

# ASSOCIATION OF ABO AND RH BLOOD GROUP WITH COVID-19 INFECTION IN PAKISTAN

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## ABSTRACT

**Background:** The role of various blood groups with COVID-19 has recently been observed. Individuals with blood group O are supposedly less susceptible when compared to those with non- O blood group. This study aimed in observing the association of ABO and Rh (D) blood groups in patients having COVID-19 in the local setting.

**Material and Methods:** In this retrospective study, 1238 patients admitted in the hospital with COVID-19 during 2020 and 2021 were studied for their demographics and blood groups. Healthy blood donors were enrolled and served as a control group. Chi-square was used to determine the association (odd ratio) of various blood groups with COVID-19.

**Results:** Blood group B was predominant (39% vs 33%) while O was less common (31% vs. 36%) in admitted patients having COVID -19 compared to blood donors. The study showed a negative association of blood group O among patients with COVID-19 (OR 0.783; 95%CI 0.677-0.906, *p*-value 0.001) while a positive association with blood group B (OR 1.266, 95%CI 1.099-1.458, *p*-value 0.001). No association was seen with blood groups A, AB and Rh.

**Conclusion:** The small scale and a single centre study showed a preponderance of blood group B while a low frequency of blood group O in patients admitted with COVID-19. This may reflect the protective nature of blood group O for COVID-19 infection. Large scale studies are needed to further understand this association.

**Keywords:** Blood group, COVID-19, Pakistan

## BACKGROUND

COVID-19 is a respiratory disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Since its first report in December 2019 from Wuhan, China, it spread rapidly<sup>1</sup> and was declared pandemic by the World Health Organization (WHO) in March 2020. A recent update showed 448 million cases of confirmed COVID-19 globally with more than a 6 million deaths. Estimated median incubation period for SARS-CoV-2 is 5.1 days and the majority will develop symptoms within 11.5 days of infection.<sup>2</sup> The clinical spectrum of COVID-19 is variable ranging from completely asymptomatic in 18-33% of individuals to a clinical illness (with fever, cough, sore throat, nausea, malaise, myalgia, shortness of breath and diarrhea) that may complicate to acute respiratory failure, shock, and multi-organ failure.<sup>3</sup> Certain risk

factors like advancing age, male gender, and comorbidities (diabetes mellitus, hypertension, cardiovascular disease, and malignancy) may be associated with the severity of disease.<sup>4</sup>

Since 1900, when blood groups were first identified, there had been attempts to associate ABO blood groups with various diseases such as malignancy, hematological disorders, cognitive disorders, circulatory/ metabolic/ cardiovascular/ infectious diseases and malaria.<sup>5</sup> Similarly, a higher level of Von Willebrand factor and factor VIII in subjects with non-O group might increase their risk to thrombotic disease when compared to the patients with group O.<sup>6</sup> Some have reported increased susceptibility to cholera and *E. coli* infections in individuals with O blood group.<sup>7,8</sup> Cooling L in 2015 provided a comprehensive review of blood groups in association of susceptibility of hosts to various infections.<sup>9</sup> Role of blood groups in COVID-19 is recently evolving. Compared to blood group O, some studies have reported individuals with group A to have a higher risk of COVID-19<sup>10-12</sup> while others have associated this infection with groups B, AB and Rh (D)-positive.<sup>13-15</sup> A systematic review in over 31,000

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subjects demonstrated that blood type A might be more susceptible to COVID-19 infection while blood type O might be less susceptible to infect COVID-19.<sup>16</sup> Mechanism of ABO blood group susceptibility to COVID-19 remains largely unknown.

Situated in Southern Asia, Pakistan is a home to more than 200 million people and approximately 1.5 million were infected with COVID-19 with a death toll of over 30,000 deaths as per WHO. Several studies have reported blood groups O and B as the most frequent in general population in Pakistan.<sup>17,18</sup> Few local studies have been conducted to demonstrate the relationship between blood groups in patients having diabetes<sup>19</sup> and ischemic heart disease.<sup>20</sup> A single report from Northern Pakistan reported a high proportion of blood group B in 1935 patients having Covid 19 compared to a similar number of blood donors (36% vs 32%; P-value 0.009).<sup>14</sup> No such information is available from Southern Pakistan. Since Karachi is a large metropolitan city with multiethnicity, it represents a good model for studying the relationship of ABO groups and COVID-19. Therefore, in this study, we aimed to evaluate the association of ABO and Rh (D) blood groups in COVID-19 infection.

## MATERIAL AND METHODS

The study was conducted at an academic medical centre, Aga Khan University Hospital (AKUH) Karachi, Southern Pakistan. It is a 600-bedded tertiary care centre and has facilities for Oncology, bone marrow transplant, ambulatory care services besides highly specialized medical and surgical care. Covid response in 2020 resulted in emergence of exclusive emergency and intensive care units for treating patients with COVID-19. Patients with COVID-19 who are critically ill and in need of respiratory or intensive care support are admitted to the hospital. AKUH has a blood bank of its own. Briefly, each blood donor is verbally screened prior to blood donation using a questionnaire based on AABB guidelines. Since emergence of COVID-19, additional questions were added to ensure that blood is collected from an individual who has no history of recent infection within past four weeks. Each donated blood is tested for anti-HIV, anti-HCV, HBsAg (chemiluminescence assay), malaria (ICT malaria) and syphilis (rapid plasma reagin) through and nucleic acid testing for

HIV RNA, HCV RNA and HBV DNA (Roche Cobas 6800).

This was a retrospective study and adult patients (aged >18 years) who were admitted in the hospital with confirmed diagnosis of COVID-19 (through either PCR or rapid antigen test) during 2020 and 2021 were enrolled after approval from the institutional ethical review board (ERC# 2022-7315-20893). Patient's demographics such as age, gender, and ABO/Rh (D) blood group were obtained from the electronic medical record. Blood group of healthy blood donors was retrieved from blood bank to serve as the control group.

Data was analyzed using Statistical Package for Software Sciences version 19 (SPSS inc., IL, USA). Descriptive statistics were used for analyzing demographic characteristics. Chi-square test was used to calculate the distribution of ABO and RhD blood groups among blood donors and patients having COVID-19. Odds ratios (OR) were reported with 95% confidence intervals (CI) to analyze the association of ABO and Rh(D) blood groups with the disease status and a *P*-value of < 0.05 was considered as statistically significant. OR for groups were estimated for one blood group vs. all other blood groups.

## RESULTS

A total of 3715 subjects were enrolled during the study period with 1238 (33%) patients having COVID-19 and 2477 healthy blood donors (67%). Among 1238 patients, 725 (59%) were male and 513 female (41%) with a mean ( $\pm$ SD) age of 62 ( $\pm$ 16) years (range 18-97) and almost 60% of the patients (n=748) were above the age of 60 years. Mean ( $\pm$ SD) stay in hospital was 6 ( $\pm$ 6) days (range 1-42 days). Clinical details are summarized in Table-1. Healthy blood donors included 2475 males (99.9%) and 2 females (0.1%) with a mean ( $\pm$ SD) age of 28 ( $\pm$ 7) years (range 18-60). ABO blood group and its association with the disease (Table-2).

The predominant blood groups were B (39%) and O (31%) among the patients having COVID-19 compared to A (22%) and AB (8%). In contrast, we observed a preponderance of O group (36%) compared to B (33%) among healthy blood donors while A (22%) and AB (8%) were less frequent. This difference in distribution of ABO blood group among the two groups were

statistically significance with a  $p$ -value of 0.002. Moreover, patients having blood group B had higher odds of getting hospital admission due to COVID-19 than the patients with other blood groups (OR=1.266; 95% CI 1.1099-1.458,  $p$ -value=0.001). Patients with blood group O had a lower odd of getting hospital admissions due to COVID-19 compared to non-O blood group (OR 0.783; 95% CI 0.677-0.906,  $p$ -value 0.001). The study did not find any association of

COVID-19 with blood groups A and AB. Association of Rh blood group with COVID-19 Table-3.

Among the 1238 case subjects 93.1% (n=1153) were Rh D positive and 6.9% (n=85) were Rh D negative, compared with the control group where Rh D positive subjects were 91.8% (n=2275) vs. 8.2% (n=202) Rh D negative subjects. The odds of having Rh (D) positive among hospitalized COVID-19 patients was 1.206 (95% CI 0.927-1.569) with a  $p$ -value of 0.162.

**Table-1: Summary of patient details with COVID-19.**

Parameters	Blood groups					
	A	B	O	AB	Rh(D)+	Rh (D)-
N (%)	278 (22.5)	480 (38.8)	380 (30.7)	100 (8.1)	1153 (93.1)	85 (6.9)
Age (years) Mean $\pm$ SD	61 $\pm$ 16	62 $\pm$ 17	63 $\pm$ 16	62 $\pm$ 16	62 $\pm$ 16	62 $\pm$ 14
Gender M/F	159/119	298/182	214/166	54/46	680/473	45/40
Hospital-stay (Days) Mean $\pm$ SD	6 $\pm$ 6	6 $\pm$ 6	7 $\pm$ 6	7 $\pm$ 6	7 $\pm$ 6	6 $\pm$ 6
Mortality n (%)	59(21)	103(21)	84(22)	22(22)	254(22)	14(16)
Other illnesses* n (%)	180 (64)	322 (67)	244 (64)	68 (68)	758 (66)	56 (66)

\*Include diabetes, hypertension and cardiovascular diseases

**Table-2: Association of ABO blood group with COVID-19 in 3715 subjects.**

Blood group	Patients (%)	Blood donors n (%)	OR (95%CI)	P-value
A	278 (22.5)	555 (22.4)	1.001(0.850-1.179)	0.988
B	480 (38.8)	825 (33.3)	1.266(1.099-1.458)	0.001
O	380 (30.7)	897 (36.2)	0.783(0.677-0.906)	0.001
AB	100 (8.1)	200 (8.1)	0.999(0.778-1.283)	0.995
Total	1238 (100)	2477 (100)	-	-

\*P-value=0.002

**Table-3: Association of Rh(D) blood group with COVID-19 in 3715 subjects.**

Blood group	Patientsn (%)	Blood donors n (%)	OR (95%CI)	P-value
Rh(D) +	1153 (93.1)	2275 (91.8)	1.206 (0.927-1.569)	0.162
Rh(D) -	85 (6.9)	202 (8.2)		
Total	1238 (100)	2477 (100)	-	-

\*P-value=0.165

## DISCUSSION

This study found a positive association of blood group B in over a thousand patients admitted with COVID-19 while a negative association with blood group O. It also showed a higher frequency of O blood group in general population compared to the hospitalized patients having COVID-19 who predominantly had group B blood group. No such relationship was observed with blood groups A, AB and Rh (D).

In comparison with the ABO and Rh (D) blood group distribution of healthy blood donors in Karachi, blood group B had higher odds of getting COVID-19 infection, whereas blood group O had a protective effect against COVID-19 infection. RhD blood group distribution among case and control group was

statistically insignificant but the likelihood of RhD positive individuals getting COVID-19 is 1.2 times higher than RhD negative individuals.

Blood group O has been reported to exhibit protective effect from COVID-19 infection in a number of studies. Ray JG *et al* recently studied 225, 556 patients having COVID-19 and found that O and Rh (D) negative blood groups may be associated with a slightly lower risk for SARS-CoV-2 infection and severe COVID-19 illness.<sup>21</sup> Similarly Franchini M *et al* studied 447 Caucasians in Italy and observed that subjects with O blood type have reduced predisposition to become infected.<sup>22</sup> Abibatou SALL from Africa reported patients with group A having twice the risk of developing a severe form, while the O group would be

protective.<sup>23</sup> However, in this study, we found no such relationship with blood group A and COVID-19 infection. Zietz M *et al* from United States reported a lower risk of getting infected with COVID-19 in individuals blood group O and Rh-negative blood type to have a protective effect.<sup>24</sup>

A national study from Peshawar region of Pakistan<sup>14</sup> and neighboring country, India<sup>13</sup> reported increased susceptibility of blood group B to infection with COVID-19 similar to our results. These studies also reported blood group AB to be less susceptible to COVID-19 infection, whereas, in our study, AB blood type did not show any statistically significant correlation among the two groups. In our study, Rh (D) was not associated with the disease, whereas, a number of studies including Rana R *et al*<sup>13</sup> and Zietz M *et al*<sup>24</sup> found a protective effect of Rh(D) negative individuals for Covid-19 infection while F Rahim *et al* found Rh (D) positive individuals to be less susceptible to COVID-19 infection<sup>14</sup>.

The question arises that how blood group O is protective? Recently, Gerard C *et al* suggested the role of anti-A antibodies which are present in subjects with both blood group O and B but not in those with blood group A.<sup>25</sup> Moreover, since anti-A are IgG in blood group O and IgM in blood group B, this may further explain the protective nature of blood group O for COVID-19 compared to other blood groups. It is postulated that anti-A antibodies in the serum of O blood group individuals inhibits virus-cell adhesion process<sup>26</sup> by binding to the SARS-CoV-2 receptor-binding domains thereby blocking the interaction with the angiotensin-converting enzyme 2 receptors (ACE2R) and subsequent entry into the lung epithelial cells.

Contrary to the majority of studies showing protective effect of blood group O in COVID-19 infection, some studies have reported contrasting results. Two studies, one from Turkey<sup>27</sup> and other from United States<sup>28</sup>, revealed a 4.1 times higher frequency and slightly higher frequency respectively of COVID-19 infection in individuals with blood group O. In both the studies, no significant risk was associated with blood group A. This distinction in relationship of blood groups within various ethnicities may be related to the varying blood

group distribution in those races/nationalities. One other reason may be the type of population included based on the location where the study has been conducted, that may influence the blood groups.

Our study is the first to report association of ABO blood groups in patients having COVID-19 from Southern Pakistan. Limitations of this study included a single-center experience and not including patients with asymptomatic or milder disease who were not admitted in the hospital. The donors screening for malaria, HIV, Syphilis, Hepatitis B & C were all negative whereas, the patients had multiple comorbidities including diabetes mellitus, hypertension, and ischemic heart disease, which could have been confounding factors, but our study did not exclude these factors.

## CONCLUSION

In conclusion, our study reports the association of ABO and Rh(D) blood group with susceptibility to COVID-19 infection from a tertiary healthcare center at Karachi in Southern Pakistan. In patients admitted with COVID-19 infection, the study revealed an ascendancy of blood group B with a low frequency of blood group O. This observation might illustrate the protectiveness of blood group O for COVID-19 infection. For a comprehensive understanding of this connection, large-scale investigations are essential.

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