoms, with signs of pneumonia on imaging
3. Severe cases: having at least one of the following criteria [Respiratory rate ≥30/min, Oxygen saturation ≤93% at rest, The ratio of arterial partial oxygen pressure to inspiratory oxygen fraction (PaO2/FiO2) ≤300 mmHg]
4. Critical cases: Respiratory failure and requiring mechanical ventilation, Shock, Other organ failure requiring intensive care support

Patients are also divided into two groups as mild and non-mild (moderate, severe, critical).

Statistical analysis

SPSS version 25.0 software and R (R Project) package program were used in the evaluation of the data in the presented study, and $P < 0.05$ was considered significant. The normality of the variables was evaluated with the Shapiro-Wilk's test. Mann-Whitney U test was used to compare medians of age between the COVID-19 patient group and control group. While, Chi-square test or Fisher's exact test were used to compare the sex, the frequencies of ABO and RH blood groups between the COVID-19 patient group and control group as well as between subgroups of COVID-19 patients who represent different severities. Data are reported as frequency (percentage) or median (interquartile range [IQR, 25th and 75th percentiles]).

RESULTS

A total of 81579 individuals, including 80219 healthy controls and 1360 COVID-19 PCR (+) patients, were involved in the analyses. However, due to the differences in gender and age distribution between these two groups, 1360 COVID-19 (+) patients were matched with a control group including 1161 cases using case-control matched method. The characteristics of the COVID-19 (+) and control groups before and after matching are presented in Table 1.

Table 1. Comparison of demographic characteristics of groups before and after case-control matching

	Before matching			After matching		
	COVID-19 patient group (n=1360)	Control group (n=80219)	p-value	COVID-19 patient group (n=1360)	Control group (n=1161)	p-value
Age, years	41.0 (29.0-61.0)	27.0 (22.0-33.0)	<0.001	41.0 (29.0-61.0)	37.0 (28.0-53.0)	<0.001
Sex			<0.001			<0.001
Female	883 (64.9)	72631 (90.5)		883 (64.9)	870 (74.9)	
Male	477 (35.1)	7588 (9.5)		477 (35.1)	291 (25.1)	

COVID-19: Coronavirus disease 2019.

Table 2. Comparison of COVID-19 positivity status of each blood group compared to other ABO blood groups

	COVID-19 patient group (n=1360)	**Control group (n=1161)**	**p**	**OR (95% CI)**
A Other	528 (38.8) 832 (61.2)	375 (32.3) 786 (67.7)	**0.001**	**1.33 (1.12-1.56)**
B Other	290 (21.3) 1070 (78.7)	271(23.3) 890 (76.7)	0.225	0.89 (0.73-1.07)
(AB) 231/2012 Other	107 (7.9) 1253 (92.1)	103 (8.9) 1058 (91.1)	0.363	0.87 (0.66-1.16)
O Other	435 (32.0) 925 (68.0)	412 (35.5) 749 (64.5)	0.068	0.85 (0.72-1.00)
RH (-) Other	131 (9.6) 1229 (90.4)	93 (8.0) 1068 (92.0)	0.154	1.22 (0.92-1.61)

COVID-19: Coronavirus disease 2019; RH: rhesus factor; OR: odds ratio; Cl: confidence interval.

A significant difference was seen between the two groups in the distribution of ABO blood groups (p=0.009), but not in the distribution of Rh blood groups (p=0.154). However, as shown in Table 2 the subgroup analyses revealed that there was a difference between these two groups which is due to the A blood group; having blood group A was found to be 1.33 times more risky for the development of COVID-19 infection compared to patients with other blood groups (p) =0.001, OR: 1.33, and 95% Cl: 1.12-1.56).

42.1% (n=572) of COVID-19 (+) cases had mild, 41.5% (n=564) moderate, 13.8% (n=187) severe, and 2.7% (n=37) critical course. As seen in the Sankey

graph in Figure 1, which summarizes the relationship between blood types and COVID-19 disease severity in the COVID-19 (+) patients, no significant difference was found between ABO and Rh blood groups in terms of COVID-19 disease severity. On the other hand, when the patients were divided into two groups as mild and non-mild (moderate, severe, and critical), O and B blood group frequency were found to be considerably more common in non-mild cases than in mild cases, with p=0.018 (53.3 %, 46.7 %, respectively) and p=0.011, (64.5 %, 35.5 % respectively). Furthermore, there was no significant difference between each blood groups compared to other blood groups in terms of severe/critical course, need for intensive care, and mortality in COVID-19 (+) individuals (Table 3).

Table 3. Comparison of each blood type's severe/critical course, intensive care follow-up, and death in COVID-19 (+) patients with other blood types

	Severe disease		*p*	Required Intensive Care Cases		*p*	Mortality		*p*
	Yes (n=224)	No (n=1136)		Yes (n=37)	No (n=1323)		Yes (n=36)	No (n=1324)	
A Other	89 (39.7) 135 (60.3)	439 (38.6) 697 (61.4)	0.760	18 (48.6) 19 (51.4)	510 (38.5) 813 (61.5)	0.214	18 (50.0) 18 (50.0)	510 (38.5) 814 (61.5)	0.163
B Other	50 (22.3) 174 (77.7)	240 (21.1) 896 (78.9)	0.690	8 (21.6) 29 (78.4)	282 (21.3) 1041 (78.7)	0.964	7 (19.4) 29 (80.6)	283 (21.4) 1041 (78.6)	0.780
(AB) 231/2012 Other	13 (5.8) 211 (94.2)	94 (8.3) 1042 (91.7)	0,209	4 (10.8) 33 (89.2)	103 (7.8) 1220 (92.2)	0.528	4 (11.1) 32 (88.9)	103 (7.8) 1221 (92.2)	0.522
0 Other	72 (32.1) 152 (67.9)	363 (32.0) 773 (68.0)	0.956	7 (18.9) 30 (81.1)	428 (67.6) 895 (32.4)	0.084	7 (19.4) 29 (80.6)	428 (32.3) 896 (67.7)	0,102
Rh - Rh +	19 (8.5) 205 (91.5)	112 (9.9) 1024 (90.1)	0.523	2 (5.4) 35 (94.6)	129 (9.8) 1194 (90.2)	0.572	1 (2.8) 35 (97.2)	130 (9.8) 1194 (90.2)	0.248

RH: rhesus factor.

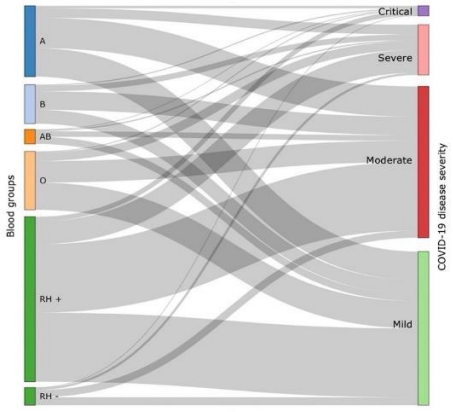

Figure 1. Sankey diagram shows the relationship between blood types and COVID-19 disease severity in the COVID-19 (+) patient population.

DISCUSSION

In our study, it was found that individuals with A blood group have a higher risk of contracting COVID-19 infection compared to other blood groups; on the other hand no relationship was found between the Rh systems and the risk of disease occurence. In addition, no significant correlation was found between ABO and Rh blood groups and COVID-19 disease severity. However, when patients were divided into two groups as mild and non-mild (moderate, severe, critical), O and B blood group rates were observed to be considerably higher in non-mild cases than in mild ones. No correlation was found between blood groups and severe/critical COVID-19 infection, disease mortality and need for intensive care.

Since blood groups were defined, their relationship with many diseases has been investigated so far[18-21]. Blood group antigens, which can be expressed in a variety of pathways, can also increase or decrease the susceptibility of the host to infections. In addition, blood groups can act as receptors/co-receptors for some microorganisms, facilitate adhesion through intracellular uptake, signal transduction or reorganization of membrane microdomains, cause direct infection and alter the innate immune response against infections[22]. There are numerious studies investigated that blood group distribution may be associated with many infectious diseases such as *P. falciparum* malaria, HIV (Human Immunodeficiency Virus), HBV (Hepatitis B Virus), HCV (Hepatitis C

Virus), syphilis, West Nile virus and *H. pylori* [23,27]. The correlation between coronaviruses and blood groups was investigated firstly by Chen et al., in which healthcare workers infected with SARS-CoV-1 involved, and it was found that individuals with O blood group were less likely to get the disease compared to other blood groups[6].

Rapidly spreading SARS-CoV-2 infection has been the theme of many studies over the past two years in order to identify the risk factors that predispose to the disease or cause the disease to be more severe and many new parameters and indices have been suggested for this purpose. According to studies revealing linkage between blood types and a variety of infectious diseases, it has been hypothesized that blood groups may also affect the course of COVID-19 infection. However, contradictory results have been reported on this subject. The majority of studies examining the link between COVID-19 and blood types indicated that patients with A blood type have a higher risk of contracting the disease than in people with O blood type[7,14,28,30]. In consistent with literature, we found that blood group A is the most risky group for the development of COVID-19 infection.

Vulnerability to disease and the clinical course after the development of disease are not the same phenomenon, and these parameters were evaluated separately in the studies. Thus, in the studies conducted by Göker et al. and Abdollahi et al., it was reported that O blood group may be protective against the disease, but no correlation was found between the severity of disease and blood groups[7,29]. Latz et al. also found that there was no relationship between the disease severity and blood groups, but the rate of COVID-19 positivity was higher in the B and AB blood groups[31]. In a recent multicenter observational study which involved 29,512 patients, AB blood group was the most frequently detected blood group in the COVID-19 cohort, and no correlation was found between blood types and disease morbidity and mortality[32]. In another newly published review, which comprises the highest number of cases so far, whereas there is little evidence of the relationship between blood types and COVID-19 disease severity; individuals with A blood group have a higher risk of developing the disease compared to O blood group[33]. In our study, the ratio of O and B blood groups was found to be significantly higher in non-mild cases than in mild cases. Contrary to these results, there are studies in which no relationship was found between blood types and neither occurrence nor the severity of disease[15,34,36].

Compared to ABO blood systems, there are limited studies examining the relationship between Rh systems and COVID-19 infection. In their study, Ray et al. found that patients with Rh (-) blood group were at a lower risk for SARS-CoV-2 infection but severe course of disease than Rh (+) ones[12]. Similarly, in other three studies, it was reported that Rh positive blood group rate among COVID-19 patients was significantly higher than Rh negative patients[31,37,38]. However, a cohort study conducted on young population, no relationship was found between Rh blood groups and the risk of contracting COVID-19 infection[35]. In another study examining the relationship between the severity of the disease and the Rh system, it was found that the intensive care need of Rh (+) patients was significantly higher than Rh (-) patients. In the same study, although it is not statistically significant, mortality was higher in the Rh (+) patients[39]. However, in our study, no relationship was found between Rh systems and the risk of developing the disease or the severity of infection.

The distribution of blood types may vary depending on ethnicity, so it is not surprising that different results were obtained in studies investigating the relationship between blood groups and COVID-19 infection. In a study, no relationship was found between blood types and the risk of COVID-19 infection and disease severity after adjusting for ethnicity difference[16]. In two separate studies conducted in our country at the beginning of the pandemic, it has been reported that blood group A may predispose to the disease, while blood group O may be protective against the disease. However, no relationship was found between blood groups and disease severity[7,40]. In another retrospective cohort study conducted in our country, in which patients were randomized for each blood group based on age and gender, was reported that blood group A slightly increased the risk of admission to the intensive care unit. On the other hand, no relationship was observed between blood groups and the hospital and intensive care unit stay, need for mechanical ventilation, and disease mortality rate[41]. In this study, blood group A was detected at a high rate in COVID-19 patients, similar to the data of our country.

Our study has some limitations. Firstly, patients whose blood types accessible were included in our study, and this may cause selection bias since there

are many patients whose blood groups were not determined. Secondly, the data of individuals whose blood groups were determined in the Blood Center were used as the control group, and the results may not reflect the data of the general population. Another limitation was that comorbidities of patients and control groups were not evaluated. Finally, our study was conducted in a single center in Sanliurfa, Turkey and a conventional power analysis was not performed before the study.

In conclusion, blood group A was found to be the most risky group for the development of COVID-19 disease in this study, which was consistent with the literature. Additionally, the rate of O and B blood groups was found to be higher in cases who did not have mild COVID-19 disease. However, no relationship was found between ABO and Rh blood groups and severe/critical COVID-19 infection, mortality and need for intensive care.

Despite many studies from early times of the pandemic, the relationship between blood groups and COVID-19 infection is still unclear. Also, there is no methodologically reliable studies that show the direct mecanism of individual's vulnerability to SARS-CoV-2 infection. Prospective multicenter studies with a large patient population are needed to elucidate the molecular and clinical mechanism of association between the blood groups and the disease.

Yazar Katkıları: Çalışma konsepti/Tasarımı: TDÇ, TB; Veri toplama: TDÇ; Veri analizi ve yorumlama: TDÇ, TB; Yazı taslağı: TDÇ, TB; İçeriğin eleştirel incelenmesi:: TDÇ, TB; Son onay ve sorumluluk: TDÇ, TB; Teknik ve malzeme desteği: TDÇ, TB; Süpervizyon: TDÇ, TB; Fon sağlama (mevcut ise): yok.
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