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Association between blood types and mortality rates in patients with COVID-19

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ABSTRACT. The literature indicates viral pathogens use blood group antigens as receptors. We studied if blood groups of COVID-19 patients differ in disease course and mortality risk.Utilizing a retrospective methodology, we scrutinized medical records of 7919 COVID-19 patients who were hospitalized at a tertiary medical center from March 2020 to February 2022. The patients were separated into two groups based on where they were treated: Group 1: Out-patient (non-hospitalized patients; n = 4908) and Group 2: In-patient (hospitalized patients; n = 3011). Rates of hospitalization, mortality, and demographics of COVID-19 patients were compared based on blood groups. The study population included 3809 (48.1%) female and 4110 (51.9%) male patients. The average age of patients was 53.8 ± 20.39 years. More than half were 65 and older. Blood group A Rh (+) was identified as the predominant one, comprising 39.9% of the total population sample. Age ⩾ 65 years and blood group AB Rh (+) were related to greater hospitalization rates (OR = 4.577 and OR = 1.200; respectively) as well as increased mortality rates (OR = 4.448 and OR = 1.339; respectively), whereas O Rh (+) and O Rh (-) had the opposite influence (OR = 0.896 and OR = 0.618 for hospitalization, OR = 0.810 and OR = 0.070 for mortality; respectively). Our research shows strong links between blood types and COVID-19, highlighting the need for personalized care.

Keywords: COVID-19; ABO blood groups; Rh blood groups; mortality; SARS-CoV-2.

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Introduction

The ABO blood group system antigens are intricate carbohydrate molecules that reside on the extracellular surface of the erythrocyte membrane. Additionally, the Rhesus (Rh) blood group encompasses over 45 autonomous antigens. These ABO and Rh antigens can serve as receptors for specific viral infections. Hence, the correlation between blood groups and various infectious diseases such as Rotavirus, Hepatitis B, Norwalk virus, cardiovascular diseases, and certain types of cancer has been extensively researched (Abegaz, 2021).

The coronavirus disease 2019 (COVID-19) pandemic, stemming from the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), precipitated an unparalleled public health crisis. Research into the correlation between blood types and COVID-19 remains current. An investigation carried out in an intensive care unit (ICU) revealed a connection between blood type O and an increased vulnerability to deterioration (Koç & Karcioglu Batur, 2022). Conversely, a separate study suggested that individuals with blood type O might have a protective advantage against COVID-19, whereas those with blood type A exhibited a notable susceptibility (Solmaz & Araç, 2021).

There is accumulating data regarding the blood groups and COVID-19 association, but we still need to establish a consensus on the subject (Solmaz & Araç, 2021; Koç & Karcioglu Batur, 2022; Zhang et al., 2023). So, our study aimed to determine whether the blood types of people infected with COVID-19 differ regarding disease progression and mortality risk.

Methods

Study design and participants

In this retrospective study, we investigated COVID-19 admissions at a tertiary care hospital with 900 beds in Ankara, Türkiye. Our cohort included patients aged 18 and above with SARS-CoV-2 infection confirmed

through real-time polymerase chain reaction (RT-PCR) tests and whose blood group could be reached from the hospital database. Data collection spanned from March 2020 to February 2022, resulting in a final sample of 7919 patients after thorough data cleansing and exclusions. The patients were separated into two groups based on where they were treated: Group 1: Outpatient (non-hospitalized patients; n = 4908) and Group 2: Inpatient (hospitalized patients; n = 3011).

We compared the demographics (age and gender) and blood types of the two groups. Then, we investigated the risk factors (age and gender) and blood types in hospitalized patients (Group 2), focusing on mortality and its possible association with blood group types.

The Hospital's Local Institutional Review Board granted ethical approval (approval date and number: April 25, 2022, 136/04).

Statistics

Statistical analyses were performed using IBM SPSS Statistics for Windows (Version 26.0; IBM Corp., Armonk, NY, USA). Demographic and clinical data were presented using descriptive statistics. The Shapiro-Wilk test was used to determine the normality of quantitative variables. Normally distributed quantitative variables were reported as mean ± SD. Categorical variables, which included personal information and blood types, were examined using frequency and percentage. Numerical variables were compared between groups using the Student t-test, while categorical variables were examined using the chi-square test. Cross-tabulation was used to investigate mortality causes and relationships using the chi-square test. The logistic regression model includes age (⩾ 65 years), and blood group types to identify independent predictors of death. All analyses used two-tailed tests, with significance.

Results

In total, 7919 COVID-19-positive patients were encompassed in this investigation. The study cohort comprised 3809 (48.1%) female and 4110 (51.9%) male patients. There existed no disparity in the mean ages of male and female patients (53±20.41 years vs 54.60±20.59 years respectively; p = 0.23). More than half of the patients (57%) were aged 65 years or older. The blood group A Rh (+) was identified as the most prevalent in both groups (39.8% in the outpatient group, and 40% in the inpatient group). It was observed that patients exceeding the age of 65, along with those possessing blood group AB Rh (+), exhibited a higher likelihood of hospitalization. Conversely, individuals with blood groups O Rh (+) and O Rh (-) were admitted at a diminished rate. The ratio of male to female was consistent between the two groups (Table 1).

Table 1. Demographic features and blood types of patients in Group 1 and Group 2.

Features		Group 1 (outpatient; n = 4908) n (%)	Group 2 (inpatient; n = 3011) n (%)	*p*
Age (years)	⩾ 65	1102 (22.5)	1716 (57)	0.000
	< 65	3806 (77.5)	1295 (43)	
Gender	Male	2523 (51.4)	1587 (52.7)	0.266
	Female	2385 (48.6)	1424 (47.3)	
Blood Types				
A Rh (+)		1952 (39.8)	1205 (40)	0.832
B Rh (+)		727 (14.8)	472 (15.7)	0.302
AB Rh (+)		343 (7.0)	249 (8.3)	0.039
O Rh (+)		1378 (28.1)	780 (25.9)	0.035
A Rh (-)		251 (5.1)	170 (5.6)	0.327
B Rh (-)		100 (2)	63 (2.1)	0.871
AB Rh (-)		42 (0.9)	28 (0.9)	0.805
O Rh (-)		115 (2.3)	44 (1.5)	0.006

Table 2 presents a comparison of the parameters of COVID-19 patients based on their risk of hospitalization. Advanced age was associated with a 4.577-fold increase in the hospitalization rate, while individuals with blood group AB Rh (+) had a 1.20 times higher likelihood of being hospitalized. Conversely, individuals with O Rh (+) and O Rh (-) blood groups exhibited lower hospitalization rates, with odds ratios of 0.896 and 0.618, respectively.

Table 2. Risk Factors for Hospitalization.

Risk factors	Odds Ratio (95% CI)
Age ⩾ 65 years	4.577 (4.147-5.050)
Male	1.054 (0.962-1.154)
A Rh (+)	1.010 (0.921-1.108)
B Rh (+)	1.069 (0.943-1.213)
AB Rh (+)	1.200 (1.012-1.422)
O Rh (+)	0.896 (0.808-0.992)
A Rh (-)	1.110 (0.909-1.356)
B Rh (-)	1.027 (0.747-1.413)
AB Rh (-)	1.087 (0.673-1.758)
O Rh (-)	0.618 (0.435-0.877)

It was found that 24.5% (n = 737) of the hospitalized patients (n = 3011) died. The comparison of mortality-related parameters revealed that advanced age raised the risk of death by 4.448 times and blood group AB Rh (+) increased the risk by 1.339 times. O Rh (+) and O Rh (-) blood types were observed to be associated with a decreased rate of death (OR = 0.810 and OR = 0.070, respectively) (Table 3).

Table 3. Odds Ratio of Mortality in Group 2 (Inpatients).

Risk factors	Odds Ratio (95% CI)	*p*
Age ⩾ 65 years	4.448 (3.635-5.444)	0.000
AB Rh (+)	1.339 (1.006-1.781)	0.045
O Rh (+)	0.810 (0.666-0.984)	0.037
O Rh (-)	0.070 (0.010-0.513)	0.000

In the logistic regression analysis involving the mortality outcome among hospitalized patients, advanced age of 65 years and possession of blood group AB Rh (+) were identified as factors linked to an elevated mortality rate, whereas individuals with blood group O Rh (-) demonstrated a decreased risk of fatality (Table 4).

Table 4. Logistic Regression Analysis of Risk Factors for Mortality.

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	90% Confidence Interval for B	
		B	Standard Error	Beta			Lower Bound	Upper Bound
1	(Constant)	- 0.015	0.018		- 0.810	0.418	- 0.050	0.021
	Age ⩾ 65 years	0.120	0.008	0.277	15.858	0.000	0.105	0.135
	AB Rh (+)	0.059	0.027	0.038	2.164	0.031	0.006	0.113
	O Rh (-)	- 0.203	0.063	- 0.057	- 3.245	0.001	- 0.326	- 0.080

Nagelkerke R2 = 0.194.

Discussion

The association between ABO blood types and infectious disease is a topic that has been widely discussed. However, the findings among COVID-19 patients are still inconclusive (Wang et al., 2021; Ray et al., 2021; Balaouras et al., 2022; Garibaldi et al., 2022; Gheshlagh et al., 2022). Multiple meta-analyses have demonstrated that individuals with blood group A are more sensitive than others (Ray et al., 2021; Garibaldi et al., 2022; Gheshlagh et al., 2022). We also found blood group A the most common among COVID-19 patients, indicating a possible association between blood group A and susceptibility to the virus.The blood group A is characterized by the presence of N-acetyl galactosamine on the surface of red blood cells, potentially serving as a receptor for the COVID-19 virus (Zaidi et al., 2020). Therefore, blood group A individuals may be considered as more susceptible to the virus. Conversely, blood group O lacks N-acetyl galactosamine on the surface of red blood cells, which could make them more resistant to infection with the virus (Zaidi et al., 2020). That hypothesis might elucidate why individuals with blood type O exhibited a diminished incidence of hospitalization and mortality upon contracting COVID-19.

In our study, we found that individuals with the AB Rh (+) blood group had higher rates of hospitalization and mortality. Previous studies suggest that the anti-A and anti-B antibodies produced against A and B antigens could potentially protect the lung epithelium and other targets from COVID-19 by preventing its interaction with the angiotensin-converting enzyme-2 (Gutiérrez-Valencia et al., 2022; Abuawwad et al., 2023). The absence of these antibodies could explain the greater sensitivity of the AB blood group. However,

Gérard et al. (2020), mentioned that although both blood groups O and B had anti-A antibodies in the serum, anti-A from blood group O was more protective than anti-A from group B. The potential explanation for this scenario suggests that the antibodies anti-A and anti-B found in group O individuals are predominantly of the IgG class, while individuals with groups A and B typically exhibit IgM as the prevailing antibody type (Gérard et al., 2020). This difference may also explain why blood groups A and B did not have the same lower rates as blood group O in terms of hospitalization and mortality rates.

A meta-analysis of the impact of ABO blood types and the Rh factor on the transmission, course, and outcome of COVID-19 found that Rh-positive persons are more likely to develop severe infection and complications than Rh-negative individuals (Abuawwad et al., 2023). Latz et al. (2020) found that Rh (+) blood was more likely to test positive for COVID-19. Previous research indicated that individuals with Rh (-) blood were shown to have a lower susceptibility to infection, intubation, and mortality, thus hinting at a potential protective attribute associated with the Rh (-) blood group (Bhandari et al.,2020; Zietz et al., 2020; Ray et al., 2021). Similarly anti-A and anti-B antibodies in blood group O, the Rh antibodies in Rh (-) blood group are of the IgG type (Dean, 2005). Individuals with blood group O were found less susceptible than blood groups A and B which had anti-A or anti-B antibodies in their serum. It is conceivable that a similar infection protection mechanism against COVID-19 also may be considered to operate in Rh (-) individuals. However, in order for Rh antibodies to develop in Rh (-) individuals, the person must be exposed to Rh (+) blood. Therefore, further investigations are necessary to substantiate these findings.

There are many studies in the literature on the same subject in different countries. Wang et al. (2021), in their meta-analysis that conducted studies from various countries, found that blood group O was associated with a lower risk. In comparison, blood groups A and AB were associated with a higher risk of COVID-19 infection. However, the same study found blood group B was associated with an increased risk of COVID-19 infection in the American population. A study was conducted in the same country as we investigated whether there was a relationship between ABO and Rh blood groups and various health outcomes, including nearly forty thousand patients, and found no significant correlation between blood groups and the rate of hospital admission, length of hospital or ICU stay, or fatality rates (Dal,2021). Another study revealed that individuals with blood type O might have a protective factor against COVID-19, whereas those with blood type A could be more susceptible to the virus. However, they found no association between those blood groups and the course of the disease or mortality (Solmaz & Araç, 2021). Variations in those outcomes may be due to factors such as sample size, ABO blood type variety, genetic variances, and virus strains.

Some research evaluating the impact of COVID-19 on gender susceptibility found that men and women are equally susceptible to COVID-19 infection, with men reporting a more severe course and death from COVID-19 infection than women (Mukherjee & Pahan, 2021; Zhang et al., 2023). It has been proposed that these discrepancies between men and women may be attributable to men having greater circulating angiotensin-converting enzyme levels than women (Cai, 2020; Mukherjee & Pahan, 2021). In our study, we found no difference between genders in terms of hospitalization or mortality.

Our study has some limitations. First and foremost, its design precludes the inference of causality. Second, its scope was limited because it was conducted at a single facility with no pediatric inpatient follow-up units. Third, patients with incomplete blood group information were excluded. Finally, we collected no information about co-morbidities, which could influence the outcomes.

Conclusion

As a consequence, we have established a correlation between blood groups and the prognosis as well as fatality rates of COVID-19. Older individuals aged over 65 with blood group AB Rh (+) exhibited elevated rates of hospitalization and mortality. Conversely, individuals with blood types O Rh (+) and O Rh (-) demonstrated a decreased risk of hospitalization and mortality when compared to other blood types. While the findings of the present study are intriguing, further investigations are imperative to delve into the connection between ABO and Rh blood group types and COVID-19, and to ascertain the risk factors affecting individuals.

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