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Exploring the relationship between ABO and Rh blood groups and susceptibility to COVID-19 infection

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ABSTRACT

Background : The rapid global spread of the novel coronavirus SARS CoV-2 has strained the existing healthcare and tested our resources. Many studies have found that the ABO blood group plays an important role in various human diseases, such as cardiovascular, oncological, and some infectious and non-infectious diseases. The present study was conducted to study the association of ABO and Rh blood groups with COVID-19 susceptibility and severity.
Materials and Methods: This study was conducted on 209 COVID-19-confirmed patients admitted for their management. Cases were categorized as mild, moderate and severe as per the protocol. The ABO/Rh blood groups of these patients were determined by the gel card method.
Results: A total of 209 COVID positive patients were included in this present study. Most of the patients susceptible to COVID belonged to B positive blood group (33.01%) followed by O positive (32.06%). The severity of COVID-19 infection was most common in patients with O positive blood group (37.4%).
Conclusion: COVID-19 infection was more common in males and more prevalent in B and O-positive blood groups.

1. Introduction

The COVID-19 pandemic has stretched the existing healthcare and tested our resources. It has hit some people harder than others, with some people experiencing only mild symptoms and others being hospitalized and requiring ventilation. Making the identification and prioritization of individuals at higher risk remains a critical challenge.

The ABO blood group is the most important blood group system in humans. Many studies have found that the ABO blood group plays an important role in various human diseases, such as cardiovascular, oncological, and some infectious and non-infectious diseases.[1,2]

An understanding of the factors with profound impacts on the pandemic is crucial for controlling the pandemic and factors associated with the pandemic must be considered when making public policy and medical decisions. Being one of the largest countries, more research and understanding is needed to overcome the rapid spread and adversities in this ongoing pandemic. There are no studies available from this part of the country studying the association between the ABO/Rh blood groups with COVID-19 infection susceptibility and severity. Hence, this study was undertaken.

2. Materials and Methods

This study was conducted on 209 COVID-19-confirmed patients admitted to the designated wards for the COVID positive patients of the institute. Patients were diagnosed as COVID-19 positive by the Reverse Transcriptase –Polymerase Chain Reaction (RT-PCR) method or the

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rapid antigen test and admitted for management in the study period. Patients were categorized into mild, moderate, and severe categories according to the National Clinical Management Protocol for COVID-19, prepared by the Ministry of Health and Family Welfare, Government of India. The data was collected from the electronic health records for the period from September 2020 to November 2021. ABO/Rh blood groups of these patients were determined by the gel card system.

2.1. Inclusion criteria

All patients diagnosed as COVID-19 positive by RT-PCR or rapid antigen test and admitted for management for whom the ABO/Rh blood grouping was performed.

2.2. Statistical analysis

The data were entered into MS Excel 2021 version and further analyzed using SPSS 20. For descriptive analysis, the categorical variables were analyzed by using percentages. The categorical data were analyzed using Pearson's chi-square test and "p-value" <0.05 was considered statistically significant.

3. Results

Of the 209 COVID-19 patients included in the study, most of the patients belonged to the middle age group (26-50 years) accounting for 54.5% as depicted in Table 1. Of these, 154(73.7%) patients were males.

Most patients belonged to the blood group B-positive 69 (33.01%) followed by O-positive 67 (32.06%) as depicted in Table 2.

Most of the patients belonged to the mild COVID-19 category accounting for 46.9% as depicted in Table 3.

Among the 69 B-positive blood group patients, 34 patients were of the mild COVID-19 category. Among the 67 O-positive blood group patients, 31 patients were of the mild COVID-19 category. Compared to other blood groups, 13 patients in the O-positive blood group were admitted under the severe COVID-19 category as shown in Table 4. The correlation of COVID-19 categories with the ABO/Rh blood groups was not statistically significant with a p-value of 0.850.

Most of the male patients (70) and female patients (28) belonged to the mild COVID-19 category as depicted in Table 5. The correlation of COVID-19 categories with gender was not statistically significant with a p-value of 0.619.

The distribution of COVID-19 categories concerning various age groups is shown in Table 6. Most of the patients were in the middle age group (26-50 years) ie.,114 patients. Among 114 patients, most of the patients belong to the mild COVID-19 category (57). Among 69 patients in the age group 51-75 years, most of the patients belong to the moderate COVID-19 category (29). In the present study, patients with severe COVID-19 category were low in all age groups. The correlation of COVID-19 categorization with age groups was showing a statistical significance of p value of 0.001.

4. Discussion

SARS-CoV-2 has caused a global health crisis, with millions of reported COVID-19 cases and deaths worldwide. Age, gender, and certain medical conditions are risk factors for serious outcomes. It is important to identify COVID-19 patients at increased risk for morbidity and mortality. Some evidence suggests that the ABO blood phenotype is associated with disease susceptibility and progression.[1,2,4,5,8]

The association between ABO blood groups and SARS-CoV-2 infection can be explained by several mechanisms, such as the presence of anti-A and/or anti-B antibodies that act as viral neutralizing antibodies or inhibit the binding of the virus to the ACE-2 receptor. Increased activity of ACE-1 in patients with blood group A, higher levels of VWF and Factor VIII, and ABH glycans that modify the affinity of SARS-CoV-2 for ACE-2 receptor or act as an alternative, lower-affinity receptors for the virus can also contribute to the risk of severe COVID-19.[7]

Chung et al investigated the association between ABO blood types and ACE activity and showed that individuals with blood type A had the lowest ACE activity, while those with type B had the highest. The mean ACE activity was significantly higher in people with only B antigen compared to blood type O individuals, and significantly lower in blood type A individuals compared to blood type O individuals. The mean ACE activity of blood type AB was between those of blood type A and B, but not significantly different from blood type O.[9]

The relationship between ABO blood type and COVID-19 severity is supported by biological evidence.[10] ABO peptides found in endothelial cells and platelets can increase the risk of thrombosis, leading to consumptive coagulopathy and thrombotic microangiopathy. A and B carbohydrate structures are expressed in the respiratory and gastrointestinal tracts and can be incorporated into the viral spike glycoprotein during SARS-CoV-2 replication. This enables the virus to be neutralized by anti-A and/or anti-B antibodies. ABO blood group antigens can also modulate the innate immune response to various pathogens through their glycan moieties.

Variants in the ABO gene group locus has been shown to correlate with the development of respiratory failure in COVID-19 patients. ABO gene polymorphisms are also associated with cardiovascular disease, angiotensin-converting enzyme activity, red blood cell indices, and venous thromboembolism, all of which play a crucial role in the pathogenesis of severe COVID-19 infection.[5]

Table 1: Age Distribution of cases

Age group (years)	Number of cases	Percentage
<25 years	21	10
26-50 years	114	54.5
51-75 years	69	33
75+ years	5	2.5

Table 2: Distribution of cases according to the ABO/Rh blood group

Blood group	Number of cases	Percentage
A+	52	24.8
A-	1	0.5
AB+	12	5.8
AB-	3	1.5
B+	69	33
B-	3	1.5
O+	67	32
O-	2	0.9

Table 3: Distribution of cases according to the COVID-19 categories

COVID-19 Category	Number of cases	Percentage
Mild	98	46.9
Moderate	76	36.4
Severe	35	16.7

Table 4: COVID-19 categories and the associated ABO/Rh blood groups

Blood group	Covid-19 Categorisation			Total
	Mild	Moderate	Severe	
A+	20	21	11	52
A-	1	0	0	1
AB+	7	4	1	12
AB-	1	2	0	3
B+	34	25	10	69
B-	2	1	0	3
O+	31	23	13	67
O-	2	0	0	2
Total	98	76	35	209

Table 5: COVID-19 categories and their association with gender

Gender	Covid-19 Categorisation			Total
	Mild	Moderate	Severe	
Female	28	17	10	55
Male	70	59	25	154

Table 6: COVID-19 categories and their association with age groups

Age group (years)	Covid-19 Categorisation			Total
	Mild	Moderate	Severe	
<25 years	18	3	0	21
26-50 years	57	41	16	114
51-75 years	22	29	18	69
75+ years	1	3	1	5

Table 7: Comparison of blood groups inCOVID-19-positive patients

Study And Place	Year	Sample Size	Blood Group A%	Blood Group B%	Blood Group AB%	Blood Group O%
Samra et al[2] (Egypt)	2021	507	75	3.5	19	2.5
Fan et al[3] (Wuhan)	2020	105	42.8	26.7	21.9	8.57
Acik et al[4] (Turkey)	2021	823	43	19	30	8
Present Study (India)	2021	209	26	35	7	32

Table 8: Comparison ofthe severe COVID category with the ABO blood group

Study	Location and Year	Severe/ICU Cases (Out of total Cases)	ABO Blood Groups affected			
			Blood Group A	Blood Group B	Blood Group AB	Blood Group O
Acik et al[4]	Turkey 2012	398(823)	**174** (351)	77 (153)	28 (69)	119 (250)
Hermel et al[5]	USA 2021	207(473)	61 (143)	15 (45)	9 (18)	**122** (267)
Almadhi et al[6]	Bahrain 2021	196(2138)	46	59	11	**80**
Hafez et al[7]	UAE 2022	44(303)	**15** (84)	9 (76)	6 (21)	14 (112)
Present Study	India 2021	35(209)	11 (53)	10 (72)	1 (15)	**13** (69)

Table 9: Comparison of gender and blood groups inCOVID-19-positive patients

Study	Sample Size	Gender	Blood Group A	Blood Group B	Blood Group AB	Blood Group O
Fan et al[3] (Wuhan)	105	Male (N)	21	17	6	11
		Female(N)	24	11	3	12
Hafez W et al[7] (UAE)	303	Male(N)	58	63	17	83
		Female(N)	26	13	4	39
Present Study (India)	209	Male(N)	41	57	12	49
		Female(N)	15	14	2	19

It is hypothesized that ABO(H) determinants on host cell surfaces may interfere with the binding of the virus and its entry into target cells through interactions with the virus' glycoprotein receptors. ABO(H) structures are found in various cells and tissues and may be involved in physiological and pathological processes during infections. Non-O individuals have been found to have higher expression of endothelial cell-associated von Willebrand factor (VWF) protein compared to those of group O, which is associated with pulmonary vascular endothelial cells and influenced by ABO determinants. Elevated levels of VWF and factor VIII (FVIII) have been found in patients with severe COVID-19 pneumonia, which indirectly links ABO blood groups with susceptibility to COVID-19.[11]

Researchers propose that the varied distribution of sialic acid-containing receptors on host cells' surfaces, modulated by ABO antigens through carbohydrate-carbohydrate interactions, may explain the association between ABO blood type and COVID-19 susceptibility. Antigens A, B, and AB stimulate carbohydrate clustering, which increases the interaction between the virus's spike protein and host cells, facilitating the infectious process. Increased interaction may increase the probability of SARS-CoV-2 successfully binding to host cells via specific binding of spike protein domains to ACE2 and CD147.

Research suggests that individuals with non-A blood types, specifically O or B, may be less susceptible to COVID-19 due to the inhibitory effects of anti-A antibodies. The distribution of sialic acid-containing receptors on host cells' surfaces, modulated by ABO antigens through carbohydrate-carbohydrate interactions, may also play a role in susceptibility. Host transmembrane protease serine subtype 2 (TMPRSS2) may play a significant role in ABO group modulation of infection by allowing for serine mobilization critical for infection. The A, B, and AB blood groups are preferential targets due to their enzymes facilitating greater viral molecular contact, whereas the O blood type only binds the virus via hybrid H-type antigen formation. TMPRSS2 inhibition is proposed as a potential therapeutic target.[12]

The study by Hafez et al explored the association between blood groups and COVID-19 outcomes. The study found that blood group O was the most common among COVID-19 patients, and patients with blood group B and RH positivity had a shorter time until viral clearance. The study found no significant association between the ABO blood group and COVID-19 outcomes except for blood group AB having higher odds of disease severity.[7]

Samra et al found that individuals with blood group A had a higher susceptibility and severity, while those with blood group O had a lower risk.[2]

However, a retrospective study of 942 hospitalized patients in San Diego County by Hermel et al found no significant association between ABO blood group type and severity outcomes, once confounding variables were accounted for.[5]

Although the association between blood type B and decreased mortality risk in COVID-19 patients was not statistically significant after multivariate analysis, the findings suggest a possible link. Patients with blood type B had the lowest peak serum D-dimer levels, the lowest peak creatinine levels, the lowest peak neutrophil percentages, and the highest mean lymphocyte percentages during hospitalization. The marginally decreased odds of death in blood type B and the stark differences in laboratory values compared with blood type AB suggest a possible mechanistic role for anti-A isoagglutinin in the pathogenesis of severe COVID-19. The lack of mortality improvement in blood type O patients with similar anti-A antibodies may be due to the predominant isotype of immunoglobulin in type O blood being IgG rather than IgM.[5]

The study by Qian et al included 105 COVID-19 cases and it was found that the frequencies of blood types A, B, AB, and O were 42.8, 26.7, 8.57, and 21.9%, respectively, in the case group. Association analysis between the ABO blood group and COVID-19 indicated that there was a statistically significant difference for blood type A, but not for blood types B, AB, or O. An analysis stratified by gender revealed that the association was highly significant between blood type A in the female subgroup but not in the male subgroup.[3]

A study by Zietz et al conducted on 14,112 individuals in the New York Presbyterian (NYP) hospital system found that non-O blood types had slightly increased infection prevalence. The risk of intubation was decreased among individuals with blood type A and increased among those with blood types AB and B. The risk of death was increased for individuals with blood type AB and decreased for those with blood types A and B. Rh-negative blood type was found to have a protective effect for all three outcomes.[8]

The study by Zhao et al found that individuals with blood group A have an increased risk of COVID-19, while those with blood group O have a decreased risk.[13]

The study by Acik et al found that individuals with blood group O had a lower prevalence of COVID-19 compared to other blood groups. The study suggests that blood group O individuals may have some resistance to clinically overt infection with SARS-CoV-2.[4]

In the present study, most of the cases belonged to blood groups B and O as seen in Table 7 in comparison to the other studies.

A study in found that blood group B was associated with a higher risk of infection, while blood group AB was associated with a lower risk. However, there was no association between blood group and the risk of severe ICU-requiring infection.[6]

In the present study, most of the severe cases belonged to blood group O when compared to other studies as depicted in Table 8.

A meta-analysis of 10 studies consisting of 54,218 subjects found that blood groups A and B are associated with an increased probability of COVID-19 infection compared to non-A and non-B blood groups, while individuals with blood group O had a significantly lower predisposition to COVID-19. Patients who were Rh-positive were more vulnerable to COVID-19 than those who were Rh-negative. Blood group A was associated with higher mortality in COVID-19 patients compared to non-A blood groups. Race differences did not significantly affect the association between blood group and COVID-19 infection.

Studies have shown that Rh(+) individuals have higher odds of testing positive and higher risks of intubation and death, while Rh(-) individuals have a lower risk of initial infection, intubation, and death. Individuals with Rh(-) blood type, especially O-negative, were found to be less susceptible to infection by SARS-CoV-2.[12]

A meta-analysis study conducted in Italy and Spain found a genetic susceptibility locus in COVID-19 patients with respiratory failure at locus 3p21.31 and locus 9q34. Another study using trans-ethnic genome-wide association studies reported a strong association between blood type and COVID-19 severity, specifically at a locus on chr3p21.31.[12]

The study by Ali H. Ad'hiah et al examined 1014 Iraqi hospitalized cases with COVID-19 and showed that the mean age of cases was significantly higher than controls, and males outnumbered females in both cases and controls. The highest percentage of cases clustered in the age group of 50 years or older. (Table) The study suggests that blood group A may be associated with an increased risk of developing COVID-19, particularly in males.[11]

Gender can indeed be considered a predisposing factor for COVID-19, and males may be more susceptible to the disease than women. Studies have consistently shown that the proportion of males among confirmed cases of COVID-19 is higher than that of females. However, most epidemiological reviews and meta-analysis studies have reported comparable rates of COVID-19 between males and females, with males tending to have higher fatality and mortality rates than females.[11]

The vulnerability of men to worse outcomes of COVID-19 is likely due to gender-based immunological differences. Sex hormones, particularly estrogen, may mediate these differences. Experimental data has shown that female mice treated with an estrogen receptor antagonist had increased mortality rates due to SARS-CoV infection.[11] In the present study too most of the cases were males as depicted inTable 9.

The gender disparity in morbidity and mortality rates among COVID-19 patients may also be related to sex-biased

differences in the lung expression of angiotensin-converting enzyme 2 (ACE2). The gene encoding ACE2 is mapped to chromosome X, and its expression is influenced by sex hormones. Collectively, these findings suggest that gender may play a role in COVID-19 outcomes, but more research is needed to fully understand the mechanisms involved.[11]

The study was limited by the smaller size of patients studied as the blood grouping was not routinely determined for all COVID-19-positive patients. Also, the susceptibility could vary with the different viral strains as was seen in the difference in hospitalizations in the different waves of the pandemic.

The controversial results of other studies could be explained by several mechanisms, including genetic susceptibility, the inhibitory effect of the human anti-A antibody, and the presence of A/B phenotypic-determining enzymes. The distribution of ABO blood types varies throughout populations, and distinct characteristics could influence COVID-19 outcomes. However, the study highlights that certain blood groups may be more vulnerable compared to others in terms of severity. This may help healthcare planners to proactively identify such cases in the present and future pandemics which the world may encounter. These persons may require more personal protection and may require more intensive treatment. A larger study across all the regions in the world will also throw light on whether there are any regional or racial variations in susceptibility.

5. Conflict of Interest

None.

6. Source of Funding

None.

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