

## ORIGINAL RESEARCH

# Association of ABO blood group with in-hospital adverse outcome and long term persistent symptoms of COVID-19 infection: A single-center longitudinal observational study

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## Abstract

**Background and Aims:** There are gaps in knowledge regarding the association between the ABO blood group and coronavirus disease 2019 (COVID-19) immediate and long-term outcomes. We aimed to investigate the association of ABO blood group with COVID-19 in-hospital adverse outcomes and to determine whether ABO blood group is associated with post-COVID-19 persistent symptoms.

**Methods:** This was a single-center longitudinal observational study that included patients who presented with symptoms suggestive of COVID-19 infection and a positive test for COVID-19 and were able to attend the out-patient clinic after 6 months following acute COVID-19. The main outcomes were intensive care unit admission, the requirement for respiratory support, in-hospital death, and persistent symptoms.  $\chi^2$  test and regression analysis were used to analyze the collected data.

**Results:** A total of 169 patients were enrolled for the assessment of in-hospital adverse outcomes of whom 86 patients were included for the assessment of persistent symptoms after the exclusion of deceased patients or patients not attended the out-patient clinic. Patients with blood group B had higher prevalence of in-hospital death compared to blood group O (39% vs. 13%,  $p = 0.01$ ) and this persisted after adjusting for sex (odds ratio, OR [confidence interval, CI] = 1.4 [1.1–2.1],  $p = 0.04$ ), while patients with blood group AB had higher prevalence of requiring respiratory support than blood group O (54% vs. 10%,  $p = 0.02$ ) and this persisted after adjusting for age (OR [CI] = 1.5 [1.1–2.3],  $p = 0.02$ ). Concerning the association of ABO blood group and long-term symptoms, blood group AB showed a higher prevalence of palpitation ( $p < 0.001$ ) and dizziness ( $p = 0.02$ ) than other blood groups.

**Conclusions:** Blood groups AB and B are significantly associated with respiratory support use and in-hospital death, respectively, compared to blood group O. Blood group AB is significantly associated with persistent palpitation and dizziness compared to other blood groups.

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## KEYWORDS

blood type, coronaviruses, COVID-19, morbidity

## 1 | INTRODUCTION

A rapidly spread coronavirus disease 2019 (COVID-19) caused by an emerging coronavirus severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is associated with protean clinical manifestations, ranging from asymptomatic/mild symptoms to respiratory failure and even death.<sup>1,2</sup> Persistent symptoms were observed following the acute phase of COVID-19 infection causing significant disability in the long term.<sup>3,4</sup> Until April 14, 2022, there have been 500,186,525 confirmed cases of COVID-19, including 6,190,349 deaths worldwide according to World Health Organization (WHO) data. The basic reproduction number of the new SARS-CoV-2 is estimated to be in the range between 1.4 and 3.9, and the infectivity of the virus is higher than other viruses, such as seasonal influenza and the Middle East respiratory syndrome.<sup>5</sup> According to WHO reports, there is no effective treatment for COVID-19 infection and the best approach against the coronavirus is prevention programs such as avoiding close contact with other people and wearing a mask.<sup>6</sup> Hence, determining the clinical or biological risk factors associated with COVID-19 mortality and morbidity is of paramount importance for health decisions and implications of preventive strategies.<sup>5</sup>

In the literature, the ABO blood group was found to be significantly associated with cardiovascular disease, cancers, and several viral infections, including hepatitis B virus, SARS, influenza, Rotavirus, and Ebola virus.<sup>7-10</sup>

Multiple hypotheses have been suggested to account for the association between the ABO blood group and viral infections and these include the presence of anti-A antibodies which could prevent the interaction between viral particles and receptors on the cell surface as epithelial cells express ABO blood type antigens, genetic variations in the ABO gene, plasma levels of von Willebrand factor and factor VIII, and variation in the expression of angiotensin-converting enzyme (ACE).<sup>2,9-12</sup> Nonetheless, the exact underlying mechanism of this association is still not fully understood.

Early during the COVID-19 pandemic, it has proposed that SARS-CoV-2 receptor-binding domain, which is responsible for the initial host cell, preferentially binds to the blood group A expressed on respiratory epithelial cells. This preferential binding may influence COVID-19 infection acquisition and contribute to disease progression.<sup>2</sup>

At present, there are conflicting and nonconclusive results regarding the association of the ABO blood group with COVID-19 morbidity and mortality. Also, the potential links between the ABO blood group and postacute COVID-19 persistent symptoms have been far less studied in the literature. While several observational and meta-analysis studies showed a significant association between ABO blood group and COVID-19 infection susceptibility and severity,<sup>6,8,13,14</sup> other studies showed no association between ABO blood group and COVID-19-related morbidity and mortality.<sup>7,15,16</sup>

In an attempt to address the gaps in knowledge regarding the potential link between ABO blood group and COVID-19 immediate

and long-term outcomes, we aimed to investigate the association of ABO blood group with in-hospital adverse outcomes related to COVID-19 infection and to determine whether ABO blood group is associated with post-COVID-19 persistent symptoms.

## 2 | METHODS

This is a single-center, observational and longitudinal study that included Arab patients who were admitted to the hospital or attended the outpatient clinic at Al-Amal Hospital for communicable diseases from April 1st to May 30, 2021. The clinical characteristics, including age, sex, hypertension, diabetes mellitus, smoking, and body mass index (BMI), and ABO blood group of patients were collected from a chart review of hospital medical records by trained physicians. Inclusion criteria were patients who presented with symptoms suggestive of COVID-19 infection and a positive test for COVID-19 and were able to attend the out-patient clinic after 6 months following acute COVID-19 illness. Exclusion criteria included patients who had not survived after hospitalization and failure to attend the out-patient clinic after 6 months following acute infection. Finally, 169 patients were included for the assessment of in-hospital adverse outcomes of whom 86 patients were included for the assessment of long-term symptoms after the exclusion of deceased patients or patients not attended the out-patient clinic. Diagnosis of COVID-19 infection was confirmed by a real-time reverse transcription-polymerase chain reaction test on nasopharyngeal swabs. Symptomatic patients without pneumonia or not requiring hospital admission were categorized as mild-moderate illness, while those with pneumonia requiring intensive care unit (ICU) admission or respiratory support were categorized as severe-critical illness. The main outcomes of this study included the need for ICU admission, the requirement for respiratory support (continuous positive airway pressure [CPAP] or mechanical ventilation), and in-hospital death.

Regarding the assessment of long-term persistent symptoms, patients who survived acute infection were invited to attend the out-patient clinic after 6 months following COVID-19 illness diagnosis. Data on long-term symptoms were obtained by asking the patients to mark out symptoms from a predesigned questionnaire, including shortness of breath interfering with routine daily activities, easy fatigue, cough, chest pain, palpitation, joint pain, dizziness, headache, smell loss, and taste loss. If there was a new symptom not mentioned in the questionnaire list, patients were asked to report it. Verbal consent was obtained from the patients or their relatives. Approval of this study was provided by the ethical committee for clinical studies of faculty of medicine/University of Kufa with approval number (MEC-01) and the Scientific Research Committee at Al-Najaf Health Directorate with the approval number (46449).

## 2.1 | Statistical analysis

Sample size calculation was not performed a priori, and the sample size was equal to the number of patients who met the inclusion criteria during the study period. Statistical analyses were achieved using Statistical Package for Social Sciences (SPSS) Version 23.0 (SPSS Inc). Categorical variables were described using frequency count and percentages. Continuous variables were represented as mean  $\pm$  standard deviation (SD). The comparison of blood group with in-hospital adverse outcomes and long-term persistent symptoms was computed using the  $\chi^2$  test. Logistic regression analysis was used to compute the odds ratio (OR) and confidence interval (CI) between the ABO blood group and in-hospital adverse outcomes after adjusting for sex. A two-sided  $p < 0.05$  was considered statistically significant.

## 3 | RESULTS

A total of 169 patients with symptoms suggestive of COVID-19 infection and a positive test for COVID-19 were enrolled in this study. Of these, 72% ( $n = 122$ ) had mild-moderate illness while 28% ( $n = 47$ ) had severe-critical illness. Blood group O had the highest distribution ( $n = 71$ , 42%), followed by A ( $n = 49$ , 29%), B ( $n = 36$ , 21%), and AB ( $n = 13$ , 8%) accordingly. The mean  $\pm$  SD of age in years of patients enrolled in the study was  $53.8 \pm 14$ , of which 57% ( $n = 97$ ) were males. About 47 (28%) patients were admitted to ICU, 36(21%) have died, and 35 (20%) required respiratory support. The clinical characteristics of patients are shown in Table 1.

Comorbidities, including hypertension, diabetes, smoking, and BMI were evenly distributed among ABO blood groups, except for the male sex which was more frequent in patients with blood group A and O ( $n = 34$  [69%] and  $n = 44$  [68%], respectively) compared to blood group B and AB ( $n = 11$  [31%] and  $n = 4$  [31%], respectively,  $p < .001$ ) (Table 2).

Patients with blood group B did have significantly higher prevalence of in-hospital death compared to blood group O (39% vs. 13%,  $p = 0.01$ ), while patients with blood group AB had a much higher prevalence of respiratory support use than blood group O (54% vs. 10%,  $p = 0.02$ ), as in Table 2. In regression analysis after adjusting for sex, blood group B (OR [CI] = 1.4 [1.1–2],  $p = .04$ ) and AB (OR [CI] = 1.5 [1.1–2.3],  $p = .02$ ) showed a significant association with in-hospital death and respiratory support use, respectively (Table 3).

With regard to the association between the ABO blood group and long-term symptoms following the acute COVID-19 phase, we were able to collect and analyze the data on long-term persistent symptoms from 86 patients after excluding 36 patients who died at the hospital and 47 patients who did not attend follow up visit. Only those long-term symptoms with a prevalence  $\geq 5$  were mentioned and included in the statistical analysis. Blood group AB showed higher prevalence of palpitation ( $p < 0.001$ ) and dizziness ( $p = 0.02$ ) than other blood groups. There was no significant difference in the

**TABLE 1** Patients' characteristics.

Characteristics	Mean $\pm$ SD or n (%)
Age, years	53 $\pm$ 14
Male	97/169 (57)
Hypertension	43/169 (40)
Diabetes mellitus	37/169 (22)
BMI	28 $\pm$ 5
Smoking	25/169 (15)
Mild-moderate COVID-19 infection	122/169 (72)
Severe COVID-19 infection	47/169 (28)
ABO blood groups	
O	71/169 (42)
A	49/169 (29)
B	36/169 (21)
AB	13/169 (8)
In-hospital adverse outcome	
Death	36/169 (21)
Respiratory support	35/169 (20)
ICU admission	47/169 (28)
Post-COVID-19 persistent symptoms	
Fatigue	34/86 (40)
Shortness of breath	20/86 (23)
Cough	14/86 (16)
Palpitation	10/86 (12)
Smell loss	9/86 (10)
Dizziness	6/86 (7)
Taste loss	5/86 (6)

Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 2019; ICU, intensive care unit.

distribution of ABO blood groups among other long-term persistent symptoms (Table 4).

## 4 | DISCUSSION

In the literature, different studies have shown contradictory results regarding the association of blood groups and adverse outcomes related to COVID-19. Also, the potential influence of blood groups on long-term persistent symptoms following acute COVID-19 infection is largely unknown. In the current study, the main aim was to assess the association of the blood groups with COVID-19-related in-hospital adverse outcomes and long-term persistent symptoms. We observed a significant association between blood group B and AB with in-hospital death and respiratory support (CPAP or mechanical ventilation) use, respectively, while blood

	O n = 71	A n = 49	B n = 36	AB n = 13	p
Comorbidity					
Age (years), mean ± SD	53 ± 13	53 ± 13	54 ± 17	54 ± 17	0.97
BMI,	28 ± 5	29 ± 5	31 ± 5	25 ± 5	0.17
Hypertension, n (%)	23 (32)	10 (20)	8 (22)	2 (15)	0.75
Diabetes, n (%)	20 (28)	8 (16)	7 (19)	2 (15)	0.53
Male, n (%)	48 (68)	34 (69)	11 (31)	4 (31)	<0.001
Smoking, n (%)	12 (17)	6 (12)	5 (14)	2 (15)	0.25
In-hospital adverse outcome					
Death, n (%)	9 (13)	11 (22)	14 (39)	2 (15)	0.01
Respiratory support use, n (%)	10 (14)	10 (20)	7 (25)	7 (54)	0.02
ICU admission, n (%)	16 (23)	15 (30)	11 (31)	5 (38)	0.22

**TABLE 2** Distribution of comorbidities and in-hospital adverse outcomes among ABO blood groups.

Abbreviations: BMI, body mass index; ICU, intensive care unit.

Blood group	In-hospital death		Respiratory support use		ICU admission	
	OR (CI)	p	OR (CI)	p	OR (CI)	p
O	0.7 (0.1–4)	0.75	0.2 (0.1–0.8)	0.03	0.6 (0.2–2)	0.38
A	1.5 (0.2–8)	0.64	1 (0.9–2)	0.06	1.4 (0.6–3)	0.44
B	1.4 (1.1–2)	0.04	0.7 (0.2–2)	0.56	1 (0.3–3)	0.94
AB	3 (0.6–6)	0.15	1.5 (1.1–2.3)	0.02	3 (0.9–13)	0.06

**TABLE 3** Adverse in-hospital outcomes between ABO blood groups using regression analysis after adjusting for age.

Abbreviations: CI, confidence interval; ICU, intensive care unit; OR, odds ratio.

**TABLE 4** ABO blood groups and long term persistent symptoms of COVID-19 infection<sup>a</sup>

	O n (%)	A n (%)	B n (%)	AB n (%)	p
Fatigue	17 (35)	9 (43)	5 (36)	3 (60)	0.29
Shortness of breath	9 (18)	4 (19)	5 (36)	2 (40)	0.20
Cough	5 (10)	4 (19)	4 (31)	1 (20)	0.41
Palpitation	4 (9)	2 (10)	1 (8)	3 (60)	<0.001
Smell loss	5 (10)	2 (10)	1 (8)	1 (20)	0.13
Dizziness	1 (2)	3 (14)	0 (0)	2 (40)	0.02
Taste loss	3 (6)	1 (5)	1 (8)	0 (0)	0.77

Abbreviation: COVID-19, coronavirus disease 2019.

<sup>a</sup>Only those long-term symptoms with a prevalence ≥5 were mentioned and included in the statistical analysis.

group O was associated with a low risk of adverse in-hospital outcomes.

Several mechanisms have been suggested to explain the protective role of blood group O in different viral or bacterial infections. Low expression of ACE, reduced levels of factor VIII and von Willebrand factor, and higher levels of inflammatory markers and

anti-A antibodies have been proposed to account for a protective role of blood group O in viral infections, including SARS-CoV-1 and 2.<sup>7,9,12,17</sup> Thus, patients with blood group O are less prone to thrombosis and vascular dysfunction causing severe respiratory damage than other blood groups.<sup>18</sup>

A recent study conducted by Gil-Manso et al.<sup>19</sup> reported that O-group persons needed less time to clear the virus than the non-O-group and that they presented lower values of inflammatory mediators, such as interferon and tumor necrosis factor, and T-lymphocytes responses against SARS-CoV-2 particles than O-group subjects. These inflammatory and cellular immune responses are associated with a lower viral load which accelerates the clearance of the virus and diminishes its impact on the immune system in O-group persons, which could bring a protective role against SARS-CoV-2 infection and replication.<sup>19</sup>

Regarding the association of blood groups B and AB with in-hospital adverse outcomes, emerging data from several studies in different regions reported a higher risk for COVID-19 infection with blood groups B and AB compared to other blood groups.<sup>7,11,13,16,20</sup>

In line with our findings, an Indian epidemiological study conducted by Padhi et al. found that blood group B was positively associated with COVID-19 death ( $r = 0.67$ ,  $p < 0.001$ ), which goes with other studies that showed group B experiencing a high risk of symptomatic disease and complications related to COVID-19 infection compared to other blood groups.<sup>3,21,22</sup> Also, a multicenter

retrospective study of critically ill patients with COVID-19 reported that patients with blood group AB or A had a higher risk of requiring mechanical ventilation after adjusting for age and sex than patients with blood group O or B.<sup>12</sup>

Concerning the possible underlying mechanism of association of blood groups B and AB with adverse outcomes in COVID-19 infection and other viral infections, it has been postulated that blood group AB facilitates a powerful contact with invading pathogen and molecularly prevents isoagglutinin activity, making this blood group the least protected group in contrast to group O.<sup>23</sup> Moreover, group B and AB cannot inhibit the formation of connections between autologous carbohydrates and/or glycopeptides and foreign peptides related to the invading pathogens.<sup>23</sup>

Looking for a possible association between ABO blood groups and long-term persistent symptoms of COVID-19, we found a significant association between blood group AB and the occurrence of cardiac palpitation and dizziness for the first time in this study, to the best of the authors' knowledge. This association could be attributed to the ABO expression on platelets among different ABO blood groups, whereby non-group O platelets adhere more strongly than group O, which would predispose patients with non-O blood groups and SARS-CoV-2 infection to vascular or cardiac problems.<sup>24</sup> According to the best of the authors' knowledge, only one study conducted by Domènech-Montoliu et al.<sup>3</sup> has assessed the relationship of the ABO blood group with long-term symptoms at 6 months following acute COVID-19 in the Falles festival of Borriana (Spain). In their study, Domènech-Montoliu et al.<sup>3</sup> reported significant differences in post-COVID-19 complications by ABO blood groups, with a higher incidence in the blood group B than in other blood groups, in contrast to our results. However, the patients in the aforementioned study were Spanish and most of them had mild illnesses and a small number of AB group (3.9% vs. 8% in our study), which could prevent conclusive assessment in this blood group.

The main strength of this study is that it is one of the first studies to describe the influence of the ABO blood group on the occurrence of long-term persistent symptoms at 6 months following acute COVID-19 infection among the Arab community in the west of Asia. However, this study has several limitations that need consideration. This is a single-center with a sample size not very large to perform further statistical or subgroup analysis. There was a possibility of recall and information bias because of the lack of objective measures or scales to assess long-term symptoms. There could be a possibility of selection bias as patients without symptoms were not enrolled in this study and therefore the results may not be representative of COVID-19 patients. There were no data on baseline inflammatory markers, such as interleukin-6 or c-reactive protein. Also, some unmeasured confounding factors, such as treatment guidelines or COVID-19-related cardiac or vascular involvement could not be ruled out, which may lead to aberrations in study findings because those factors could play a role in COVID-19 severity and long-term sequel. Additional studies are required to address these limitations and confirm our findings.

## 5 | CONCLUSION

Blood groups AB and B are significantly associated with respiratory support use and in-hospital death, respectively, compared to blood group O. ABO blood group patients presented significant differences in post-COVID-19 persistent symptoms with more palpitation and dizziness observed in the AB group than in other blood groups.

### AUTHOR CONTRIBUTIONS

**Ahmed Nafakhi:** Conceptualization; data curation; formal analysis; investigation; methodology; resources; and visualization. **Ihsan S. Rabeea:** Conceptualization; funding acquisition; project administration; resources; and supervision. **Rasha Al-Darraj:** Data curation; methodology; resources; and writing—original draft. **Hussein Nafakhi:** Conceptualization; formal analysis; methodology; supervision; validation; visualization; writing—original draft; and writing—review and editing. **Ahmed Mechi:** Investigation; methodology; resources; software; visualization; and writing—review and editing. **Alhan Al-Khalidi:** Data curation; resources; validation; and visualization. **Mohammed Alareedh:** Data curation; validation; writing—original draft; and writing—review and editing. All authors have read and approved the final version of the manuscript. The corresponding author had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

### CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

### DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

### TRANSPARENCY STATEMENT

Hussein Nafakhi, the corresponding author, affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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#### SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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