

Association of blood groups on the risk of COVID-19 infection, morbidity, and mortality

 Meltem Sertbas,¹  Volkan Kizilay,²  Selma Dagci,²  Pinar Eker,²  Zeynep Yazici,³
 Ebru Elci Solak,³  Serkan Elarslan,¹  Nurettin Yiyit,⁴  Yasar Sertbas,¹  Kamil Ozdil²

¹Department of Internal Medicine, Health Sciences University Fatih Sultan Mehmet Training and Research Hospital, Istanbul, Turkey

²Department of Gastroenterology, Health Sciences University Umraniye Training and Research Hospital, Istanbul, Turkey

³Department of Cardiology, Health Sciences University Siyami Ersek Training and Research Hospital, Istanbul, Turkey

⁴Department of Thoracic Surgery, Health Sciences University Sehit Prof. Ilhan Varank Training and Research Hospital, Istanbul, Turkey

ABSTRACT

OBJECTIVE: We aimed to compare the effects of blood groups and Rh factor on the development of coronavirus-19 disease (COVID-19) with all aspects such as clinical course, inflammatory parameters, and organ-specific biochemical parameters with a significant number of patients.

METHODS: This multicenter study was carried out retrospectively on 3551 patients hospitalized with the diagnosis of COVID-19 and whose blood groups were recorded during the time of hospitalization. As control groups, 22133 individuals' medical data who were admitted to the blood bank affiliated with our hospitals during the last year was used. The differences between the blood groups and clinical characteristics were analyzed.

RESULTS: Of the 3551 patients, A Rh (+) blood group was found to be in a higher ratio in the case group than controls, with increased risk to be infected (case: 41.3% vs. control: 38.8%), (OR 1.113; 95% CI: 1.036–1.197; p=0.003). Meanwhile O Rh (+) blood group ratios were significantly lower in the case group than in the control group (case: 26% vs. control: 28.3%) (OR 0.862; 95% CI: 0.823–0.966; p=0.005). There was no significant difference between blood groups in terms of admission to the intensive care units and mortality, it was observed that patients with AB Rh (+) blood group have a greater risk for intubation than others (OR: 1.467; 95% CI: 1.040–2.071; p=0.028).

CONCLUSION: We demonstrated that people with blood group A Rh (+) more susceptible to COVID-19, whereas blood group O Rh (+) have a protective effect against the infection. Once a person has been infected with severe acute respiratory syndrome coronavirus 2, we should be mindful that patients with blood group AB Rh (+) would be prone to intubation more than other blood groups.

Keywords: Blood groups; coronavirus-19 disease; severe acute respiratory syndrome coronavirus 2.

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The novel coronavirus-19 disease (COVID-19) due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus was first reported in Wuhan, China, in December 2019 [1]. Since then, it has spread throughout the World with significant morbidity and

mortality. In March 2020, the World Health Organization (WHO) reported COVID-19 as a pandemic and, over time, reported 110749023 confirmed cases of infection and 2455131 deaths until February 22, 2021 [2]. Due to the high morbidity and mortality associated with

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Correspondence: Yasar SERTBAS, MD. Saglik Bilimleri Universitesi, Fatih Sultan Mehmet Egitim ve Arastirma Hastanesi, Ic Hastaliklari Klinigi, Istanbul, Turkey.

Tel: +90 216 578 30 00 e-mail: yserzincan24@gmail.com

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COVID-19, the risk factors that lead to COVID-19 are increasing in importance. Numerous studies have focused on factors that may make individuals more vulnerable to COVID-19. Advanced age, male sex, and chronic diseases (hypertension, diabetes mellitus, respiratory tract diseases, etc.) were considered to be the risks of the disease [3, 4].

There are various studies in the literature that show blood types associated with certain diseases and infections, including, *Plasmodium falciparum*, *Helicobacter pylori*, hepatitis B virus (HBV), Norwalk virus, and pancreas cancer [5–8]. Recent studies have focused on investigating the association of blood types and COVID-19. Although there are studies conducted in this area, conflicting results have been obtained. In most of the studies, COVID-19 is more common in those with blood type A and less in patients with type group O, but there are also some studies that have different results from the majority [9–12]. Besides the ABO blood group, there are also conflicting results about Rh factor as while Goker et al. claimed that the Rh factor did not show any significant difference, in their study, Arac et al. reported that the Rh (–) blood type is protective and Rh (+) blood type is significantly prone to COVID-19 [10–13]. We thought that the different results might be due to the small number of cases in these studies or due to the fact that Rh factor and ABO blood groups could affect the results when they were evaluated separately, as seen in some of the studies. The purpose of our study was to compare the impact of blood types on the development of COVID-19 with all aspects such as clinical course, inflammatory parameters, and organ-specific biochemical parameters with a significant number of patients.

MATERIALS AND METHODS

Sample Collection

This multicenter study was performed retrospectively on 3551 patients (over 18 years old) who were hospitalized with the diagnosis of COVID-19 and whose blood groups were recorded during the time of hospitalization in three main hospitals of Istanbul between 15.3.2020 and 15.12.2020. All these patients had a COVID-19 diagnosis by the RNA test through PCR and/or by the computed tomography imaging. The demographic information and laboratory parameters were derived from the patient's hospital medical records. Peak laboratory values were recorded for white blood cell count (WBC), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), procalcitonin, and D-dimer as inflammatory

Highlight key points

- People with blood type A Rh (+) were found to be more susceptible to COVID-19.
- People with blood type O Rh (+) had a protective effect against infection.
- Patients infected with SARS-CoV-2 were more prone to intubation if their blood type was AB Rh (+) than other blood groups.

markers with other biochemical markers such as alanine aminotransferase, aspartate aminotransferase, creatinine, and hemogram, as organ-specific parameters for liver, kidney, and bone marrow.

Other than these 3551 case groups, in order to compare the distribution of blood groups of community controls with cases, we have obtained 22133 individuals' medical data who were admitted to the blood bank affiliated with our hospitals during the last year as a control group. All procedures followed were conducted according to ethical standards. The Turkish health ministry and local ethical committee approval were obtained (FSM EAH- KAEK 2021/2). The Helsinki Declaration of Human Rights was followed.

Statistical Analysis

The analyses were carried out using the Statistical Package for the Social Sciences (SPSS) version 22.0 (SPSS for Windows Inc., Chicago, Illinois, USA). In the assessment of the study data, the compliance of the parameters with the normal distribution was assessed using the Shapiro–Wilk's test. In addition to descriptive statistics (mean, standard deviation, and frequency), while considering the study data, the one-way ANOVA test was used to compare the normally distributed parameters among the groups with quantitative data. The Kruskal–Wallis test was used to compare inter-group parameters, not showing normal distribution. The Student's t-test was used to compare parameters normally distributed and Mann–Whitney U test was used to compare parameters that did not have a normal distribution between the two groups. A Chi-square test was used to compare the qualitative data. Probability values were two-tailed and a p-value below 0.05 was considered meaningful.

RESULTS

In this study, we have recruited 3551 patients with a mean age of 57.54 ± 20.07 years as a case group, and among

TABLE 1. Blood group distribution of COVID-19 diagnosed patients and healthy controls

Blood groups	Control group (%)	Case group (%)	*p	OR	95% CI
A Rh (+)	38.8	41.3	0.003*	1.113	1.036–1.197
A Rh (–)	5.3	5.8	0.214	1.102	0.946–1.284
B Rh (+)	13.9	13.7	0.682	0.979	0.883–1.011
B Rh (–)	1.9	1.7	0.491	0.910	0.695–1.022
AB Rh (+)	6.7	7	0.636	1.034	0.900–1.189
AB Rh (–)	1	0.9	0.746	0.940	0.647–1.366
O Rh (+)	28.3	26	0.005*	0.892	0.823–0.966
O Rh (–)	4.1	3.6	0.124	0.862	0.714–1.042

Chi-square test, *: P<0.05; CI: OR: Odd ratios; Confidence interval.

TABLE 2. The distribution of the blood groups according to clinical outcomes

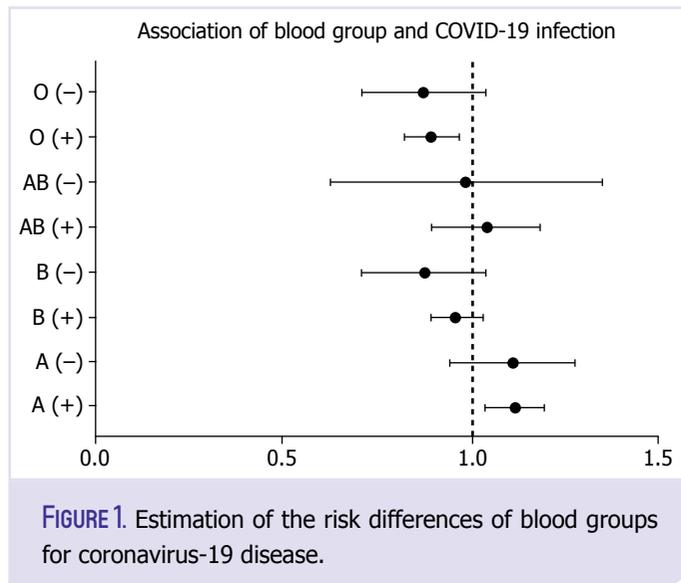
Blood groups	n	ICU n (%)	*p OR (95% CI)	Intubation n (%)	*p OR (95% CI)	Death n (%)	*p OR (95% CI)
A (+)	1468	384 (26.2)	0.421	190 (12.9)	0.946	337 (23)	0.562
Non-A (+)	2083	520 (25)	1.065 (0.91–1.24)	268 (12.9)	1.007 (0.83–1.23)	461 (22.1)	1.048 (0.89–1.23)
A (–)	205	47 (22.9)	0.391	23 (11.2)	0.421	41 (20)	0.382
Non-A (–)	3346	857 (25.6)	0.864 (0.62–1.21)	435 (13)	0.846 (0.54–1.32)	757 (22.6)	0.855 (0.60–1.22)
B (+)	486	116 (23.9)	0.387	58 (11.9)	0.495	104 (21.4)	0.542
Non-B (+)	3065	788 (25.7)	0.906 (0.72–1.13)	400 (13.1)	0.930 (0.74–1.17)	694 (22.6)	0.930 (0.74–1.47)
B (–)	62	14 (22.6)	0.600	5 (8.1)	0.252	11 (17)	0.368
Non-B (–)	3489	890 (25.5)	0.852 (0.47–1.55)	452 (13)	0.588 (0.23–1.47)	787 (22.6)	0.741 (0.38–1.43)
AB (+)	247	64 (25.9)	0.865	43 (17.4)	0.028	54 (21.9)	0.812
Non-AB (+)	3304	840 (24.4)	1.026 (0.76–1.38)	415 (12.6)	1.467 (1.04–2.07)	744 (22.5)	0.963 (0.70–1.32)
AB (–)	32	9 (27.1)	0.728	6 (18)	0.321	9 (28.1)	0.442
Non-AB (–)	3519	895 (25.4)	1.147 (0.53–2.49)	452 (12.8)	1.566 (0.64–3.83)	789 (22.4)	1.354 (0.82–2.94)
O (+)	924	241 (26.1)	0.612	121 (13.1)	0.835	218 (23.6)	0.343
Non-O (+)	2627	663 (25.2)	1.045 (0.88–1.24)	337 (12.8)	1.024 (0.83–1.28)	580 (22.1)	1.090 (0.91–1.30)
O (–)	127	29 (22.8)	0.490	12 (9.4)	0.238	24 (18.9)	0.326
Non-O (–)	3424	875 (25.6)	0.862 (0.57–1.31)	446 (13)	0.607 (0.38–1.27)	774 (22.6)	0.798 (0.51–1.72)

*: Chi square test; ICU: Intensive care unit; OR: Odd ratios; CI: Confidence interval.

these patients, 1854 (52.2%) of them were male and 1651 (47.8%) of the participants were female. In Table 1, we compared the blood group distribution of 22133 normal individuals with patients. As a result, the A Rh (+) blood group ratio was found to be significantly higher in the case group than in the control group (41.3% vs. 38.8%). People in blood group A Rh (+) were at a higher risk of getting the disease compared to other blood

groups (OR 1.113; 95% CI: 1.036–1.197; p=0.003). Meanwhile, blood group O Rh (+) ratios were significantly lower in the case group than in the control group (26% vs. 28.3%), and blood group O Rh (+) was found to be less risky in terms of COVID-19 (OR 0.862; 95% CI: 0.823–0.966; p=0.005) (Fig. 1).

While the average length of stay in the hospital was 9.91±7.5 days, it was 17.09±13.98 for the patients in



intensive care units (ICU). There was no association between the blood types of the patients and the duration in the hospital ward or ICU ($p > 0.05$). To reveal the relationship between the severity of the disease and blood groups, we compared blood groups with hospitalization in ICU, intubation rates, and mortality of the patient (Table 2). While there was not a significant difference among blood groups for admission to the ICU and mortality, it was observed that patients in blood group AB (+) were found to have a greater risk for intubation than others (OR: 1.467; 95% CI: 1.040–2.071; $p = 0.028$) (Fig. 2).

In terms of organ-specific biochemical parameters, no difference was found between blood groups and liver, kidney function values, and hemoglobin levels in COVID-19 patients ($p > 0.05$) (Table 3). There was not also any significant difference between the blood groups and the biochemical parameters which reveal the severity of inflammation during the disease (Table 4).

DISCUSSION

In total, 3551 patients with COVID-19 patients were recruited to the study. We have noticed that blood group A Rh (+) might be a risk factor for COVID-19. In contrast, the risk was less with blood group O Rh (+) for this infection. Our data did not show any significant difference among the blood group with ICU admission and mortality for the clinical outcome of the patients. On the other hand, the intubation proportion was significantly higher on blood group AB Rh (+) than others. Blood groups were not associated with inflammatory markers and organ-specific biochemical parameters.

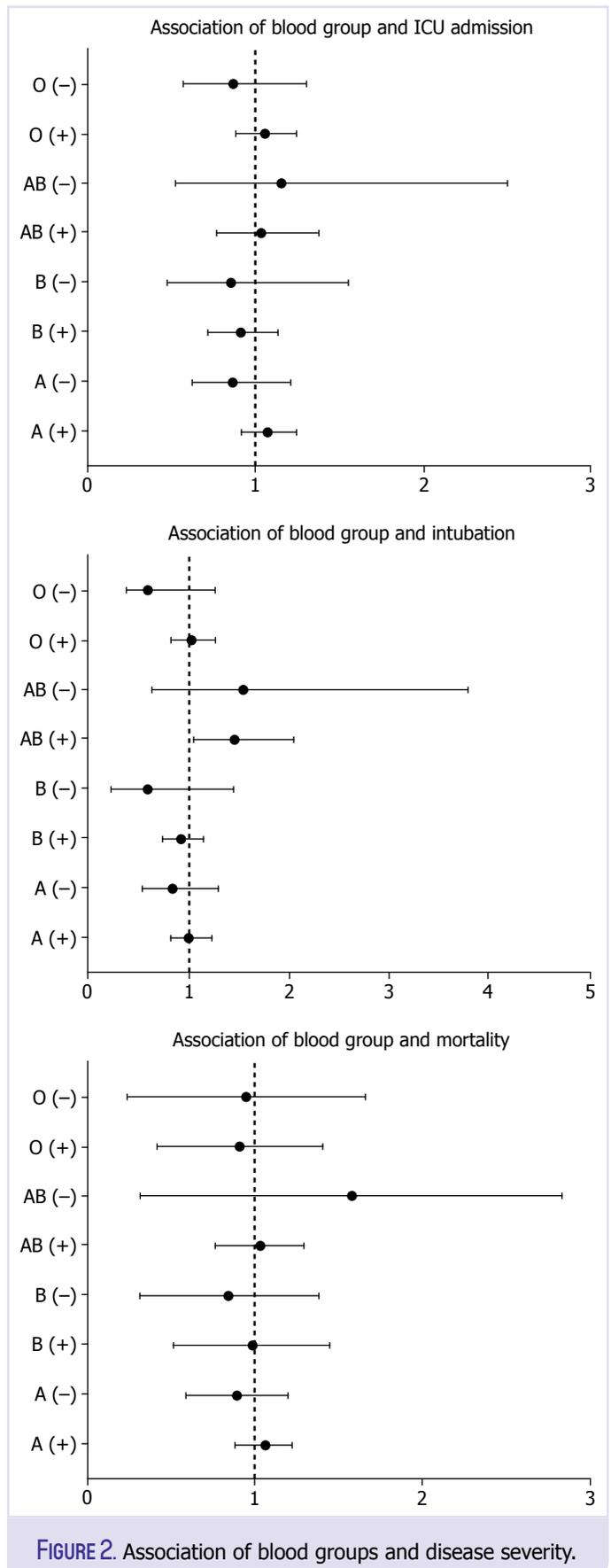


TABLE 3. Blood group effects on organ specific biochemical parameters

Blood groups	Alanine aminotransferase (u/l)	Aspartate aminotransferase (u/l)	Blood urea nitrogen (mg/dl)	Creatinine (mg/dl)	Hemoglobin (g/dl)	Hematocrit (%)
A Rh (+)						
Mean±SD	150.91±488.66	214.27±1183.4	57.76±55.37	1.85±2.12	13.23±1.96	39.94±5.44
Median (IQR)	51 (27–1102)	53 (31–95)	38.5 (21–79)	1.1 (0.82–1.81)	13 (13.1–13.3)	40.1 (39.6–40.2)
A Rh (–)						
Mean±SD	194.18±706.46	253.42±1055	56.15±54.5	1.73±1.77	13.39±2.11	40.43±5.76
Median (IQR)	52 (96–291)	48 (108–399)	40 (48–63)	1 (1.5–1.97)	13 (13–13.67)	41 (39.6–41.2)
B Rh (+)						
Mean±SD	120.49±284.83	153.61±526.69	59±59.8	1.81±1.99	13.14±2.04	39.74±5.82
Median (IQR)	47 (95–145)	49 (106–200)	37.5 (53–64)	1.1 (1.6–1.98)	13.2 (12.9–13.3)	40 (39.3–40.2)
B Rh (–)						
Mean±SD	95.26±235.54	81.53±100.3	57.3±56.16	1.43±1.23	13.31±2.11	40.11±5.9
Median (IQR)	45.5 (35–155)	49 (56–106)	38.5 (43–71)	1 (1.1–1.7)	13.5 (12.7–13.8)	40.8 (38.6–41.6)
AB Rh (+)						
Mean±SD	161.25±444.06	226.8±927.54	53.2±46.21	1.58±1.48	13.29±2.03	40.21±5.67
Median (IQR)	55 (105–216)	51 (110–343)	39 (47–58)	1.1 (1.4–1.76)	13.5 (13–13.5)	40.5 (39.6–40.2)
AB Rh (–)						
Mean±SD	149.88±330.6	162.13±358.6	55.74±42.27	1.82±1.66	12.71±2.39	38.21±6.89
Median (IQR)	67 (30–269)	67.5 (32–291)	47.5 (40–70)	1.1 (1.2–2.4)	12.4 (11.8–13.5)	37 (35.7–40.7)
O Rh (+)						
Mean±SD	168.93±607.27	243.15±1235.53	58.78±56.92	1.87±2.13	13.25±1.96	39.96±5.52
Median (IQR)	49 (129–131)	50 (163–323)	39 (55–62)	1.1 (1.7–2.0)	13.3 (13.1–13.4)	40 (39.6–40.3)
O Rh (–)						
Mean±SD	99.55±184.68	116.85±279.48	56.3±58.74	1.79±2.23	13.45±2.19	40.31±6.49
Median (IQR)	42 (67–131)	49 (67–166)	34.2 (45–66)	1.1 (1.3–2.1)	13.6 (13.1–13.3)	41.4 (39.1–41.4)
*p	0.313	0.710	0.938	0.63	0.493	0.426

SD: Standard deviation; IQR: Interquartile range; Kruskal-Wallis Test; *: p<0.05.

Since Australian physician Karl Landsteiner first described ABO blood groups in 1901, many studies have been done to describe the relation of blood groups with bacterial and viral infections [4, 6–8, 14]. Blood group antigens are found on a gene which is located on chromosome 9q34. 1–34. 2, and these antigens can be susceptible factors for some diseases and resistance factors for others. In their study, Batool et al. [4] discovered that blood type O could have some influence on protection against blood transmitted infections. They also indicated that people with blood Group A were more likely to become infected with HBV and HIV. In another study, although blood Group O did not affect the risk of infection with *Vibrio cholerae*. It had a considerable impact on the severity of the illness, as people with

blood type O were 8 times more likely to be hospitalized with severe cholera [7]. According to Lin [8], the prevalence of *H. pylori* was significantly higher in the blood Group O patients than the ones having other blood groups. They assumed that this might be due to the low number of receptors for *H. pylori* in blood Groups A and B. In the study from Germany, pancreatic cancer has been proven to be associated with ABO blood groups. At that study, Pelzer [6] identified that larger number of patients with blood type A had pancreatic cancer, while blood type O was less frequent in patients with pancreatic cancer. It has also been demonstrated that the Rh (Rhesus) blood group system is associated with other diseases, but the number of studies is very rare when compared to the studies related to the ABO

TABLE 4. Blood group effects on inflammatory markers for COVID19

Blood groups	White blood cell (10 ³ /ul)	Sedimentation (mm/hour)	C-reactive protein	Procalcitonin (ng/ml)	D-Dimer (ng/ml)
A Rh (+)					
Mean±SD	15.32±13.53	41.19±29.62	13.45±9.41	1045.72±6124.54	1116.09±2431.66
Median (IQR)	12.4 (8.8–18.07)	34 (11.75–18.07)	12.8 (6.15–20.6)	0.2 (0.03–1.57)	10.1 (1.98–1511)
A Rh (-)					
Mean±SD	15.35±15.17	36.04±31.3	13.86±9.31	1535.74±7457.25	1612.2±3246.65
Median (IQR)	12.4 (8.82–18.07)	26 (11.75–60)	12.9 (6.15–20.6)	0.2 (0.03–1.57)	24.9 (1.98–1511)
B Rh (+)					
Mean±SD	14.41±8.5	41.98±33.36	13.54±9.49	668.38±5283.94	1151.07±2389.39
Median (IQR)	11.9 (8.75–17.5)	31.5 (16.25–57)	12.8 (5.94–19.4)	0.2 (0.01–1.4)	9.7 (1.47–1302)
B Rh (-)					
Mean±SD	14.15±16.27	39.44±26.52	10.65±9.71	942.09±6442.22	1726.29±3169.18
Median (IQR)	10.5 (7.75–16.11)	39 (14.5–64.5)	8.6 (1.65–16.72)	0.1 (0.001–0.63)	575 (1.13–1618)
AB Rh (+)					
Mean±SD	15.25±9.89	44.29±28.65	13.25±9.22	842.49±5408.63	1314.38±2656.9
Median (IQR)	12.5 (9.31–17.61)	48 (18–69)	12.3 (5.5–20.4)	0.1 (0.01–1.01)	16.5 (1.73–1445)
AB Rh (-)					
Mean±SD	12.51±6.09	24.33±33.62	12.96±9.42	1571.03±8294.53	1840.41±3907.54
Median (IQR)	11 (8.85–15.79)	8 (12.55)	11.6 (4.7–21.32)	0.1 (0.001–2.36)	580 (1.49–1978)
O Rh (+)					
Mean±SD	15.51±11.62	38.35±29.67	13.23±9.53	853.77±5597.69	1091.43±2306.19
Median (IQR)	12.7 (8.9–11.1)	30.5 (15.00–57.00)	11.8 (5.82–19.7)	0.2 (0.001–2.13)	9.5 (1.81–1122)
O Rh (-)					
Mean±SD	13.76±7.67	41.13±24.48	12.69±8.81	1480.25±8086.52	1130.38±2502.75
Median (IQR)	12 (8.4–16.5)	50 (14–59)	12.4 (5.9–18.7)	0.2 (0.01–2.52)	4.4 (1.14–899)
*p	0.162	0.763	0.332	0.445	0.475

SD: Standard deviation; IQR: Interquartile range; Kruskal–Wallis Test; *: p<0.05.

blood group. One of these two studies we can mention is related to latent toxoplasmosis, and the other one is about West Nile infection [15, 16]. In both studies, the researchers demonstrated that Rh (+) blood groups have protective effects against these illnesses.

With the COVID-19 outbreak in December 2019, several studies have been carried out to determine whether blood groups have any association with COVID-19 or not, but the results were contradictory. In their research, Zhao [9] indicated that while patients with blood group A have increased risk for COVID-19 (OR: 1.279; 95% CI: 1.136–1.440), patients with blood group O were associated with decreased risk (OR: 0.680; 95% CI: 0.599–0.771). In a similar study, Goker et al. [10] concluded that blood type A could play a role in increasing vulner-

ability to COVID-19 infection, the blood type O may be somewhat protective. They also had looked at the association of Rh factors and COVID-19, but they could not find any effect between Rh positivity and COVID-19 infection. In another study, blood groups a ratio of the patients were significantly higher than controls (OR: 1.544; 95% CI: 1.222–2.104; p=0.006), whereas patients with blood Group O had a lower risk for SARS-CoV-2 infection (OR: 0.649; 95% CI: 0.457–0.927; p=0.018) [17]. In a study involving 14122 patients, Zietz et al. [18] observed a slight increase in the prevalence of infection in non-O blood groups. They considered that the Rh (-) blood type to have a protective effect against infection. Besides these studies, which indicate that blood Group A patient has a higher risk and blood group O has a lower risk factor for COVID-19, Arac et al. [13] have not

found any difference between blood groups ratio of patients with COVID-19 and healthy controls. In addition, they suggested that blood type Rh (–) is protective, while blood type Rh (+) is prone to infection. Contrary to previous studies, Latz et al. [11] found that AB and B blood groups had more COVID test positivity and, as in most of the studies, the test positivity was lower in the O blood group. They also indicated that the test was found to be more positive in Rh (+) patients. In our research, in line with most of the studies, the rate of patients with A Rh (+) was found to be higher than that of control. There was no significant difference in patients with A Rh (–). The proportion of patients with blood group O Rh (+) was significantly lower than the control group, whereas we could not find similar results for O Rh (–) group.

In addition to studies showing the relationship between COVID-19 and blood groups, some other studies also have been conducted to show the reason for these relationships. Although the mechanism that will explain the association of blood groups and COVID-19 is not clear, Cooling [19] claim that blood group could play a direct role in infection by their receptors or co-receptors for parasites, microorganisms, and viruses. Guillon et al. [20] also reported that human anti-A antibodies could pre-vent the association of SARS-CoV with its receptors. In light of all these studies, we can say that anti-A antibodies might be a factor for why blood type O patients being less likely to be infected with SARS-CoV-2.

In various studies, it has been shown that in addition to blood groups' role in being infected with SARS-CoV-2, they may also affect the outcome of the illnesses. In their study Yaylaci et al. [21] defined that ICU admission was higher in rate with the Rh (+) blood group ($p=0.011$), but no meaningful association was found between mortality and blood groups or Rh factors ($p>0.05$). In another study with 14112 participants, Zietz and Tatonetti [18] (2020) showed that the risk of intubation was significantly reduced in blood Groups A and marginally increased in blood Groups AB and B. On the other hand, the risk of death increased in the AB group and decreased for A and B blood groups. This study also indicated that Rh (–) blood group has an apparent protective effect for both intubation and mortality. Apart from these studies, in which the association of blood groups and clinical outcomes such as ICU admission, intubation, and mortality was shown, there are also other two studies without any significant relationship between blood groups and clinical outcomes of the patients [10, 11]. In our study, although we could not find any relationship in terms of admission to the ICU

and mortality, we observed that patient with AB (+) blood group has a greater risk for intubation than others, as seen in the study performed by Zietz and Tatonetti [12].

Apart from the previously mentioned risk of infection and clinical outcomes, some other studies show that ABO blood group antigen may improve the overall inflammatory response. Serum inflammatory markers, such as the soluble intercellular adhesive molecule-1 and tumor necrosis factor- α , were found to be increased in the case of single nucleotide polymorphisms at the ABO locus [22, 23]. Latz et al. [11] has investigated the relationship among the peak inflammatory markers (WBC, ESR, CRP) and blood groups but could not find any difference between the blood groups. Zhang et al. [24] demonstrated that procalcitonin could increase up to 8 times than normal due to the severity of COVID-19. In the study evaluating liver function test anomalies in a patient with COVID-19, Cai et al. [25] demonstrated that hepatic function tests can be up to 3 times of the upper limit of normal. They may also be higher due to progression to severe disease, with the exception of lopinavir/ritonavir, which could explain the reason for the increase in these parameters. In our study, we could not find an association between the blood groups and either organ-specific laboratory parameters or inflammatory markers.

Conclusion

In conclusion, we demonstrated that people with blood Group A Rh (+) more prone to COVID-19, whereas blood group O Rh (+) have a protective effect against the infection. Once a person has been infected with SARS-CoV-2, we should be mindful that patients with blood group AB Rh (+) would be prone to have so severe disease that earlier intubation might be needed before than other blood groups.

Ethics Committee Approval: The Fatih Sultan Mehmet Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 14.01.2021, number: FSM EAH- KAEK 2021/2).

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