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COVID-19 clinical course and blood groups: Turkish population-based study

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Background/aim: SARS-CoV-2 enters the cell through the binding of the S glycoprotein on the surface of the virus to the angiotensin-converting enzyme 2 (ACE-2) in the host cells and also SARS-CoV S protein binding to ACE-2 was inhibited by anti-A antibodies. The aim of the study was to investigate the relationship between blood groups and the course of COVID-19 in Turkey.

Materials and methods: Laboratory confirmed COVID-19 patients aged 18 and over (n = 39.850) were randomized in age and sex-matched groups according to blood groups

Results: Advanced age, male sex and blood group A were found to be related with increased rate of intensive care unit (ICU) admission (OR = 1.089, 95% CI: 1.085–1.093 for age; OR = 1.963, 95% CI: 1.737–2.218 for male sex; OR = 1.216, 95% CI: 1.023–1.446 for blood group A). When blood group O individuals were compared to non-O individuals, no significant difference was observed regarding the rate of hospital and ICU admission, mechanical ventilation (MV) support, length of hospital and ICU stay, and case fatality rate (CFR). The CFR in patients with blood group A, B, O, and AB were 2.6%, 2.2%, 3.1%, and 2.3%, respectively. There were no significant differences between Rh-negative and positive patients regarding the rate of hospital and ICU admission ($p = 0.280$ and $p = 0.741$, respectively), also the rate of MV support and CFR was similar ($p = 0.933$ and $p = 0.417$).

Conclusion: Our study revealed that ABO and Rh blood groups do not have any impact on the rate of hospital admission, hospital and ICU stay, MV support, and CFR.

Key words: Blood groups, COVID-19, SARS-CoV-2

1. Introduction

At the end of 2019, a cluster of pneumonia patients caused by SARS-CoV-2 was first detected in China [1–3]. The virus spread all over the world rapidly and on March 11, 2020; it was declared a pandemic [4].

Antigens of the ABO blood group system is found on the extracellular surface of erythrocyte membranes, and these antigens are defined as complex carbohydrate molecules. In addition to the ABO blood group system, the Rhesus (Rh) blood group is present and consists of at least 45 independent antigens. Both ABO and Rh blood group systems have been associated with several diseases. In some studies, ABO blood group system has been shown to play a role in the development of cardiovascular,

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oncologic, and other diseases [5]. Blood group antigens are known to participate in cell recognition and cell adhesion. Therefore, they are likely to play a role in tumour formation, metastasis, and prognosis [6]. In addition to these, blood group antibodies have been reported to have a role in immunity against a variety of viruses [7].

In recent studies, it was shown that SARS-CoV-2 enters the cell through the binding of the S glycoprotein on the surface of the virus to the angiotensin-converting enzyme 2 (ACE-2) in the host cells [8,9]. The entry of the virus into the cell initiates the immune response [10]. The S protein of SARS-CoV-2 and SARS-CoV spike is approximately 75% homologous [11,12]. Researchers revealed that the heavily glycosylated SARS-CoV S protein binding to ACE-2 was inhibited by anti-A antibodies [13]. Since SARS-CoV2 uses the same receptor as SARS-CoV, anti-A antibodies are expected to have similar effects against SARS-CoV2. There are clusters of glycosylation sites in the receptor-binding motif of the SARS-CoV and SARS-CoV2 S protein [14].

Many papers published regarding the blood groups and COVID-19 association, but still no consensus established on the subject [15]. The blood group and COVID-19 course may differ among countries since some studies suggested blood groups A was related to severe COVID-19, other studies did not confirm it [16–20]. So far, some studies with limited sample size have been published to give an insight for Turkish national population; however, big sample size studies needed to have stronger evidence [20,21].

Here, we are presenting the largest sample and age-sex-comorbidity matched cohort with an aim to investigate the relationship between blood groups and the course of COVID-19 in Turkey.

2. Materials and methods

2.1. Patients

The data of laboratory-confirmed COVID-19 patients diagnosed between March 11, 2020 and June 15, 2020 included in the Republic of Turkey, Ministry of Health database, were analysed retrospectively. Laboratory confirmed COVID-19 patients at the age of 18 and over and whose blood group could be reached from the database were randomized to age and sex-matched A, B, AB, and O blood groups.

2.2. Statistical analysis

Statistical analyses were executed with IBM SPSS Statistics for Windows, (Version 26.0; IBM Corp., Armonk, NY, USA). Demographic and clinical data were presented with descriptive statistics. Blood groups, Rh groups, sex, and age were included in the logistic regression model to determine independent predictors of outcomes. A 5% type-I error level was used to assess statistical significance.

3. Results

The characteristics and outcomes of the patients, according to ABO blood groups, are given in Table 1. Out of 39.850 patients, 15.663 (39.3%) were with blood group A, 13.963 (35%) were with O, 5865 (14.7%) were with B, and 4359 (10.9%) were with AB. When patients were classified according to ABO blood groups, the median age and male/female ratio were similar across the groups. The length of hospital stay was nine days in patients with blood group O, whereas it was eight days in patients with non-O blood groups. The length of the intensive care unit (ICU) stay was six days in patients with blood group B, whereas it was seven days in patients with non-B blood groups. 8148 (20.4%) patients were Rh-negative, and 31.702 (79.6%) patients were Rh-positive. When patients were classified according to Rh groups, the median age and male/female ratio were similar between groups (Table 2).

The rate of hospital admission was increased 1.188 times by male sex and 1.037 times by each 1-year increase in age (OR=1.037, 95% CI: 1.035-1.038 for age; OR=1.188, 95% CI: 1.136-1.242 for male sex). Advanced age, male sex and blood group A were found to be related with increased rate of ICU admission (OR = 1.089, 95% CI: 1.085–1.093 for age; OR=1.963, 95% CI: 1.737–2.218 for male sex; OR=1.216, 95% CI: 1.023–1.446 for blood group A) (Table 3). Advanced age and male sex were found to be related with increased rate of mechanical ventilation (MV) support (OR = 1.095; 95% CI: 1.090–1.099 for age; OR = 1.982; 95% CI: 1.715–2.290 for male sex). Male sex and age were found to be a risk factor for case fatality rate (CFR) (OR = 1.132, 95% CI: 1.126–1.138 for age; OR = 2.828, 95% CI: 2.393–3.342 for male sex) (Table 4).

When blood group O was compared to non-O blood groups, no significant difference was observed regarding the rate of hospital and ICU admission, MV support, length of hospital and ICU stay, and CFR. The CFR in patients with blood group A, B, O, and AB were 2.6%, 2.2%, 3.1%, and 2.3%, respectively. Rh groups were not found to be influencing the rate of hospital and ICU admission (OR = 1.031, 95% CI: 0.975–1.091 and OR = 0.977, 95% CI: 0.853–1.120, respectively) (Table 3). Moreover, Rh groups were not likely to affect the rate of MV support, and CFR (OR = 0.993, 95% CI: 0.847–1.164 and OR = 0.931, 95% CI: 0.784–1.106) (Table 4). The length of ICU stay was seven days, both in Rh-negative and positive patients. The length of hospital stay was nine days in Rh-negative patients and eight days in Rh-positive patients.

4. Discussion

The main findings of the study were as follows: (i) Advanced age, male sex and blood group A was found to be related with an increased rate of ICU admission; (ii) the CFR in patients with blood group A, B, O, and AB were

Table 1. The characteristics and outcome of patients according to ABO blood groups.

	0 (n = 13963, 35.1%)	A (n = 15663, 39.3%)	AB (n = 4359, 10.9%)	B (n = 5865, 14.7%)
Median age, years	39 (18–95)	38 (18–98)	38 (18–100)	37 (18–93)
Sex-Male	8270 (59.2%)	9507 (60.7%)	2763 (63.4%)	3548 (60.5%)
Sex-Female	5693 (40.8%)	6156 (39.3%)	1596 (36.6%)	2317 (39.5%)
Hospitalization	4612 (33%)	5035 (32.1%)	1382 (31.7%)	1829 (31.2%)
Hospital stays (days)	9 (2–59)	8 (2–72)	8 (2–63)	8 (2–56)
ICU admission	613 (4.4%)	634 (4%)	150 (3.4%)	191 (3.3%)
ICU stay (days)	7 (1–59)	7 (1–71)	7 (1–55)	6 (1–51)
MV support	435 (3.1%)	444 (2.8%)	116 (2.7%)	134 (2.3%)
CFR	433 (3.1%)	404 (2.6%)	102 (2.3%)	130 (2.2%)

CFR: case fatality rate; ICU: intensive care unit; MV: mechanical ventilation.

Table 2. The characteristics and outcome of patients according to Rh groups.

	Rh (-) (n = 8148, 20.4%)	Rh (+) (n = 31702, 79.6%)
Median age, years	40 (18–94)	38 (18–100)
Sex-Male	4727 (58%)	19361 (61.1%)
Sex-Female	3421 (42%)	12341 (38.9%)
Hospital admission	2790 (34.2%)	10068 (31.8%)
Hospital stays (days)	9 (2–72)	8 (2–67)
ICU admission	395 (4.8%)	1193 (3.8%)
ICU stay (days)	7 (1–71)	7 (1–62)
MV need	288 (3.5%)	841 (2.7%)
CFR	288 (3.5%)	781 (2.5%)

CFR: case fatality rate; ICU: intensive care unit; MV: mechanical ventilation.

similar; (iii) hospital, ICU admissions, MV support, and CFR were similar between Rh-negative and the positive patients.

Viruses may carry ABH structures, and natural anti-blood group antibodies have been reported to have a role in immunity against viruses [7]. In a previous study, the anti-A antibody was shown to neutralize HIV [22]. In another study, anti-A or anti-B antibodies were shown to sensitize HIV to complement-mediated inactivation [23]. Similar to the reports about HIV, researchers demonstrated that the measles virus was neutralized by anti-A antibodies [24]. If anti-A or -B antibodies have a role in antiviral immunity, it is expected that blood group O people should experience a lower risk of a viral infection than people with other blood groups. During the outbreak of SARS, the O blood group was reported to be related to a lower risk of SARS-CoV infection than other blood groups [25]. SARS-CoV infects cells such as pneumocytes, enterocytes, kidney distal tubular epithelium cells, and all these cells synthesize ABH antigens [26,27]. In a previous study, anti-A antibody was shown to inhibit the S protein/ACE2-dependent adhesion, therefore, could inhibit the entry of the virus into the host cell [13]. In addition to the blocking of entry of the virus into the host cell, anti-blood group antibodies can opsonize viral particles and can cause complement-mediated neutralization. Moreover, anti-blood group antibodies can contribute to help the generation of cytotoxic T cells against the virus [28,29]. Elderly males have reductions in anti-blood group antibody titres, and previous studies showed that the clinical course of COVID-19 is more severe in elderly males [30–31]. A recent publication showed that the odds ratio for acquiring COVID-19 is higher in blood group A than in blood group O [32].

Our findings have in common with some previous reports. Regarding the Turkish data, Goker et al. observed no effect of ABO blood groups on clinical outcomes and Solmaz et al. observed that group A was not associated with increased mortality and has no effect on clinical severity [20,21]. Similarly, we observed no effect of ABO and RH groups on hospitalization, MV need and CFR; however, we observed that blood group A was associated with increased risk of ICU admission. Other large sample size studies from other countries have conflicting results. Ray et al. published a population-based report from Canada, and observed group O could be associated with severe disease [17]. Elinghaus et al. reported ICU population from Italy and Spain; observed group A was associated with increased risk of respiratory failure, which was similar to

Table 3. The effects of blood groups on hospitalization and ICU admission.

	Hospitalization		Intensive care unit (ICU) admission	
Risk factors	OR (%95 CI)	p-value	OR (%95 CI)	p-value
Age	1.037 (1.035–1.038)	<0.001*	1.089 (1.085–1.093)	<0.001*
Sex (based = female)				
Male	1.188 (1.136–1.242)	<0.001*	1.963 (1.737–2.218)	<0.001*
ABO groups (based = B)				
O	1.018 (0.950–1.090)	0.614	1.123 (0.938–1.344)	0.208
A	1.027 (0.961–1097)	0.435	1.216 (1.023–1.446)	0.027*
AB	1.004 (0.921–1.095)	0.922	1.019 (0.811–1.281)	0.872
B		0.855		0.076
Rh groups (based = Rh(+))				
Rh (-)	1.031 (0.975–1.091)	0.280	0.977 (0.853–1.120)	0.741
Constant	10.344	<0.001	1.089	<0.001

*<0.05 significant; n = 39850; Nagelkerke r^2= 0.073 for hospitalization, n = 1588/39850; Nagelkerke r^2:0.21 for ICU admission; estimation by logistic regression.

Table 4. The effects of blood groups on MV and CFR.

	Mechanical ventilation (MV)		Case fatality rate (CFR)	
Risk factors	OR (%95 CI)	p-value	OR (%95 CI)	p-value
Age	1.095 (1.090–1.099)	<0.001*	1.132 (1.126–1.138)	<0.001*
Sex (based = female)				
Male	1.982 (1.715–2.290)	<0.001*	2.828(2.393–3.342)	<0.001*
ABO Groups (based = B)				
O	1.098 (0.888–1.359)	0.389	1.059 (0.842–1.331)	0.623
A	1.206 (0.983–1.480)	0.072	1.120 (0.898–1.397)	0.314
AB	1.135 (0.871–1.478)	0.348	1.011 (0.756–1.351)	0.943
B		0.299		0.696
Rh Groups (based = Rh(+))				
Rh (-)	0.993 (0.847–1.164)	0.933	0.931 (0.784–1.106)	0.417
Constant	1.095	<0.001	.000	<0.001

*<0.05 significant; n = 1129/39850; Nagelkerke r^2:0.22 for MV, n = 1069/39850; Nagelkerke r^2:0.35 for CFR; estimation by logistic regression.

our findings supporting that group A was associated with increased risk of ICU admission [33]. Li et al. published data from the China population, and observed that group A was associated with increased risk of hospitalization, on the contrary, group O has reduced risk of hospitalization. Barnkob et al. indicated no effect of ABO blood groups on clinical outcomes, which was similar to our findings regarding hospitalization, CFR and MV need [18].

In conclusion, contrary to the studies revealing the antiviral effect of anti-A and Anti-B antibodies, in our study, no significant difference was observed regarding the rate of hospital and ICU admission, MV support, length of hospital and ICU stay, and CFR between blood group O and non-O blood groups. Blood group A was found to be related to an increased rate of ICU admission compared to non-A blood groups. The superior side of this study

compared to other studies investigating the impact of blood groups on COVID-19 course is that the randomized patients in each blood group are age and sex matched. We did not observe any differences between blood group O and non-O blood groups regarding the rate of hospital admission, MV support, and CFR. In addition, we did not find any significant difference regarding the rate of hospital and ICU admission, MV support, and CFR when Rh-negative patients were compared to Rh-positive patients.

In summary, our study revealed that ABO blood groups and Rh groups do not have any impact on the course of COVID-19 and CFR.

Informed consent

Informed consent was waived since it is a population database study. We obtained approval of the Ministry of Health.

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