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Association of ABO blood group with susceptibility, severity and breakthrough COVID-19 infections in Indian Population

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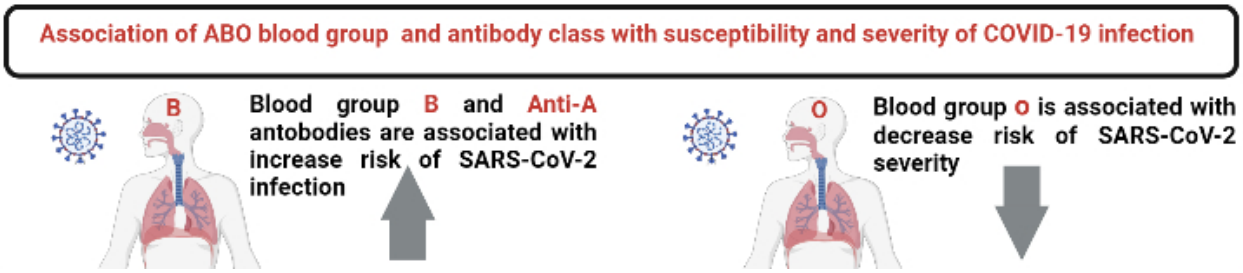
ABSTRACT



Since the COVID-19 eruption in December 2019, the investigation has been focused on its treatment and preventing the disease spread. Currently, there is no biomarker available that can predict the predisposition and severity of COVID-19 infection. In the present study, we have used the cross-sectional survey study data to decipher the association between the ABO blood group and susceptibility, severity and breakthrough COVID-19 infections. Further, we have also investigated the association between antibody class and the risk of contracting COVID-19 infection. Our results indicated that individuals with blood group B had higher susceptibility to acquire COVID-19 infection. In contrast, blood group A was found to be associated with a low risk of acquiring severe COVID-19. In addition, we did not find any correlation between ABO blood group and breakthrough COVID-19 infections. Further, we examined the association of antibodies; anti-A (blood groups B and O) and anti-B (blood groups A and O) with COVID-19 infection. The analysis of antibody classes showed that anti-A antibody associated with a high predisposition to acquire COVID-19 infection. The present study indicates that blood group B and anti-A antibodies are associated with proneness to COVID-19 infection and severity.

Keywords: ABO blood group; COVID-19; Disease susceptibility; India; SARS-CoV-2

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel coronavirus has affected the unprecedented life of billions of people, especially during the second wave of COVID-19 in India.[1] Although extensive research and growing knowledge aid in understanding the nature and mechanisms of the SARS-CoV-2 virus, the emergence of new variants of the virus influences the epidemiological curve of COVID-19. These new SARS-CoV-2 variants may have a higher rate of transmission or increased risk of breakthrough infections resulting in an inflicted burden on the healthcare system.[2,3] Therefore, identifying individuals most susceptible to COVID-19 is critical in dealing with the pandemic. There is currently no biomarker that can anticipate the risk of COVID-19 infection. However, certain risk factors have been identified that affect morbidity and mortality of COVID-19 infection.[4–6]

Several studies have reported the influence of blood groups on contracting the disease. A variety of factors influence the expression of a blood group as well as the type of antibodies produced against it. According to the literature, there is a symbiotic relationship between intestinal flora and the expression of blood groups. Also, bacteria can induce antibodies against different antigens of ABO blood groups. A study by Makivuokko et al. revealed that different blood groups people inhabit different microbiomes in the intestine.[7] The bacterial colonization and dietary modifications transform sialylated glycans (present at birth) to fucosylated antigens of ABO blood groups. These symbiotic bacteria utilize fucose as their food and induce FUT2 (fucosyltransferase 2) in the colon and rectum, resulting in the

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formation of naturally occurring antibodies in the absence of transfusion. The type of diet can also influence the presence and titer of ABO blood group antibodies. A study has shown that feeding of *E. coli* to O and A blood group people results in the generation of anti-B antibodies. Also, patients undergoing bowel surgery reported as high as a 32-fold rise in anti-A and anti-B antibody titers due to bacterial exposure at the time of surgery.[8] The consumption of a probiotic supplemental diet has shown an increase in anti-B antibody titers in a study. Hence, the literature has confirmed that bacteria and diet have a role in the stimulation of a particular type of antibody formation or can increase its titer. In the past, several studies have shown a relationship between ABO blood group and other diseases.[8,9] For instance, individuals having blood group O were reported to be less susceptible to Dengue and SARS.[9,10] In contrast, individuals having blood group O were reported to be susceptible to *Helicobacter pylori* infection and cholera in Gangetic plain populations.[11,12] The first report in China population by Zhao et al. demonstrated that blood group A individuals are at a greater risk of COVID-19 infection and mortality.[13] Similar findings were observed in several other investigations.[14–17] However, Latz et al. found contradicting results in the US population, where individuals with blood group B were more susceptible to COVID-19 infection.[18] Therefore, we investigated the link between the ABO blood group and the susceptibility, severity and breakthrough COVID-19 infections in the Indian population. Furthermore, we looked into the impact of antibody class on the risk of COVID-19 infection.

Materials and Methods

Study Population

The present study is a cross-sectional web-based and offline survey using a pre-validated questionnaire encompassing social, demographic, general health, the status of SARS-CoV-2 infection, and blood group among the Indian population. The participants aged ≥18 years were included in the present study as at the time of the onset of the survey (May 1, 2021), the Government of India had allowed COVID-19 vaccination for all above 18 years. Also, study participants aged ≥18 years are cognizant and can provide volunteered consent to share their personal information for scientific research. Hence, the data were collected from participants during the second wave of the COVID-19 pandemic starting from May 1, 2021 to August 31, 2021. People participating in the present survey were requested to fill in the most appropriate answers to the best of their knowledge. Before beginning the survey, the participants gave their informed consent. Participants in the study were not offered any incentives in exchange for their participation.

Statistical analysis

Analysis of data was done in accordance with the objective. For all statistical tests, the chi-square test (χ^2) and Fisher's exact test were employed to compare the distribution of blood groups and antibodies of individuals. GraphPad Prism 5 software was used for all statistical analysis. A significant difference was defined as a statistical *P*-value of less than 0.05.

Ethical approval

The present study has been approved by the Institutional Human Ethics Committee of Dr. B.R. Ambedkar Centre for Biomedical Sciences, University of Delhi, India as per ICMR guidelines (ACBR/IHEC/DS-09/08-2021).

Results

Demographic profile of respondents

A total of 1146 people responded to the online and offline surveys. Out of 1146 respondents, 52.79% (n=605) were infected with COVID-19 infection, including 41.32% (n=250) females and 58.68% (n=355) males, respectively. A total of 953 respondents reported their blood group, where 46.90% (n=447) respondents were COVID-19 positive and the remaining 53.10% (n=506) were COVID-19 negative. Among 953 respondents who reported their blood group, a total of 52.15% (n=497) were vaccinated while the remaining 47.85% (n=456) were unvaccinated. Among 497 vaccinated individuals, 17.30% (n=86) individuals took Covaxin and 81.69% (n=406) individuals took Covishield vaccine and remaining 1% (n=5) respondents did not mention the name of the vaccine.

Relation between blood group and SARS-CoV-2 infection

Out of the 507 respondents representing the COVID-19 negative control group, we found a high frequency of blood group B (n= 187, 36.88%), followed by blood group O (n= 160, 31.56%), A (n= 110, 21.69%) and AB (n=50, 9.86%) respectively. Similarly, the COVID-19 positive group (n=447) also showed a similar order of frequency of blood group, i.e. blood group B (n= 213, 47.65%) followed by blood group O (n=125, 27.96%), A (n= 77, 17.22%) and AB (n=32, 71.6%) respectively. Figure 1 shows the distribution of blood group among COVID-19 negative and positive groups.

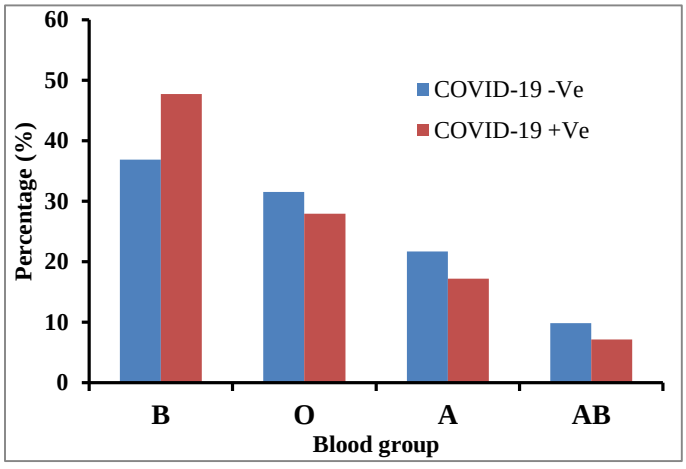

Figure. 1. Distribution of blood group among COVID-19 negative and COVID-19 positive groups

The results showed a significant difference in the distributions of blood groups among COVID-19 negative and positive groups (χ^2= 12.04, *P*= 0.007). In addition, blood group B was found to be associated with an increased risk of infection (OR: 1.56, 95% CI: 1.20-2.02, *P*= 0.001). However, other blood group did not show any association with SARS-CoV-2 infection (Table 1).

Further, analysis based on antibody class showed that anti-A antibodies were associated with increased risk while anti-B antibodies were associated with a decreased risk of COVID-19 infection (Table 1).

Table 1: The ABO blood group distribution and antibodies present in patients with COVID-19 infected and non-infected Individuals

Blood Group	χ^2	OR	95% CI	*P*-Value
A	3.01	0.75	0.54-1.03	0.083
B	11.31	1.56	1.20-2.02	0.001*
AB	2.21	0.70	0.44-1.12	0.137
O	1.47	0.84	0.64-1.11	0.226
Antibodies				
Anti-A	6.04	1.43	1.07-1.90	0.014*
Anti-B	6.18	0.72	0.56-0.93	0.013*

Analysis of the severity of the COVID-19 infection

Blood group distributions among varied severity of COVID-19 were compared to find out the association between blood group and predisposition to severe COVID-19 infection. Among 78 individuals who had reported severe COVID-19 infection, 58.97% were blood group B, followed by 28.21%, 6.41%, and 6.41% were blood group O, A, and AB respectively. Among moderate COVID-19 cases, 46.84% were of blood group B, followed by 30.63%, 16.21%, and 6.31% of blood groups O, A, and AB respectively. In mild COVID-19 cases, 42.61% belonged to blood group B, followed by 28.98%, 21.59%, and 6.82% to blood groups O, A, and AB, respectively. The distribution of the two group in the clinical outcome of COVID-19 infection is shown in Figure 2. Blood group A was found to be significantly associated with a decreased risk of severity of COVID-19 infection (χ^2 = 8.98, *P* = 0.01).

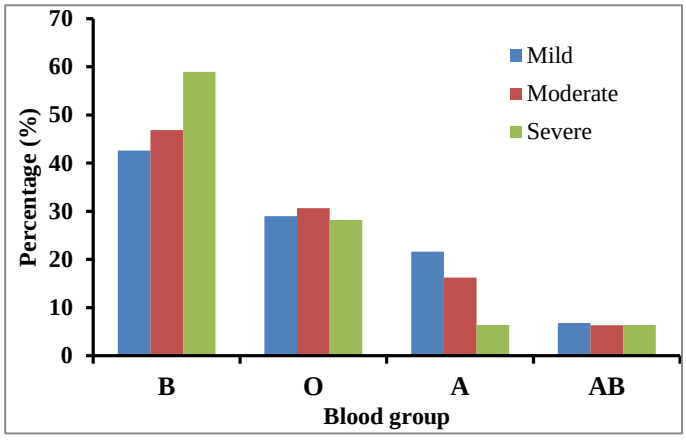

Figure. 2. The impact of ABO blood group on the severity of COVID-19.

Relation between blood group and adverse events after vaccination

Out of 497 vaccinated respondents, 73.44% (n=365) experienced adverse events after vaccination. Adverse events include fever, body ache, headache, pain at the injection site and nausea/vomiting. However, blood group did not show any significant association with the adverse events after the COVID-19 vaccine (Table 2).

Relation between blood group and breakthrough COVID-19 infections

A total of 6.84% (n=34) out of 497 vaccinated individuals got COVID-19 after vaccination. Since blood groups showed a significant association with COVID-19 infection and its severity, we also examined the association of blood group with breakthrough infection. The results showed no association between blood group and breakthrough COVID-19 infection (*P* =0.341).

Table 2: The ABO blood group distribution and adverse events after COVID-19 vaccination

Symptoms	A	B	AB	O	*P*-Value
Fever	52 (67.53)	94 (68.61)	18 (50.00)	71 (61.74)	0.241
Body ache	39 (55.71)	61 (50.83)	15 (53.57)	57 (56.44)	0.098
Headache	23 (32.86)	45 (37.50)	12 (42.86)	35 (34.65)	0.395
Pain at injection site	26 (37.14)	50 (41.67)	12 (42.86)	36 (35.64)	0.065
Nausea/vomiting	3 (4.29)	8 (6.67)	2 (7.14)	6 (5.94)	0.947

DISCUSSION

The emergence of COVID-19 throughout world led to the exploration of new methods for its diagnosis,[19] prevention[20] and therapeutics development[21–25] along with the progress of iunderstanding of its progeny and infectivity. Several studies have revealed the relationship between blood group and susceptibility to COVID-19 infection, however, the results are ambiguous across different populations. Therefore, we investigated the association of blood group with proneness to COVID-19 infection and severity in the Indian population. We found similar blood group distribution among the control or normal population as previously reported by Patidar and Dhiman in the Indian population.[26]

Further, the present cross-sectional survey study clearly indicates that blood group B is associated with an increased risk of COVID-19 infection. The results from this study are consistent with previous studies demonstrating the association of blood group B with the risk of COVID-19 infection.[17,18,27] A report by Chung et al. revealed that ACE activity is higher in blood group B compared to blood group O, resulting in higher infection in blood group B individuals that may lead to higher severity and mortality in blood group B patients than in blood group O.[28] A possible mechanisms of association of blood group B with high risk of COVID-19 infection is shown in figure 3. In contrast to our results, several studies showed that blood group A was associated with an increased risk of COVID-19 infection. Also, the frequency of blood group A was found to be the highest among COVID-19 positive individuals.[14–18,29] In addition, we did not find any association between blood group O and decreased susceptibility to COVID-19 infection as shown by other studies.[13,27,29,30] Our findings also showed an inverse relationship between blood group AB and the risk of SARS-CoV-2 infection as reported by Zhao et al.[13] and

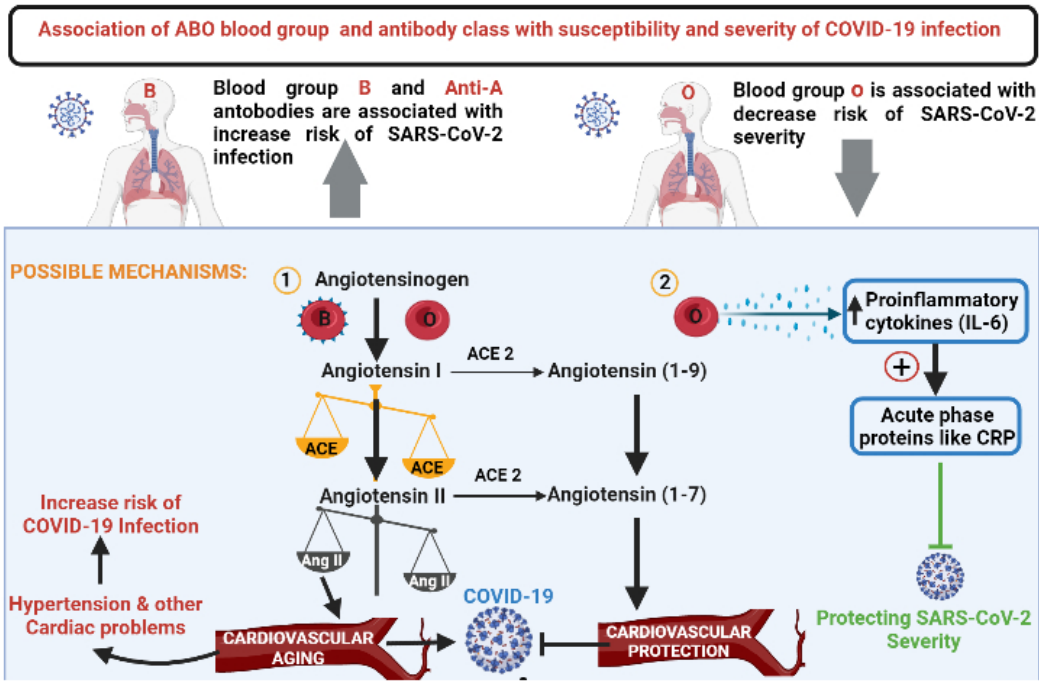

Figure 3. Possible mechanisms: association of ABO blood group with the risk of COVID-19 infection.

Almadhi et al.[27] However, the results were insignificant, may be due to the low number of participants. We have also investigated the relationship between antibodies present in the blood and the risk of COVID-19 infection. We found a significant association between anti-B antibodies and decreased odds of COVID-19 infection, which is directly proportional to the increased risk of COVID-19 infection with blood group B. In addition, we also found a significant relationship between anti-A antibodies and increased odds of COVID-19 infection in contrast to the report by Gerald et al.[31]

We extended the analysis by investigating the distribution of blood group and the clinical outcome of COVID-19 infection to find out the relationship between blood group and the severity of infection. In agreement with the previous reports,[15,30] we found no link between the increased risk of severe COVID-19 illness and any of the blood group. However, several studies reported the association of decreased risk of severe COVID-19 illness with blood group O in agreement with our results.[32] There are several reasons to support this finding. The low COVID-19 severity in O blood group individuals could be due to low levels of ACE (angiotensin-converting enzyme) in them.[33] The levels of ACE are directly proportional to hypertension risk, therefore, the lower level of ACE might reduce hypertension in blood group O individuals, a risk factor for COVID-19 infection and severity.[34] Also, O blood group people have high levels of interleukin 6 (IL-6), a pro-inflammatory cytokine produced by several body cells, found to have a role in cell defense in the acute phase of infection.[35] It might play a role in protecting against SARS-CoV-2 severity. In addition, various studies reported that Rh-negative blood groups were also associated with a decreased risk of COVID-19 infection as well as severe COVID-19 illness.[36–38] In contrast, another study reported by Bhandaria et al., documented the increased mortality in COVID-19 illness in Rh-negative patients.[39] Nonetheless, due to time constraints, we were unable to conduct this survey; however, in future studies, we would like to assess the role of the Rh factor in COVID-19 infection and severity. Further, we investigated the association of blood groups with adverse events after vaccination. The results showed no association between blood groups and adverse events. However, our results are inconsistent with another study reported by Allan et al.[40] In addition, no significant association was observed between ABO blood group and breakthrough infections.

Conclusion

In conclusion, our results indicated that blood group B and anti-A antibodies are associated with an increased risk of COVID-19 infection. Also, blood group O might have a role in decreasing the severity of COVID-19 infection. However, the ambiguity between the present study and other findings suggests that other underlying factors such as age, gender, comorbidities, and the body's immune system may have a role in the severity of COVID-19 infection along with blood group distribution.

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Authors' contributions

PB, JT, SKY and DS designed the survey form. PB, JT, SKY and DS collected the epidemiological data. PB and JT analyzed the data. PB and JT drafted the manuscript. All authors read the manuscript and approved it.

Conflict of interest

The authors declare that there are no conflicts of interest for publication of this article. The views expressed in this article are of the authors alone and do not necessarily represent the views of their organizations.

Participant consent

Participants were informed that their participation was voluntary, and consent was implied on the completion of the questionnaire.

Consent for publication

Not applicable as no identifying data of the individual person is shown in the manuscript.

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