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Association between blood groups and COVID-19 susceptibility

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Abstract

COVID-19, become one of the biggest global problems in human history since the final days of 2019. Fever, dry cough, dyspnea, myalgia and fatigue are frequently encountered among the clinical symptoms of the patients. Although COVID-19 causes mild to moderate symptoms in most infected individuals, people with comorbid illness or people over the age of 60 have a higher risk of developing severe illness as well as death. In more severe cases, the infection causes pneumonia, severe acute respiratory failure, multiple organ failure, and even death. In this study, we aimed to examine the effects of ABO and Rh blood groups on the severity of COVID-19 infection (admission to intensive care units, intubation and death) among patients hospitalized in COVID-19 pandemic wards. Of the patients who were hospitalized in COVID-19 pandemic inpatient services in Malatya Training and Research Hospital; a tertiary health care facility serving as 1040-bed situated in Eastern Turkey, 300 adult patients with known blood groups, and the patients who had applied to the hospital's blood bank during the same dates (control group=21911) were included in the study. Intensive care unit admission and mortality rates were found to be significantly higher in B blood group as compared to other blood groups, while intubation and death rates were found to be significantly lower in O blood group when compared to other groups. When the blood groups of the population (control group=21991) and COVID-19 patients were compared, it was seen that there was no significant difference between the blood groups, and the distribution was observed to be similar to that of the population. As a result, more research is needed in order to clarify the relationship between COVID-19 and the ABO and Rh blood groups to better understand the COVID-19 infection, which has affected the whole world.

Keywords: ABO blood groups, coronaviruses, COVID-19, SARS-CoV-2, comorbidity

Introduction

Coronaviruses (CoVs) are classified in the Nidovirales genus, Coronaviridae family. The family Coronaviridae includes four genera namely alpha, beta, gamma, and delta. The coronaviruses that have caused three major pandemics known to be MERS-CoV, SARS-CoV and SARS-CoV-2 in last two decades are known to be single-stranded, enveloped, non-segmented and positive-polar Ribonucleic acid (RNA) viruses Coronaviruses may infect humans as well as animals and may cause different infections, including renal, neurological, respiratory and enteric diseases [1].

The World Health Organization (WHO) named the disease caused by the virus as Coronavirus Disease-2019 (COVID-19), and named the agent as "Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2)" on February 11, 2020. After declaration of COVID-19 as a global pandemic on March 11, 2020, governments around the world began implementing strategies to slow down the spread of the infection [2]. Despite all the precautions and measures that were taken, COVID-19, which continues to spread rapidly all over the world, is known to have infected over 120 million people as of today and has caused over 2.6 million deaths [3].

The Spike transmembrane glycoprotein (S) on SARS-CoV-2 surface helps the virus cohere to a host cell by attaching to receptors called angiotensin converting enzyme (ACE-2) in human cells. This receptor is spread on the surface of various cell types such as the cells of upper respiratory tract and lungs, central nervous system, pancreas, kidneys, heart, liver and endothelial cells. In addition to ACE-2, which plays a central role in this interaction, the transmembrane proteins such as TMPRSS2 (transmembrane serine protease-2) and CD147 are also known to be involved in this interaction [4,5].

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While COVID-19 usually shows mild symptoms (80%), the mortality risk increases in patients who are admitted to intensive care units (ICUs) and need invasive mechanical ventilation (50%). Recent studies show that the age of the patient, male gender, and some chronic diseases (cardiovascular disease, diabetes, COPD, etc.) increase risk as well as severity of infection [6,7]. In patients with severe illnesses, it is reported to cause respiratory failure, acute respiratory distress syndrome (ARDS) or acute lung injury, heart failure, sudden cardiac arrest and sepsis within a few days. If not treated adequately, multiple organ failure and ARDS may lead to death [8].

A relationship between blood groups (ABO) and bacterial and viral infections such as Helicobacter pylori, rotavirus, noroviruses, dengue virus, Norwalk virus, hepatitis B virus, SARS-COV, and MERS-COV has been confirmed. By examining this relationship, it is possible to evaluate the susceptibility of the people having different blood groups to the virus [9].

Due to the number of cases and deaths that have reached dangerous levels around the world, scientists continue to get to know the COVID-19 disease more closely and to search for preventive and therapeutic methods against the disease. This study aims to investigate the effects of ABO blood groups and Rh blood types on COVID-19 infection severity on three severe COVID-19 outcomes: admission to ICU, intubation and death.

Materials and Methods

The study was carried out with the approval of Malatya Clinical Research Ethics Committee with protocol number 2021/02 on January 22, 2021. Furthermore, an approval was received from T.C. Ministry of Health, General Directorate of Health Services, Scientific Working Platform for the study (Date of Approval: 19.12.2020 and Applicant: Esra Erdogan).

In this retrospectively designed study, of the patients who were hospitalized in COVID-19 pandemic inpatient services in Malatya Training and Research Hospital; a tertiary health care facility serving as 1040-bed situated in Eastern Turkey, 300 adult patients with known blood groups, and the patients who had applied to the hospital's blood bank during the same dates (control group=21911) were included. COVID-19 diagnosis of patients were performed using Bio-Speddy® (Bioeksen R&D Technologies Inc. COVID-19 RT-qPCR Detection Kit v2.0, Istanbul, Turkey) and Diagnovital® (RTA Laboratories Inc, SARS-CoV-2 Real-Time PCR Kit v2.0, Istanbul, Turkey) PCR kits. The data of infected patients were obtained using Information Management System of our hospital.

Statistical analyses

SPSS 22 program was used in order to analyze the obtained data. Binary logistic regression and Chi-square test were used to make the analyses. Categorical variables n, (%) and continuous variables were determined as mean ± standard deviation. P value smaller than 0.05 ($P<0.05$) was considered to be significant

Results

In total, 300 adult patients including 173 males and 127 females with known blood groups, an average age of 68.68±13.34 and age range of 24-101, who received inpatient treatment in COVID-19 pandemic wards between March 15, 2020 and November 15, 2020, were included in our study. Blood group data of patients (control group=21 911) who applied to the hospital's blood bank during the same dates were used as the control group.

The socio-demographic characteristics, comorbidities, distribution of blood groups and course of disease of the patients have been shown in Table 1.

All cases were laboratory-confirmed as SARS-CoV-2 positive using quantitative reverse transcription polymerase chain reaction (RT– PCR) amplification on pharyngeal swab specimens. Of the 300 patients included in the study, 7 had chronic renal failure (CRF), 8 had Alzheimer's, 30 had diabetes, 93 had chronic obstructive pulmonary disease (COPD), 18 had hypertension (HT), 19 had congestive heart failure (CHF), 17 had arrhythmia and 13 had coronary artery disease (CAD). The number of patients having blood group A, B, AB and O were 146 (48.7%), 53 (17.7%), 13 (4.3%), and 88 (29.3%), respectively. Of the patients, 260 were found to be Rh positive and 40 were found to be Rh negative; 154 patients were treated in ICU, 75 patients were intubated, and 112 patients died after hospitalization. The hospitalization periods of the patients were grouped as 0-7 days, 8-10 days, 11-13 days, and 14 days and above (Table 1).

Table 1. Comparison of the sociodemographic variables of the participants

Variables	**X ± S.S. (min-max)**
Age, mean ± SD	68.68 ± 13.34 (24-101)
	n (%)
Sex, male/female	173 (57.7) / 127 (42.3)
Comorbidity	
CRF	7(2.3)
Alzheimer	8(2.7)
Diabetes	30(10.0)
COPD	93(31.0)
HT	18(6.0)
CHF	19(6.3)
CAD	13(4.3)
Arrhythmia	17(5.7)
Blood Group A/B/AB/O	146(48.7)/53(17.7)/13(4.3)/88(29.3)
Rh +/-	260(86.7)/40(13.3)
ICU yes/no	154(51.3)/146 (48.7)
Intubation yes/no	75(25.0)/225(75.0)
Death yes/no	112(37.3)/188(62.7)
Hospitalization day 0-7/8-10/11-13/14+	67(22.3)/103(34.3)/50(16.7)/80 (26.7)
Total	300 (100.0)

Abbreviations: CRF chronic renal failure, COPD chronic obstructive pulmonary disease, HT hypertension, CHF congestive heart failure, CAD coronary artery disease, ICU intensive care unit

Of the 112 patients who died from COVID-19, 12 died after being treated in the intensive care unit for 6-7 days, 33 for 8-10 days, 24 for 11-13 days, and 44 for 14-55 (20.7 on average) days.

The prognosis of the disease with blood groups was evaluated

depending on whether or not the patients were hospitalized in the ICU, whether or not they were intubated, and their death status. Considering the relationship between ICU admission, intubation, and death status, the B blood group admission to intensive care unit (p=0.040) and mortality rates (p=0.006) were found to be significantly higher than other blood groups, whereas, intubation (p=0.005) and death rates (p<0.001) were significantly lower in O blood group than other groups (Table 2).

When comparisons were made between all the blood groups, intubation and death rates were it were found to be significantly higher in blood groups A and B, whereas, intubation and death rates were comparatively lower in O blood group (Table 3). No significant relationship could be observed between Rh groups and intensive care admission, intubation, and death.

Logistic regression models which were established to predict mortality and ICU admission risk in patients were found to be significant. According to the blood group variable, there was a significant difference (p<0.001) in mortality risks. As compared to O blood group, the mortality risk was 3.37 times higher in blood group A, 6.35 times higher in blood group B, and 4.61 times higher in blood group AB (Table 4).

When 21 991 people in the control group were evaluated in terms of ABO blood groups, it was seen that 45% had blood group A, 17.4% had blood group B, 6.9% had blood group AB and 30.6% had blood group O, respectively. The blood groups of COVID-19 patients were detected to be distributed as follows; 48.7% had A, 17.7% had B, 4.3% had AB and 29.3% had O blood group. When the blood groups of control group (control group=21 991) and COVID-19 infected patients are compared, it is seen that there is no significant difference, and the distribution is similar to the population (Table 5).

When the COVID-19 patients were compared according to their blood group type, their ages and hospitalization periods were not found to be significantly different (Table 6).

Table 2. Relationship between ICU, intubation and death status according to blood type

(n/%)	n	ICU	p	Intubation	p	Death	p
A	146	72/49.3	0.496	41/28.1	0.230	62/42.5	0.074
Non A	144	82/53.2		34/22.1		50/32.5	
B	53	34/64.2	0.040	18/34.0	0.137	29/54.7	0.006
Non B	247	120/48.6		57/23.1		83/33.6	
AB	13	7/53.8	0.853	4/30.8	0.743	6/46.2	0.563
Non AB	287	147/51.2		71/24.7		106/36.9	
O	88	41/46.6	0.290	12/13.6	0.005	15/17.0	<0.001
Non O	212	113/53.3		63/29.7		97/45.8	
Rh +	260	136/52.3	0.490	68/26.2	0.327	101/38.8	0.228
Rh -	40	14/45.0		7/17.5		11/27.5	

Table 3. Comparison of ICU, intubation and death status according to blood types

	A	B	AB	0	p
ICU	n/%	n/%	n/%	n/%	
No	74/50.7	19/35.8	6/46.2	47/53.4	0.208
Yes	72/49.3	34/64.2	7/53.8	41/46.6	
Intubation					
No	105/71.9	35/66.0[a]	9/69.2	76/86.4[b]	0.026
Yes	41/28.1[a]	18/34.0[a]	4/30.8[a,b]	12/13.6[b]	
Death					
No	84/57.5	24/45.3	7/53.8	73/83.0	<0.001
Yes	62/42.5[a]	29/54.7[a]	6/46.2[a]	15/17.0[b]	
Rh					
+	131/89.7	41/77.4	12/92.3	76/86.4	0.137
-	15/10.3	12/22.6	1/7.7	12/13.4	

Table 4. Mortality and ICU hospitalization logistic regression analysis

	Mortality		ICU	
	p	**O.R.**	**p**	**O.R.**
Rh	0.107	1.947	0.326	1.435
Blood Group	<0.001		0.257	
O-A	<0.001	3.372	0.980	0.993
O-B	<0.001	6.355	0.085	1.912
O-AB	0.017	4.615	0.517	1.482
Age	0.022	1.025	0.017	1.024
CRF	0.259	0.345	0.966	0.965
Alzheimer	0.261	2.492	0.379	2.128
Diabetes	0.637	1.252	0.782	0.878
COPD	0.468	1.236	0.826	0.941
HT	0.369	1.673	0.232	1.984
CHF	0.412	1.548	0.035	4.066
CAD	0.291	0.482	0.531	0.666
Arrhythmia	0.284	1.885	0.331	1.832

Table 5. Comparison of society and COVID-19 patients blood groups

			Groups		
			COVID-19	**Control**	**p**
Blood groups	A	n	146	9897	
		%	48.7	45.0	
	B	n	53	3835	
		%	17.7	17.4	0.269
	AB	n	13	1522	
		%	4.3	6.9	
	O	n	88	6737	
		%	29.3	30.6	

Table 6. Comparison of age and hospitalization day according to blood groups

Blood groups		**Age**	**Hospitalization day**
A	Mean	69.48	12.404
	Std. Deviation	12.518	7.5215
	Median	71.00	10.000
B	Mean	68.00	10.509
	Std. Deviation	15.722	4.1353
	Median	71.00	9.000
AB	Mean	66.31	12.923
	Std. Deviation	10.547	8.1901
	Median	66.00	9.000
O	Mean	68.10	11.852
	Std. Deviation	13.604	5.6863
	Median	71.00	10.000
	p	0.768	0.451

Discussion

In a review conducted by Ridwan et al. on 1885 COVID-19 patients, it was reported that male gender, HT, diabetes, coronary heart disease and COPD comorbidities, respectively, are important risk factors in the progression of the disease [10]. Similarly, majority of the patients in our study who were hospitalized in pandemic wards were observed to be male (57.7%). The comorbidity rates of our patients were as follows; chronic obstructive pulmonary disease (31%), diabetes (10%), hypertension (6%), congestive heart failure (6.3%), arrhythmia (5.7%), coronary artery disease (4.3%), Alzheimer (2.7%) and chronic renal failure (2.3%), respectively.

In another study by Vena et al. in Italy, average age of the patients was found to be 71 (60-82), whereas, HT, cardiovascular diseases, diabetes and neurological diseases were observed to be 47%, 19.9%, 15% and 8.8%, respectively [11]. In our study, average age of the patients was found to be 68.68%.

In a study on serious COVID-19 patients in China, He et al. determined the average age of the patients as 65 (50-77), and common comorbidities as HT (38.1%), diabetes (23.2%), and coronary heart diseases (17.6%). In this study, 47% of the patients were treated in the ICU, 40.5% were connected to a mechanical ventilator, and 39.6% died [12]. In our study, 51.3% of the patients hospitalized in pandemic wards were treated in the ICU, 25% were intubated, and 37.3% of the patients died.

The blood group system in humans known as ABO Blood groups, are localized on chromosome 9 (9q34.2). This system contains 4 groups, namely A, AB, B and O. Studies have shown that blood groups have a vital role in many diseases. In a study performed by Fan et al., the relationship between COVID-19 and blood types was investigated. According to a study, a significant relationship between patients with blood group A and COVID-19 was found [13].

In a study by Zietz et al., Rh negative individuals were reported to have a protective effect against SARS-CoV-2 infection, intubation and death [14]. In our study, we also evaluated the patients based on Rh positivity and negativity. However, we could not find a statistically significant relationship.

In a study performed by Wu et al., patients with A blood group were shown to have increased risk of infection, whereas, patients with O blood group were reported to have a lower risk [15]. In our study, ICU admission and mortality rates of blood group B were significantly higher than other blood groups, whereas, intubation and mortality rates ($p<0.001$) in blood group O were significantly lower than other groups.

In a study conducted in Denmark, individuals with O blood group were reported to be at lower risk; however, it did not make a difference in terms of hospitalization and death due to COVID-19 [16]. In our study, when hospitalization periods of COVID-19 infected patients were compared according to their blood type, no significant difference was found.

In a study conducted by Erec et al. in Diyarbakir, Rh positivity was reported to be statistically significantly higher in COVID-19 patients when examined in terms of Rh blood group system [17]. In our study, no relationship was found between Rh positivity or negativity of patients and COVID-19.

In a study conducted on 186 patients with PCR-confirmed COVID-19 diagnosis in Ankara, Goker et al. reported that blood group A was more susceptible to COVID-19 infection, whereas, blood group O was slightly protective [18]. In our study, when the blood groups were compared with each other, it was found that the mortality risk was 3.37 times higher in blood group A, 6.35 times higher in blood group B and 4.61 times higher in blood group AB as compared to blood group O.

In our study on blood groups in COVID-19 infected patients, we compared the blood groups of individuals with COVID-19 disease with those of the general population in order to obtain more accurate and reliable results. When the distribution of blood groups of the population (control group) and COVID-19 patients were compared, we observed no significant difference and the distribution was similar to the distribution in control group.

Consequently, association between blood groups and SARS-CoV-2 has been found in case of susceptibility to the COVID-19, and studies have revealed that blood groups can be a potential biomarker in determining susceptibility to COVID-19 infection. Specifically, people with blood group O have a lower risk for SARS-Cov-2 infection and COVID-19 severity.

Having different degrees of infection susceptibility of different blood groups means more protection of the individual who has the most susceptible blood group. Due to it is important to understand susceptibility of blood groups to COVID-19 for decrease the number of infected and death cases. People with B blood group might need particularly strengthened personal protection to reduce the chance of infection or COVID-19 patients might need to receive more vigilant surveillance and aggressive treatment. It might be helpful to introduce ABO blood typing in the management of SARS-CoV-2 infection and COVID-19.

Since majority of people infected with SARS-CoV-2 remain asymptomatic and hospital data in this regard are limited to patients with symptoms only, we believe that screening the entire population in order to assess relationship between blood types and COVID-19 susceptibility accurately will yield more precise results.

It is evident that further studies with vulnerable blood groups are needed to help prevent COVID-19 infection and achieve the goal of eliminating COVID-19 as a cosmopolitan public health problem. However, the association between COVID-19 disease and blood groups should not be evaluated alone, and the fact that the rate of being infected with COVID-19 depends on many factors should not be ignored.

Conclusion

It is evident that further studies with vulnerable blood groups are needed to help prevent COVID-19 infection and achieve the goal of eliminating COVID-19 as a cosmopolitan public health problem. However, the association between COVID-19 disease and blood groups should not be evaluated alone, and the fact that the rate of being infected with COVID-19 depends on many factors should not be ignored.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval
The study was carried out with the approval of Malatya Clinical Research Ethics Committee with protocol number 2021/02 on January 22, 2021.

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