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Investigating the Relationship between Blood Group and the Severity, Complications, and Mortality of COVID-19

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ABSTRACT

Background and Aim: The association between blood groups and susceptibility to certain infectious diseases has been previously explored. This study aimed to investigate the relationship between ABO and Rh blood groups and the severity, complications, and mortality of COVID-19.

Methods: In this cross-sectional study conducted in 2021, 632 patients aged over 18 years hospitalized with confirmed COVID-19 (positive PCR) at Masih Daneshvari Hospital were enrolled. After obtaining consent, their ABO and Rh blood groups were determined. Disease severity was classified as moderate, severe, or critical based on the lowest recorded oxygen saturation in room air. Data on the highest disease severity during hospitalization, acute renal failure, ICU admission, and mortality were collected without interfering with treatment.

Results: His most prevalent blood type was A+ (192 patients, 30.4%), while the least common was AB- (4 patients, 0.6%). Statistical analysis revealed a significant association between the A- blood group and disease severity. Specifically, 46.2% of A- patients required ICU admission, compared to 27.9% of patients with other blood groups (P-value= 0.044; OR=2.216, 95% CI: 1.005-4.890). Furthermore, the incidence of acute renal failure was significantly higher in A+ patients (19.8%) compared to others (13.6%) (P-value=0.049; OR=1.56, 95% CI: 0.999-2.455).

Conclusion: The A- blood group was associated with increased COVID-19 severity, indicated by a higher rate of ICU admission. The A+ blood group was linked to a greater incidence of acute renal failure. However, no significant relationship was found between any ABO or Rh blood group and mortality.

INTRODUCTION

Coronaviruses are naturally common in mammals and birds (1) and can cause various diseases, from the common cold to extensive lung involvement and acute respiratory failure. The outbreak of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) occurred in December 2019 in Wuhan, China, and the disease resulting from it was named Coronavirus Disease 2019 (COVID-19) (2).About 80% of COVID-19 patients experience mild illness. However, in 20% of cases, the disease becomes severe, necessitating hospitalization, and in 5% of cases, it may progress to respiratory distress or multiple organ failure. The mortality rate is estimated to be between 1% and 5% but varies with age and other conditions. The definitive diagnosis of

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COVID-19 is based on the Polymerase Chain Reaction (PCR) test (2). While the pathophysiology of COVID-19 is not fully understood, patients with severe disease often exhibit elevated serum levels of various cytokines and chemokines, and cytokine release syndrome is considered a primary cause of mortality (3).

Previous studies have indicated a relationship between blood groups and susceptibility to certain infectious diseases. For example, infection with the Norwalk virus and Hepatitis B virus has been associated with specific blood groups (4, 5). During the SARS epidemic, individuals with blood group O were reported to be more susceptible to the disease(6). Given the similarity between SARS-CoV and SARS-CoV-2, a potential relationship between blood group and COVID-19 was suggested. Furthermore, due to the unclear pathogenic mechanism of SARS-CoV-2, investigating the relationship between blood group and COVID-19 severity, complications, and mortality could aid in understanding the disease's pathogenesis and serve as a prognostic factor.

This study aimed to investigate the relationship between ABO and Rh blood groups and the severity of disease, complications (particularly renal complications), and mortality in COVID-19 patients.

MATERIALS and METHODS

Patients

This cross- sectional study conducted in 2021, included 632 COVID-19 patients with lower respiratory tract infection symptoms admitted to Masih Daneshvari Hospital. The inclusion criteria were age over 18 years and a positive PCR test from a nasopharyngeal sample.

Classification of Patients Based on COVID-19 Severity

Patient respiratory status was classified according to NIH guidelines based on the lowest O2 saturation at rest in room air during the disease course (7). Patients were categorized as mild (normal chest X-ray), moderate (abnormal chest X-ray and O2 saturation ≥ 94%), severe (O2 saturation < 94%), or critical (requiring non-invasive or invasive ventilation or ICU admission). For this study, the highest severity recorded during hospitalization was considered.

Blood samples were collected from each patient to determine ABO and Rh blood groups. No interventions were made in the diagnostic or therapeutic processes. Data regarding pulmonary involvement severity, Acute Respiratory Distress Syndrome (ARDS), acute renal failure, ICU admission, and mortality were recorded using a clinical questionnaire and Excel software. Statistical analysis was performed using SPSS version 16.

Data Analysis

Data were analyzed using SPSS version 21. Qualitative and numerical variables were described using ratios and mean ± standard deviation, respectively. Descriptive analysis for qualitative variables involved frequency tables, while numerical variables were summarized using mean and standard deviation. Inferential analysis employed the paired t-test, Wilcoxon signed-rank test, and McNemar test for quantitative variables. A significance level of 0.05 was used for all tests.

Ethical Considerations

The study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences (code: IR.SBMU.NRITLD.REC.1400.235). All procedures followed the Helsinki Declaration and ethical research guidelines. Written informed consent was obtained from all patients for the use of clinical data and blood samples. Patient names and personal information remained confidential.

RESULTS

General and demographic characteristics of the patients:

The study included 632 COVID-19 patients, of whom 344 (54.4%) were men and 288 (45.6%) were women. The mean age was 56.3 years, and 31.7% were over 65. Among the patients, 374 (59.4%) had at least one comorbidity or risk factor for severe COVID-19, with diabetes being the most common (23.5%). Regarding disease severity, 102 patients (16.1%) had moderate, 314 (49.7%) severe and 216 (34.2%) critical disease; no mild cases were hospitalized. ICU admission was required for 181 patients (28.6%), elevated creatinine was noted in 98, and 113 patients (17.9%) died. Table 1 summarizes the demographic characteristics, comorbidities, and disease outcomes.

Distribution of blood types in patients

The distribution of ABO and Rh blood groups among the patients is shown in Table 1. The most common blood group was A, followed by O and B. Considering the Rh factor, A+ was the most frequent, and AB- was the least frequent.

Table 1. Demographic, laboratory, blood group, and disease outcome characteristics in 632 patients with COVID-19

Parameter	n (%)
Age (mean)*	56.3 ± 16.23
Age > 65	200 (31.7)
Gender	
Male	344 (54.4)
Female	288 (45.6)
Comorbidity	**374 (59.4)**
HTN	135 (21.4)
DM	148 (23.5)
CRF	31 (4.9)
Obesity	118 (19.6)
Others	158 (25)
Laboratory results*	
WBC (per µL)	7871.1 (3985)
Lymphocyte (%)	20.1 (10.4)
Lymphocyte count	1373.1 (796.4)
Ferritin (ng/mL)	503.98 (460.67)
CRP (mg/dL)	34.65 (25.37)
IL-6 (pg/mL)	16.92 (22.82)
ABO Group	
A	218 (34.5)
B	146 (23.1)
AB	61 (9.7)
O	207 (32.8)
Rh	
Positive	560 (88.6)
Negative	72 (11.4)
ABO group & Rh	
A+	192 (30.4)
A-	26 (4.1)
B+	128 (20.3)
B-	18 (2.8)
AB+	57 (9.0)
AB-	4 (0.6)
O+	183 (29.0)
O-	24 (3.8)
Severity of disease	
Moderate	102 (16.1)
Severe	314 (49.7)
Critical	216 (34.2)
Acute renal Failure	98 (15.5)
ICU admission	181 (28.6)
Outcome	
Cure	113 (17.9)
Death	519 (82.1)

Abbreviations: SD: Standard Deviation, HTN: Hypertension, DM: Diabetes Mellitus, CRF: Chronic Renal Failure, WBC: White Blood Cells, CRP: C-Reactive Protein, IL-6: Interleukin-6, ICU: Intensive Care Unit.

- Mean ± Standard Deviation

Missing Laboratory Data: WBC: 60, Ferritin: 449, CRP: 288, IL-6: 352

Comparison of Demographic Indicators and Comorbidities across Blood Groups

Demographic indicators and comorbidities were compared across ABO and Rh blood groups. The analysis included age (over 65 years), sex, and comorbidity status. For this purpose, each blood group was first analyzed as a cohort, and then compared against all patients not belonging to that group. Both analytical approaches yielded consistent results, with no statistically significant differences observed.

Association of COVID-19 Severity and Outcomes with ABO Blood Groups

To investigate potential associations in detail, patients were stratified by the presence or absence of each specific ABO blood group, and disease severity and outcomes were compared between these strata.

No significant differences were found in mean arterial oxygen saturation across the different blood groups. Similarly, no significant differences were observed in laboratory parameters typically associated with COVID-19 severity, including white blood cell count, absolute and relative lymphocyte counts, and levels of the inflammatory markers ferritin, C-reactive protein (CRP), and interleukin-6 (IL-6).

Disease severity was further assessed using two classification systems: a three-tiered system ("moderate," "severe," and "critical") and a binary system ("non-severe" vs. "severe to critical"). However, disease severity, as defined by these classifications and blood oxygen levels, did not differ significantly among ABO blood groups.

Additional outcome measures, including duration of hospitalization, incidence of acute renal failure, need for intensive care unit (ICU) admission, and mortality, also showed no statistically significant differences between ABO blood groups. Detailed results are presented in Table 2.

Association of COVID-19 Severity and Outcomes with Rh Status

No significant differences were observed between Rh-positive and Rh-negative patients in mean arterial oxygen saturation or in the laboratory parameters analyzed (white blood cell count, absolute and relative lymphocyte counts, ferritin, CRP, and IL-6). Furthermore, disease severity, hospitalization duration, incidence of acute renal failure, need for ICU admission, and mortality rate did not differ significantly based on Rh status. Table 2 provides detailed information on these findings.

Table 2. Comparison of disease severity and outcome by ABO blood group in 632 patients with COVID-19

Parameter / Blood Group			A			B			O			AB			RH		
			YES	NO	p-value	YES	NO	p-value	YES	NO	p-value	YES	NO	p-value	Positive	Negative	p-value
ICU admission		Count	68	113	0.303	40	141	0.705	56	125	0.538	17	164	0.889	155	26	0.136
		%	31.2	27.3		27.4	29.0		27.1	29.4		27.9	28.7		27.7	36.1	
Severity	Moderate	Count	33	69	0.514	21	81	0.741	38	64	0.537	10	92	0.866	93	9	0.438
		%	15.1	16.7		14.4	16.7		18.4	15.1		16.4	16.1		16.6	12.5	
	Severe	Count	104	210		76	238		102	212		32	282		280	34	
		%	47.7	50.7		52.1	49.0		49.3	49.9		52.5	49.4		50.0	47.2	
	Critical	Count	81	135		49	167		67	149		19	197		187	29	
		%	37.2	32.6		33.6	34.4		32.4	35.1		31.1	34.5		33.4	40.3	
Severity	Non-severe	Count	33	69	0.619	21	81	0.511	38	64	0.290	10	92	0.955	93	9	0.795
		%	15.1	16.7		14.4	16.7		18.4	15.1		16.4	16.1		16.6	12.5	
	Severe/ Critical	Count	185	345		125	405		169	361		51	479		467	63	
		%	84.9	83.3		85.6	83.3		81.6	84.9		83.6	83.9		83.4	87.5	
ARF		Count	42	56	0.058	23	75	0.925	25	73	0.096	8	90	0.587	86	12	0.773
		%	19.3	13.5		15.8	15.4		12.1	17.2		13.1	15.8		15.4	16.7	
Outcome	Dead	Count	35	78	0.385	28	85	0.641	39	74	0.660	11	102	0.974	102	11	0.54
		%	16.1	18.8		19.2	17.5		18.8	17.4		18.0	17.9		18.2	15.3	
	Recovered	Count	183	336		118	401		168	351		50	469		458	61	
		%	83.9	81.2		80.8	82.5		81.2	82.6		82.0	82.1		81.8	84.7	

Abbreviations: ICU: Intensive Care Unit, ARF: Acute Renal Failure
Missing Data: WBC: 60, Ferritin: 449, CRP: 288, IL-6: 35

Table 3. Comparison of disease severity and outcomes by ABO and Rh blood group in 632 patients with COVID-19

Parameter / Blood Group			A+		p-value	A-		p-value	B+		p-value	B-		p-value
			Yes	No		Yes	No		Yes	No		Yes	No	
ICU admission		Count	56	125	0.846	12	169	**0.044***	33	148	0.423	7	174	0.329
		%	29.2	28.4		46.2	27.9		25.8	29.4		38.9	28.3	
Severity	Moderate	Count	29	73	0.891	4	98	0.081	19	83	0.682	2	100	0.618
		%	15.1	16.6		15.4	16.2		14.8	16.5		11.1	16.3	
	Severe	Count	96	218		8	306		68	246		8	306	
		%	50.0	49.5		30.8	50.5		53.1	48.8		44.4	49.8	
	Critical	Count	67	149		14	202		41	175		8	208	
		%	34.9	33.9		53.8	33.3		32.0	34.7		44.4	33.9	
Severity	Moderate	Count	29	73	0.640	4	98	0.915a	19	83	0.656	2	100	0.556[a]
		%	15.1	16.6		15.4	16.2		14.8	16.5		11.1	16.3	
	Severe/Critical	Count	163	367		22	508		109	421		16	514	
		%	84.9	83.4		84.6	83.8		85.2	83.5		88.9	83.7	
ARF		Count	38	60	**0.049 ****	4	94	0.986a	18	80	0.613	5	93	0.144[a]
		%	19.8	13.6		15.4	15.5		14.1	15.9		27.8	15.1	
Outcome	Dead	Count	31	82	0.452	4	109	0.735a	25	88	0.585	3	110	0.892[a]
		%	16.1	18.6		15.3	18.0		19.5	17.5		16.7	17.9	
	Recovered	Count	161	358		22	497		103	416		15	504	
		%	83.9	81.4		84.6	82.0		80.5	82.5		83.3	82.1	

Continuation of Table 3:

Parameter		Blood Group	O+ Yes	O+ No	p-value	O- Yes	O- No	p-value	AB+ Yes	AB+ No	p-value	AB- Yes	AB- No	p-value
ICU admission		Count	50	131	0.640	6	175	0.688	16	165	0.921	1	180	0.872[a]
		%	27.3	29.2		25.0	28.8		28.1	28.7		25.0	28.7	
Severity	Moderate	Count	36	66	0.298	2	100	0.223	9	93	0.888	1	101	0.863[a,b]
		%	19.7	14.7		8.3	16.4		15.8	16.2		25.0	16.1	
	Severe	Count	86	228		16	298		30	284		2	312	
		%	47.0	50.8		66.7	49.0		52.6	49.4		50.0	49.7	
	Critical	Count	61	155		6	210		18	198		1	215	
		%	33.3	34.5		25.0	34.5		31.6	34.4		25.0	34.2	
Severity	Moderate	Count	36	66	0.123	2	100	0.289[a]	9	93	0.940	1	101	0.629[a,b]
		%	19.7	14.7		8.30	16.4		15.8	16.2		25.0	16.1	
	Severe/ Critical	Count	147	383		22	508		48	482		3	527	
		%	80.3	85.3		91.7	83.6		84.2	83.8		75.0	83.9	
ARF		Count	22	76	0.122	3	95	0.678[a]	8	90	0.748	0	98	0.390[a,b]
		%	12.0	16.9		12.5	15.6		14.00	15.70		0	15.6	
Outcome	Dead	Count	35	78	0.602	4	109	0.874[a]	11	102	0.770	0	113	0.349[a,b]
		%	19.1	17.4		16.7	17.9		19.3	17.7		0	18.0	
	Recovered	Count	148	371		20	499		46	473		4	515	
		%	80.9	82.6		83.3	82.1		80.7	82.3		100	82.0	

a. More than 20 of the cells in this sub-table have expected cell counts of less than 5. Chi-square results may be invalid.
b. The minimum expected cell count in this sub-table is less than one. Chi-square results may be invalid.
* OR: 2.216 (95% Confidence Interval: 1.005 – 4.890)
** OR: 1.563 (95% Confidence Interval: 0.999 – 2.455)
Abbreviations: ICU: intensive care unit, ARF: acute renal failure

DISCUSSION

In our study population, the most prevalent blood group was A+, while the least common was AB-. Our findings suggest that blood group A may be associated with ICU admission and acute renal failure in COVID-19 patients. Specifically, the A- blood group was linked to a higher rate of ICU admission, and the A+ group was associated with an increased incidence of acute renal failure. However, blood group did not significantly influence mortality, oxygen saturation levels, or other prognostic indicators.

The ABO blood group system has been linked to susceptibility to various diseases, including infections (8). For instance, blood group O has been associated with a higher incidence of cholera, plague, tuberculosis, and mumps, while blood group A has been linked to smallpox and Pseudomonas infections. For individuals with blood group B, it has been suggested that the incidence of gonorrhea, tuberculosis, and infections caused by Streptococcus pneumoniae, E. coli (particularly urinary tract infections), and Salmonella is elevated. Additionally, in blood group AB, a higher incidence of smallpox, E. coli, and Salmonella has been noted (9-11).

The Rh antigen may also influence susceptibility to certain parasitic infections (12, 13). Viral infections such as Norwalk virus and hepatitis B have also shown associations with specific blood types (14). In one study, the incidence of influenza was significantly higher in individuals with blood types A and B compared to those with blood types O and AB (15). Conversely, another study indicated that having an O-positive blood type was a risk factor for influenza. Similar responses to the influenza vaccine have also been noted across blood types, although serologic responses to the live vaccine were reported to be higher in individuals with blood type A (16). The mechanisms involved remain poorly understood. The observed variation in ABO blood groups across different regions of the world may be attributed to past epidemics. It could also stem from similarities between microbial antigens and blood group antigens. An H-like antigen has been identified in the plague bacillus and an A-like antigen on the smallpox virus. These similarities render individuals who can produce antibodies against the H antigen (blood groups A and B) resistant to plague and cholera, while those with anti-A antibodies (groups B and O) exhibit greater resistance to smallpox (9).

During the COVID-19 pandemic, several studies reported a higher risk of infection and severe disease in individuals with

blood group A compared to those with group O (6, 17-25). A study from Denmark revealed that individuals with blood group O, along with higher titers of anti-A (IgG) and anti-B (IgM), are at a lower risk of COVID-19 (26). A case-control study in Northern Cyprus, which compared 297 COVID-19 patients with 18,342 healthy controls, found a higher incidence of COVID-19 among men, especially those with blood group A (27).

Multiple meta-analyses concur that blood group A is associated with an increased risk of SARS-CoV-2 infection compared to non-A blood groups, whereas blood group O appears to be protective. For instance, one meta- analysis of approximately 31,100 participants reported significantly higher odds of infection for group A (OR ~1.25) and significantly lower odds for group O (OR ~0.70) (28). Similarly, another meta-analysis concluded that individuals with blood group A or B had elevated odds of infection, again confirming a protective effect for blood group O (29).

In addition to the influence of blood types on the risk of COVID-19, their effect on patient symptoms and disease severity has also been explored (30). Several studies have demonstrated that patients with blood type A are at a greater risk of developing more severe forms of COVID-19 (4, 31-33) and that having blood type O decreases the risk of critical and severe outcomes compared to blood type A (34, 35). One of the primary hypotheses to explain this observation is that individuals with blood types O and B, unlike those with blood type A, possess anti-A antibodies; this antibody may serve as a partial defense against the SARS-CoV-2 virus(18, 31). This antibody has been demonstrated to bind to the S protein of SARS-CoV-2 and inhibit its interaction with the ACE II receptor, potentially preventing the virus from entering the lung epithelium (35). Anti-A antibodies have also been found to offer greater protection in patients with blood group O compared to those with blood group B, which may be linked to the isotype of this antibody, as the predominant isotype of anti-A antibodies in blood group O is IgG, while in blood group B it is IgM (36). Conversely, individuals with blood group O exhibit lower serum levels of ACE II protein, whereas those with blood group A have the highest serum levels of ACE II. Since angiotensin II can worsen inflammatory responses and elevate blood pressure, this may explain the differences observed in patients with blood groups A and O, although it has been noted that serum ACE II levels do not influence the incidence of disease complications, including mortality, acute renal failure, and acute respiratory failure (23).

Other studies have also been conducted regarding the incidence of complications. Among them is the study by Hoiland et al., which found that patients with blood types A and AB were at a greater risk of requiring mechanical ventilation, and dialysis, and experiencing an increased length of stay in the ICU compared to those with blood types O and B. Higher levels of biomarkers associated with liver and kidney failure (creatinine and liver enzymes) were also observed in COVID-19 patients with blood types A and AB (37). Another relevant study is by Nasiri et al., which was conducted cross-sectionally in a hospital in Qom between April and July 2020 on 329 patients. Although it took longer for individuals with blood type B to reach normal oxygen levels after recovery, this study did not find a relationship between the severity of complications from COVID-19 and blood type (38). A study by Zeitz et al. showed that the incidence of COVID-19 was higher in individuals with blood types other than O, especially type A; however, compared to blood type O, the risk of intubation was lower for group A and higher for blood types AB and B, while the risk of death was higher for blood type AB and lower for groups A and B (39) .Additionally, a study by Al-Ansari et al. indicated that the risk of mortality and the duration of ICU stay in patients with COVID-19 were higher in individuals with blood types A and AB than in those with blood types O and B. However, there was no difference between these blood types regarding the need for mechanical ventilation (40). In another retrospective study by Ayatollahi et al. in Gorgan involving 1,554 patients, the mortality rate was found to be higher in individuals with blood group A negative and B negative compared to those with blood group A positive. Conversely, the mortality rate was lower in blood groups O negative, O positive, AB positive, and B positive (41). Behnaz et al.'s study, which examined 130 patients hospitalized in the ICU of Shohada Tajrish Hospital in Tehran, revealed that the highest need for intubation was observed in patients with blood group A positive, while those with blood group B positive required intubation less frequently. Regarding mortality rates, the highest was recorded among patients with blood group A positive (39.6), followed by individuals with blood group AB negative (33.3). However, the limitations of this study indicate that the increased incidence of complications in individuals with blood group A positive may be attributed to the higher number of hospitalizations for this blood group in this facility (42).

Studies have indicated that the severity of mortality in patients with COVID-19 is linked to the occurrence of cardiovascular events. It is possible that individuals with blood type O have elevated levels of coagulation factor VIII and von Willebrand factor, resulting in a lower risk of developing cardiovascular disease during COVID-19 infection, and consequently, a reduced mortality rate from cardiovascular complications (43). In contrast, individuals with blood type A have experienced a higher risk of thrombotic events during COVID-19(44, 45). Overall, the findings from studies in this area are inconsistent and occasionally contradictory.

LIMITATIONS

This study has several limitations. A primary constraint was the relatively small patient cohort, which may have reduced the statistical power to detect significant associations, particularly given the multitude of factors influencing COVID-19 severity. The absence of a control group further limited the ability to draw definitive comparative conclusions. Inconsistencies in the definition of disease severity across the literature, coupled with variations in population demographics (e.g., ethnicity and age), geographic location, circulating viral variants, and disparities in healthcare access, also contribute to divergent findings among studies. Finally, the evolving nature of the pandemic- including improvements in medical management, vaccine rollout, and the emergence of new viral variants- mean that associations identified in the early phases of the outbreak may not be generalizable to later stages.

CONCLUSION

COVID-19 patients with blood type A- had an increased likelihood of ICU admission, while those with blood type A+ faced a higher incidence of acute kidney failure. However, blood type was not significantly associated with mortality or disease severity based on oxygen levels.

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CONFLICT OF INTEREST

None.

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AI USE DECLARATION

The authors declare that no Artificial Intelligence (AI) tools or Large Language Models were used in the preparation of this manuscript. All content was produced solely by the authors, who take full responsibility for its accuracy and integrity.

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