




# Association between blood groups and COVID-19 outcome in Iranian patients

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**Aim:** Many factors have been speculated to explain the COVID-19 complex clinical phenotype. Due to the inconsistent data published on blood groups and COVID-19, we conducted a study on Iranian patients to further assess this association. **Materials & methods:** This retrospective study was conducted on data collected from confirmed COVID-19 hospitalized patients during March and December 2020 in a referral hospital for COVID-19, 5 Azar Hospital, Gorgan, north of Iran. A total of 1554 confirmed COVID-19 cases were enrolled in the study with blood group (ABO and Rh), demographic, and clinical data available. **Results:** Of 1554 patients, 1267 and 287 cases had recovered and deceased (due to COVID-19) outcomes, respectively. Most of the cases had O+ (29.6%), the least number had AB- (0.5%), and most of the deceased cases had O+ blood types (31.4%). Logistic regression analysis revealed that groups A- and B- had higher and groups B+, AB+, O+ and O- had lower odds of death than the A+ group. **Conclusion:** This study indicates that blood types may be related to the clinical outcome of COVID-19. Further studies with a large cohort for multiple people are required to validate this association.

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**Keywords:** ABO • blood groups • COVID-19 • Iran • Rh • SARS-CoV-2

COVID-19, an infectious disease caused by SARS-CoV-2, emerged in late November 2019 in Wuhan, China, and has become a pandemic disease. The WHO has identified the disease as a public health priority of international concern [1]. As an emerging virus, all people may be susceptible to SARS-CoV-2 infection, but the clinical course and outcome of COVID-19 vary significantly among individuals. While most infected cases present asymptomatic or mild symptoms, a small number are severely affected by COVID-19 [2]. It is unclear why severe disease and death occur only in a small subset of COVID-19 patients [3]. Despite efforts to elucidate mechanisms for differential clinical responses to SARS-CoV-2 infection, they remain largely elusive.

Although older patients with predisposing risk factors are more susceptible to severe forms of COVID-19, several cases of severe infection occur among previously healthy individuals [4]. Many factors (related to host, virus and environment) have been speculated to explain the COVID-19 complex clinical phenotype, but the exact contributions of each factor remain contentious [3]. It is well accepted that host differences (mainly genetic makeup) could dictate any viral infection's clinical course and outcome [3,5]. People are different in many aspects, and we are in the preliminary stage to characterize stimulating factors for this complex disease. Since we have to live with SARS-CoV-2 for a long time, finding specific factors associated with the complicated disease outcome is very important.

**Table 1. Demographic, sex, age, blood group and hospitalization wards of all, recovered and deceased cases.**

Variables	All cases (%)	Recovered (%)	Deceased (%)	p-value
<b>Sex</b>				
Female	740 (47.6)	606 (47.8)	134 (46.7)	
Male	814 (52.4)	661 (52.2)	153 (53.3)	
Total	1554 (100)	1267 (81.5)	287 (18.5)	0.354
<b>Age (years)</b>				
1–29	92 (5.92)	85 (6.71)	7 (2.44)	
30–39	174 (11.20)	159 (12.55)	15 (5.23)	
40–49	279 (17.95)	254 (20.05)	25 (8.71)	
50–59	314 (20.21)	271 (21.39)	43 (14.98)	
≥60	695 (44.72)	498 (39.31)	197 (68.64)	<0.001
<b>Blood group</b>				
A+	427 (27.5)	342 (27)	85 (29.6)	
A-	45 (2.9)	31 (2.4)	14 (4.9)	
B+	401 (25.8)	353 (27.9)	48 (16.7)	
B-	35 (2.3)	18 (1.4)	17 (5.9)	
AB+	105 (6.8)	86 (6.8)	19 (6.6)	
AB-	7 (0.5)	7 (0.6)	0 (0.0)	
O+	460 (29.6)	370 (29.2)	90 (31.4)	
O-	74 (4.8)	60 (4.7)	14 (4.9)	<0.001
<b>Hospitalization wards</b>				
Infectious Disease	1102 (70.91)	1078 (85.08)	24 (8.36)	
ICU/CCU/Emergency	288 (18.53)	52 (4.10)	236 (82.23)	
Post-ICU/isolated room	74 (4.76)	54 (4.26)	20 (6.97)	
Other wards	90 (5.79)	83 (6.55)	7 (2.44)	<0.001

CCU: Cardiac care unit; ICU: Intensive care unit.

The association between blood groups and susceptibility to some viral infections has been well established [6–11]. The blood group antigens are cell-surface glycoproteins present principally on erythrocytes that may affect infectious diseases [12]. During the current pandemic, several studies have investigated the association of blood groups and COVID-19 [13–18]. Some studies suggested that patients with blood group A are more susceptible to severe infection, but there are other controversial results [19–24]. More studies are needed to confirm the association between blood grouping and COVID-19 susceptibility and severity. Here, we investigated the association between blood groups (ABO and Rh) and COVID-19 outcomes in Iranian hospitalized patients.

## Materials & methods

This retrospective study was conducted on data collected from patients hospitalized during March and December 2020 in a referral hospital for COVID-19, 5 Azar Hospital, Gorgan, north of Iran. A total of 1554 confirmed COVID-19 cases were enrolled in the study with blood group (ABO and Rh), demographic, and clinical data available. All COVID-19 patients had been confirmed by reverse transcriptase real-time PCR assay targeting the SARS-CoV-2 nucleoprotein (N) and ORF1ab genes (Pishtazteb, Iran). Data such as blood group, gender, age, hospitalized ward and disease outcome was collected from the patients' case report forms. Because the frequency of participants in different age groups was different, the patients were classified into different age groups according to the literature. The patients were also classified into different hospitalized wards. Two outcomes, recovered and deceased (due to COVID-19), were examined in this study. All of the patients were from Golestan Province and had the same geographical origin.

Analyses were performed using SPSS version 25.0 (IBM Corp., NY, USA). Data were presented in proportions. We performed a chi-square test to compare the proportion of blood groups, age group, sex and hospitalization wards between the recovered and deceased groups. Multiple logistic regression was computed to assess the odds of death (dependent variable). Independent variables included the blood groups, age group, sex and hospitalization wards. The reported p-value is two-sided, and p-values less than 0.05 were considered statistically significant.

**Table 2. Association of sex, age, blood group and hospitalization wards of COVID-19 patients with risk of death.**

Variables	All cases (%)	OR (CI: 95%)	p-value
<b>Sex</b>			
Female	740 (47.6)	Ref.	0.27
Male	814 (52.4)	1.15 (0.88–1.51)	
Total	1554 (100)		
<b>Age (years)</b>			
1–29	92 (5.92)	Ref.	
30–39	174 (11.20)	1.16 (0.45–2.96)	0.75
40–49	279 (17.95)	1.22 (0.51–2.93)	0.65
50–59	314 (20.21)	1.97 (0.85–4.55)	0.11
≥60	695 (44.72)	4.95 (2.24–10.91)	<0.001
<b>Blood group</b>			
A+	427 (27.5)	Ref.	
A-	45 (2.9)	1.817 (0.925–3.566)	0.083
B+	401 (25.8)	0.547 (0.372–0.803)	0.002
B-	35 (2.3)	3.8 (1.879–7.683)	<0.001
AB+	105 (6.8)	0.888 (0.512–1.541)	0.675
AB-	7 (0.5)	.	
O+	460 (29.6)	0.978 (0.702–1.362)	0.899
O-	74 (4.8)	0.938 (0.500–1.759)	0.844
<b>Hospitalization wards</b>			
Infectious disease	1102 (70.91)	Ref.	
ICU/CCU/emergency	288 (18.53)	203.85 (123.178–337.362)	<0.001
Post-ICU/isolated room	74 (4.76)	16.635 (8.655–31.972)	<0.001
Other wards	90 (5.79)	3.788 (1.585–9.051)	0.003

CCU: Cardiac care unit; ICU: Intensive care unit.

## Results

Of 1554 patients, 1267 and 287 cases had recovered and deceased outcomes, respectively. Of all cases, 814 (52.4%) and 740 (47.6%) were male and female, respectively. The mean age of all patients was  $56.66 \pm 17.15$  (median: 57 years; range: 1–101 years). The patients were distributed into five groups: 1–29 years, 30–39 years, 40–49 years, 50–59 years and  $\geq 60$  years. Hospital wards were ICU (intensive care unit)/CCU (cardiac care unit)/emergency, infectious disease, post-ICU/isolated room and other wards. Details of the distribution of the demographic, gender, age, hospitalization ward and blood groups of all, recovered and deceased cases are presented in Table 1.

In this study, there was no significant association between gender and the outcome of COVID-19. The data showed a significant association between age and the outcome of the disease. The number of COVID-19 cases and deaths gradually increased with age, so the odds of the deaths were higher in the age group over 60 years compared with the reference group. We found a significant association between hospitalization ward and outcome of the disease. The odds of death were higher in those hospitalized in the ICU/CCU/emergency wards than in the infectious disease group. Most of the COVID-19 cases in this study had O+, the least had AB- and most deaths had O+ blood types. Logistic regression analysis revealed that odds of death in group A- versus A+ were 1.81-times higher, though it was not significant. Blood type B+ had lower odds of death than A+. Patients with type B-, 3.8-times more likely for COVID-19 death than the A+ blood group. Patients with the AB+ group had lower odds of death than the A+. Finally, group O+ and O- had a lower odds of death than the A+ blood group. The details association of sex, age, blood group and hospitalization wards of COVID-19 patients with risk of death are presented in Table 2.

## Discussion

This study indicates that blood types may be related to the clinical outcome of COVID-19. The main findings of this study are: no significant association between gender and outcome of COVID-19, a significant association between age and the outcome of the disease, a significant association between hospitalization ward and outcome of

**Table 3. The literature regarding the association between blood types and COVID-19.**

Study (year)	Countries	Sample size	Main findings	Ref.
Zhang <i>et al.</i> (2021)	Literature review	23 study	Greatest risk for susceptibility to COVID-19 infection was found among individuals with blood type A	[13]
Kabrah <i>et al.</i> (2021)	Systematic review and meta-analysis	16 study	Blood group A cases were vulnerable to COVID-19 infection, and blood type AB linked to a lower risk of COVID-19 infection	[14]
Liu <i>et al.</i> (2020)	Systematic review and meta-analysis	10 study	Individuals with blood groups A and B were more susceptible to COVID-19 infection, whereas the blood group O appeared to be protective	[15]
Franchini <i>et al.</i> (2021)	Systematic literature review and meta-analysis	21 study	Blood group O individuals were less susceptible to SARS-CoV-2 infection compared with those in the non-O group. No evidence was found indicating an effect of the O type on disease severity in SARS-CoV-2 infection	[17]
Mahmud <i>et al.</i> (2021)	Bangladesh	438	Although ABO blood groups were not associated with the presentation or recovery period of COVID-19, patients with blood group A had delayed seroconversion	[18]
Garg <i>et al.</i> (2021)	India	383	COVID-19 patients with A and B blood groups exhibit greater disease severity. There are no differences between distribution of Rh (D) +ve type and Rh (D) -ve in severe, moderate and mild patients	[19]
Kim <i>et al.</i> (2021)	Review	9 study	Blood type A patients had higher risk and blood type O patients had lower risk of becoming infected with SARS-CoV-2	[20]
Samra <i>et al.</i> (2021)	Saudi Arabia	507	The incidence, severity, and mortality of COVID-19 were common in nonblood group O, while blood group O was protected against COVID-19	[24]
Zietz <i>et al.</i> (2020)	United States	14112	Blood type O was protective against SARS-CoV-2 infection compared with non-O blood. Blood type A patients had lower risk of intubation and death compared with blood type O patients, whereas blood type AB had higher risk of both intubation and death. The Rh- patients had a 2.7% lower risk of initial infection after adjustment, and also lower risk for both intubation and death	[27]
Ray <i>et al.</i> (2020)	Canada	225,556	Blood type A and AB had higher risk of severe illness or death. B+ was associated with higher odds of testing positive, whereas O- was associated with lower infection rate. The Rh+ cases had higher risk of severe illness or death	[28]
Taha <i>et al.</i> (2020)	Sudan	557	The O+ blood group had the lowest risk of having severe symptoms, and A+ individuals were the most vulnerable when exposed to the virus	[29]
Abdollahi <i>et al.</i> (2020)	Iran	397	Blood group A was significantly associated with a higher risk of infection and blood group O was associated with a lower risk. The Rh blood group phenotype was not statistically significant in determining a patient's vulnerability	[30]
Dal <i>et al.</i> (2021)	Turkey	39,850	ABO and Rh blood groups did not have any impact on the rate of hospital admission, hospital and ICU stay, mechanical ventilation support and case fatality rate. Blood group A was found to be related with increased rate of ICU admission	[31]
Fan <i>et al.</i> (2020)	China	Cases: 105 Controls: 103	Blood type A patients had higher risk and blood type O patients had lower risk of becoming infected with SARS-CoV-2	[32]
Zhao <i>et al.</i> (2020)	China	2173	Blood type A patients had higher risk and blood type O patients had lower risk of becoming infected with SARS-CoV-2	[33]
Golinell <i>et al.</i>	Meta-analysis	Cases: 7503 Controls: 2,962,160	Blood type A patients had higher risk and blood type O patients had lower risk of becoming infected with SARS-CoV-2	[34]
Barnkob <i>et al.</i> (2020)	Denmark	Cases: 7422 Controls: 466,232	Blood type O was protective against SARS-CoV-2 infection compared with non-O blood type	[35]
Wu <i>et al.</i> (2020)	Systematic review and meta-analysis	31,100	Blood type A patients had higher risk and blood type O patients had lower risk of becoming infected with SARS-CoV-2	[36]
Padhi <i>et al.</i> (2020)	India	277,649	Blood type O was protective against COVID-19 death, while blood type B was more strongly correlated with death	[37]
Li <i>et al.</i> (2020)	China	Cases: 2153 Controls: 3694	Blood type A patients had higher risk and blood type O patients had lower risk of becoming infected with SARS-CoV-2	[38]
Goker <i>et al.</i> (2020)	Turkey	186	Blood group A might have a role in increased susceptibility to the COVID-19 infection, and the blood group O might be somewhat protective	[39]
Leaf <i>et al.</i> (2020)	USA	3239	Type A blood may be a risk factor for COVID-19-related critical illness among White patients, and that type O blood may be protective	[40]
Zeng <i>et al.</i> (2020)	China	97	Blood type A individuals were more sensitive to SARS-CoV-2 infection. Blood type distribution was not a relevant factor of ARDS, AKI and mortality in COVID-19 patients	[41]
Chegni <i>et al.</i>	Iran	76	Blood group A was significantly associated with a higher risk of infection and blood group O was associated with a lower risk of infection	[42]
Zhang <i>et al.</i> (2020)	China	134	Blood group A was significantly associated with a higher risk of infection and blood group O was associated with a lower risk of infection	[43]

AKI: Acute kidney injury; ARDS: Acute respiratory distress syndrome; CRRT: Continuous renal replacement therapy; ICU: Intensive care unit.

**Table 3. The literature regarding the association between blood types and COVID-19 (cont.).**

Study (year)	Countries	Sample size	Main findings	Ref.
Roberts <i>et al.</i> (2020)	USA	2417	Blood group A was significantly associated with a higher risk of infection	[44]
Marcos <i>et al.</i> (2020)	Spain	226	Blood group A was significantly associated with a higher risk of infection and blood group O was associated with a lower	[45]
Franchini <i>et al.</i> (2020)	Italy	447	Blood type O may be protective against COVID-19	[46]
Aljanobi <i>et al.</i> (2020)	Saudi-Arabia	72	Blood group A was significantly associated with a higher risk of infection and blood group O was associated with a lower	[47]
Valenti <i>et al.</i> (2020)	Italy/Spain	505	Blood group A was associated with higher risk of severe COVID-19 than group O, while group B was not. Increased risk of severe disease was observed in carriers of the AB group	[48]
Hoiland <i>et al.</i> (2020)	Canada	95	A greater proportion of blood group A or AB patients required mechanical ventilation and CRRT compared with blood group O or B patients	[49]
Wu <i>et al.</i> (2020)	China	187	Blood type A patients had higher risk and blood type O patients had lower risk of becoming infected with SARS-CoV-2. There is no correlation between blood type and COVID-19 severity or mortality	[50]
Diaz <i>et al.</i> (2021)	Spain	854	Blood group A was significantly associated with a higher risk of infection and blood group O was associated with a lower	[51]
Ahmed <i>et al.</i> (2021)	UK	86	Blood group A women had a significantly higher relative risk of developing COVID-19 infection	[52]
Solmaz <i>et al.</i> (2021)	Turkey	1667	Blood group A was significantly associated with a higher risk of infection and blood group O was associated with a lower	[53]
Cordero <i>et al.</i> (2021)	International	9859	Blood group A was significantly associated with a higher risk of infection and blood group O was associated with a lower	[54]
Solhpour <i>et al.</i> (2020)	Iran	93	Blood group type A is usually more susceptible to be involved by severe form of the COVID-19	[55]
Almadhi <i>et al.</i> (2021)	Bahrain	Cases: 2334 Controls: 4985	Blood group AB was associated with a decreased risk of infection, while blood group B was associated with an increased risk. No association between blood group A and risk of COVID-19 infection was found	[22]
Ishaq <i>et al.</i> (2021)	Pakistan	1067	Hospital stay, severity of disease and mortality were associated with blood group A	[23]
Niles <i>et al.</i> (2021)	USA	34,178	The SARS-CoV-2 positivity rate was significantly higher among type O and Rh+ patients	[56]
Latz <i>et al.</i> (2020)	USA	1289	Blood type B and AB were associated with higher risk of testing positive for COVID-19. Blood type O was associated with lower risk of testing positive. There is no correlation between blood type and COVID-19 intubation and death. Individuals with Rh- blood type were less susceptible to infection by SARS-CoV-2	[57]
Bai <i>et al.</i>	Systematic review	24 study	There is no true relationship between ABO blood type and COVID-19 infection, severity or mortality	[16]
Anderson <i>et al.</i> (2021)	USA	Cases: 11,468 Controls: 96,328	No ABO associations were found with either disease susceptibility or severity	[21]
Levi <i>et al.</i> (2021)	Brazil	2037	Absence of a relationship between ABO blood type and susceptibility to SARS-CoV-2 infection	[58]
Boudin <i>et al.</i> (2020)	France	1769	Absence of a relationship between ABO blood type and susceptibility to SARS-CoV-2 infection	[59]
Dzik <i>et al.</i> (2020)	USA	957	No association was found between ABO type and death among individuals hospitalized with COVID-19	[60]
Samra <i>et al.</i> (2021)	Saudi Arabia	507	The severity of COVID-19 infection was common in Rh+ patients and Rh- patients	[24]
Garg <i>et al.</i> (2021)	India	383	There was no differences between distribution of Rh (D) +ve type and Rh (D) -ve in severe, moderate and mild patients	[19]

AKI: Acute kidney injury; ARDS: Acute respiratory distress syndrome; CRRT: Continuous renal replacement therapy; ICU: Intensive care unit.

COVID-19 and blood groups A- and B- have higher and groups B+, AB+, O+ and O- have lower odds of death than the A+ group (Table 1 & 2).

Previous studies demonstrated that male cases have an increased risk of death compared with females [25]. However, in this study, there was no significant association between gender and the outcome of COVID-19. Studies also demonstrated that age could be considered as a death-associated risk factor for COVID-19 [3,26]. Most of the data in this context agree that the infection and death were mostly observed in cases with advanced ages. Our data showed a significant association between age and the outcome of the disease. The number of COVID-19 cases and deaths gradually increased with age, so the odds of the deaths were higher in the age group over 60 years. This finding might be expected because elderly tend to have a higher prevalence of comorbidities such as diabetes, heart disease, hypertension, chronic respiratory diseases and they have a reduced immune response. A significant

association between hospitalization ward and outcome of the disease was found, and also odds of death were higher in those hospitalized in the ICU/CCU/emergency wards. This finding also might be expected because critically ill COVID-19 patients are hospitalized in these wards.

Regarding blood groups, our data showed that odds of death in the group A- versus A+ were 1.81-times higher, and patients with type B-, 3.8-times more likely for COVID-19 death than the A+ blood group. However, other blood groups such as B+, AB+, O+ and O- had a lower odds of death than the A+ blood group. It is not yet clear which blood type is most likely to be susceptible to COVID-19. Some studies considered that people with blood type A to be the most susceptible to the disease, and people with blood type O are less likely to develop the disease [13–15,17–20,24,27–55]. But other studies reported conflicting results [22,23,56,57], and some did not find a significant relationship between blood type and COVID-19 [16,21,58–60]. Moreover, studies reported that individuals with Rh- blood type had a lower risk of infection, intubation and death, and cases with Rh+ were more sensitive to COVID-19 [24,27–29,56,57]. However, a study from Iran did not find any relation between COVID-19 and Rh type [30]. Another study in Turkey also did not report a relationship between Rh blood groups and any impact on the rate of hospital admission, ICU stay, mechanical ventilation support and case fatality rate [31]. The literature studies regarding the association between blood types and COVID-19 are summarized in Table 3.

The discrepancy between studies may be due to the different sample sizes, heterogeneity of ABO between populations or geographical areas, differences in genetic background and differences in viral strains. Variation between blood group phenotypes in countries and different genetics may affect heterogeneity of COVID-19 clinical phenotypes [21,61]. Susceptibility to SARS-CoV-2 infection and ABO blood system might be for some reasons: blood group O patients had natural anti-A and anti-B antibodies that could be partially protective against SARS-CoV-2 virions, carbohydrate–carbohydrate interactions, which could maximize or minimize the virus spike protein binding to the host cell, furin levels might be reduced in blood type O individuals, so the infectivity of virus is reduced, the levels of C-reactive protein and alkaline phosphatase appear to be higher in blood group A individuals in comparison with blood group O and microbiota trigger the synthesis of anti-A and anti-B antibodies [61,62].

## Conclusion

Finding high-risk groups for severe infection and death are important to manage the current pandemic disease. The results of such studies could lead to individuals with a higher risk of severe infection being vaccinated earlier or monitored more closely and treated earlier. Together, these findings suggest that the blood group may interplay with susceptibility to SARS-CoV-2 infection and clinical course of COVID-19; however, the mechanism(s) is subjected to speculations. The limitation of this study was the small sample size, and further studies with a large cohort for multiple people are required to validate this association.

### Summary points

- Due to the inconsistent data published on blood groups and COVID-19, we conducted a study on Iranian patients to further assess this association.
- A total of 1554 confirmed COVID-19 cases were enrolled in the study with blood group, demographic and clinical data available.
- Of 1554 patients, 1267 and 287 cases had recovered and deceased outcomes, respectively.
- Most of the cases had O+ (29.6%), the least number had AB- (0.5%), and most of the deceased cases had O+ blood types (31.4%).
- Logistic regression analysis revealed that groups A- and B- had higher and groups B+, AB+, O+ and O- had lower odds of death than the A+ group.
- Our findings indicate that blood types may be related to the clinical outcome of COVID-19.
- Further studies with a large cohort for multiple people are required to validate this association.

### Author contributions

A Tahamtan and AA Ayatollahi conceptualized and designed the study. B Aghcheli, A Amini, H Nikbakht and P Ghassemzadehpirsala collected data. A Rajabi and B Aghcheli analyzed the collected data. B Aghcheli and E Behboudi drafted the manuscript. All authors evaluated and edited the manuscript and have read and approved the final manuscript.

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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### Ethical conduct of research

This study was approved by the Ethics Committee of the Golestan University of Medical Sciences (IR.GOUMS.REC.1400.141).

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