IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 21, Issue 1 Ser.7 (January. 2022), PP 01-07
www.iosrjournals.org

An observational study to determine COVID-19 susceptibility with reference to blood groups

Himanshu Prasad[1], Smruti Ghetla[2a], Harshal Rawtani[2b], Sumayya Ansari[3a], Priyansh Nathani[3b], Ushma Bhutala[4]

[1,2a,4](Department of General Surgery, HBTMC & Dr. R. N. Cooper Hospital, Mumbai, India)
[2b](Department of Anatomy, HBTMC & Dr. R. N. Cooper Hospital, Mumbai India)
[3a](Department of Obstetrics & Gynecology, HBTMC & Dr. R. N. Cooper Hospital, Mumbai India)
[3b](Intern, HBTMC & Dr. R. N. Cooper Hospital, Mumbai, India)

Abstract:
Background*: COVID-19 became one of the most rapidly spreading disease in the world, being declared a pandemic in the early 2020. India faced 2 waves of rapidly increased cases, with the omicron variant emerging as a cause for the third wave. While nearly one half of the Indian population is double vaccinated, we still have a long way to go. Clinical observations suggested a possible relationship between the ABO blood group type and COVID-19 infection and severity rates. However, there is not much data on the Indian population, hence this observational study was conducted to assess the possibility of this said relationship, and guide further regarding its impact.*
Materials and Methods*: In this observational cross section study, history of patients admitted at Dr. R. N. Cooper Hospital between June'20- August'20 were analyzed. Those who were admitted and tested positive for COVID-19 were analyzed and categorized based on various criteria like age, sex and mainly ABO blood types & Rh antigen. The statistical data was then tabulated and analyzed and inferences made.0*
Results*: Majority of severe cases had A blood group, while those in the mild category had mainly the B and O blood groups.*
Conclusion: *There is a strong relationship between ABO & Rh blood group and COVID-19 susceptibility, including severity of infection.*
Key Word*: ABO blood group, Rh antigen, COVID-19 susceptibility, Indian population, severity of infection*

Date of Submission: 01-01-2022 Date of Acceptance: 12-01-2022

I. Introduction

The novel coronavirus SARS-CoV-2, causing the infectious coronavirus disease-2019 (COVID-19) was declared a pandemic by WHO on March 11,2020. India has been one of the "hotspots" having already been through two waves, with the omicron variant being on the rise. Clinical observations and various reports suggest that patient age, male sex and certain chronic medical conditions (e.g., cardiovascular disease, diabetes, COPD) seemed to represent a risk factor for SARS-coV-2 infection as well as higher disease severity[1]. There is currently no biological marker known to predict the susceptibility to COVID-19.

Landsteiner's ABO blood types are carbohydrate epitopes that are present on the surface of human cells. The antigenic determinants of A and B blood groups are trisaccharide moieties GalNAcα1-3-(Fucα1,2)-Galβ- and Galα1-3-(Fucα1,2)-Galβ-, while O blood group antigen is Fucα1,2-Galβ. While blood types are genetically inherited, the environment factors can potentially influence which blood types in a population will be passed on more frequently to the next generation.

Susceptibility to various viral infection has been previously found to be related to ABO blood group. For example, Norwalk virus and Hepatitis B have clear blood group susceptibility[2,3]. It was also reported that O blood group individuals were less likely to become infected by SARS-CoV-2 virus (4-6).

Here, we investigated the relationship between the ABO blood type and the susceptibility to COVID-19 infection & its severity in patients admitted at Dr. R. N. Cooper Hospital. The present study was undertaken by the department of General Surgery at Hinduhridaysamrat Balasaheb Thackeray Medical College & Dr. Rustom Narsi Cooper Municipal General Hospital, Mumabi, India to test if the former may be a biomarker for the latter.

II. Aims & Objectives

1) To estimate the relationship between ABO blood type and COVID-19 infection.
2) To estimate complications and treatment response in different blood groups.
3) To estimate if introduction of ABO blood group typing will be helpful in the management of SARS-CoV-2 infection and COVID-19.

III. Materials & Methods

Study design: Hospital-based observational cross sectional study.
Study period: June 2020 to August 2020
Study population: Patients receiving treatment at Dr. R. N. Cooper Hospital during the study period.
Sample size: 279
Inclusion Criterion:

- ≥ 18 years of age admitted and diagnosed with COVID-19 at Dr. R. N. Cooper Hospital, Juhu, Mumbai, India.

Exclusion criterion:

- Congenital disease
- Autoimmune disorder
- Malignancy
- Patients with age under 18 years
- Pregnant females

Data collection methods:

- A prior informed verbal consent from the participants was taken.
- Data will be collected using details of patients and blood group.
- The collected data will be analyzed using MS EXCEL.

We collected and ABO-typed blood samples from 279 patients, infected with SARS-CoV-2, admitted at Dr R. N. Cooper Hospital, Juhu, Mumbai, India
The diagnosis of COVID-19 was confirmed by a positive real-time reverse transcriptase polymerase-chain-reaction test of SARS-CoV-2 on nasal and pharyngeal swab specimens from patients.
Statistical analyses were performed using chi-squared test. Data from hospital were analyzed using random effects models, with calculation of odds ratio (OR) and 95% confidence interval (CI). Statistical analyses were performed using SPSS software (version 16.0) and STATA software (version 13).
Blood grouping:- In simple testing, a blood grouping reagent (containing specific antibodies) is mixed with a sample of the patient's red blood cells. The reaction that occurs then illustrates what blood type the patient is. Whichever antibodies makes the red blood cells agglutinate (clump together), that is the blood group of the patient. For instance, if the red cells (or erythrocytes as they are known) agglutinate when mixed with a reagent containing Anti-A antibodies, then the patient's red blood cells contain A antigens (and the patient is said to be group A positive). Each blood grouping reagent is able to detect a specific blood group. In Dr. R.N. Cooper Hospital, blood is typed for at least 8 different blood groups, requiring 8 different blood grouping reagents, before the blood donation is released for transfusion into a patient.
Confidentiality*:* Identity of the participants will be kept absolutely confidential.

IV. Results

Our study group included 279 patients of laboratory-confirmed COVID-19 infection who were admitted at Dr. R. N. Cooper Hospital. After examining their history in detail, they were categorized, based on their severity of infection, into mild, moderate and severe groups. The data was also scrutinized based on age, gender, ABO blood group and Rh antigen distribution. Out of our 279 patients, there were 229 patients *(82.08%)* grouped under the mild severity, 45 patients *(16.12%)* were under the severe category, and only a mere 5 patients *(1.8%)* under the moderate category.
***COVID-19 & Gender*:** Of 279 patients, we had 143 female patients (51.25%) and 136 male patients (48.75%) confirming a near equal representation of both in the study group. As seen in **Figure 1**, there was a similar pattern of near equal distribution of females [114*(49.78%),* 3*(60%)*] and males [115*(50.12%),* 2*(40%)*] in the mild and moderate infection groups respectively. However, severe infection was seen in 26 females *(57.78%)* as compared to just 19 males *(42.2%).*
COVID-19 & Age: The patients were divided into different age groups like >75 years, 75-60, 45-59, 30-44 and <30 years **Figure 2**. In contrast to what was expected, the majority of our cases were <45 years. According to our data analysis, 38% of those in the severe category were over the age of 45 **Figure 3**(c). Similarly, *32%* of the mild category group **Figure 3**(a) and *60%* of the moderate category **Figure 3**(b) group also were over 45

years of age. This possibly suggests that age **alone** cannot predict the severity with which one might be affected by COVID-19.

***COVID-19 & ABO blood group*:** The prevalence of ABO blood group and Rh antigen in our sample **(Table 3)** was compared to the average prevalence of these in the general population to make sure the sample size was representative of the entire general population. The average prevalence of the blood group was calculated using data from four different epidemiological studies **(Table 2)** conducted in separate time periods. This average was compared to our study population average, and we found that it was nearly the same. **Figure 4** shows ABO blood group distribution in our study group and then also subdivided into different severity groups. Amongst the 45 patients in the severe group, 20 *(44.44%)* had A blood group, as compared to only 7 (15.56%), 9 *(20%)* and 9 *(20%)* with the blood groups AB, B & O respectively. Amidst the 229 patients in the mild group, majorly included those with B [78*(34.07%)*] and O [68 *(29.69%)*] blood groups. This implies that there is some association between blood group A and the higher severity of COVID-19 infection. Those who had the AB blood group had almost an equal distribution amongst the mild *(13.10%)*, moderate *(20%)* and severe *(15.55%)* categories.

We had very little representation of patients in the moderate severity group, with only 5 patients in B *(40%)*, O *(40%)* & AB *(20%)* blood groups.

***COVID-19 & Rh Antigen*:** Rh(D) + antigen was almost equally distributed amongst mild *(91.70%)*, moderate *(100%)* and severe *(92.11%)* groups, however there was near zero/very small number of Rh(D)- antigen patients present in all three groups of severity.

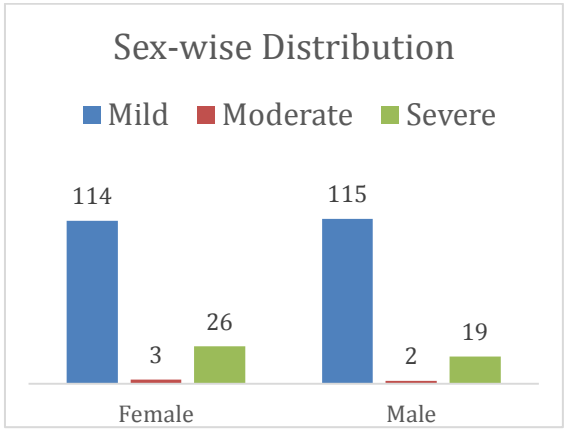

Figure 1. Gender wise distribution of COVID-19 cases: This bar graph has been divided into genders on the X-axis, and each graph is then divided into three groups based on their severity as mild, moderate and severe.

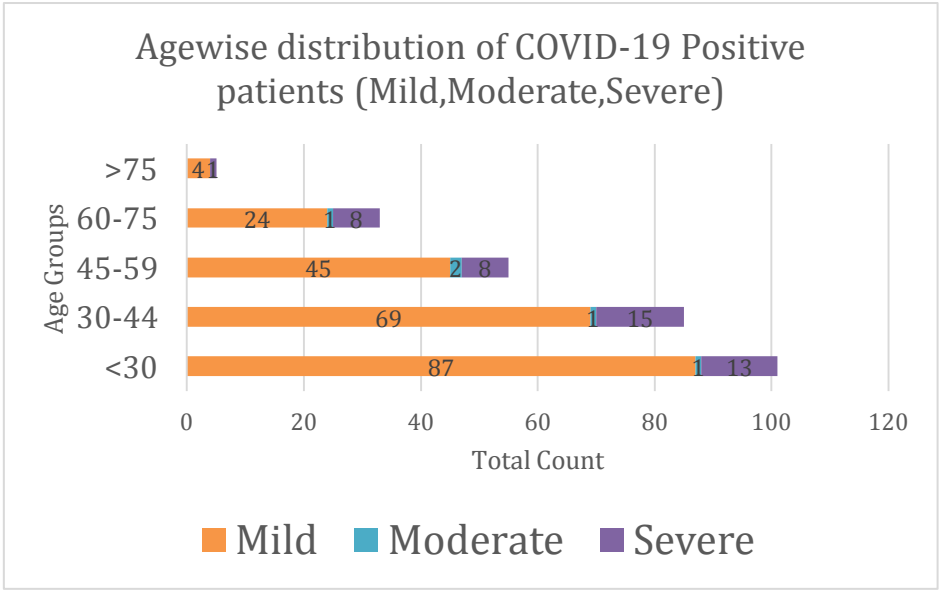

Figure 2. Age wise distribution of COVID-19 cases**:** On the Y axis, the different age groups as >75,60-75,45-59,30-44 and <30 years, while on the X-axis we have the number of patients. Further, this image categorizes patients in each age group as mild, moderate and severe.

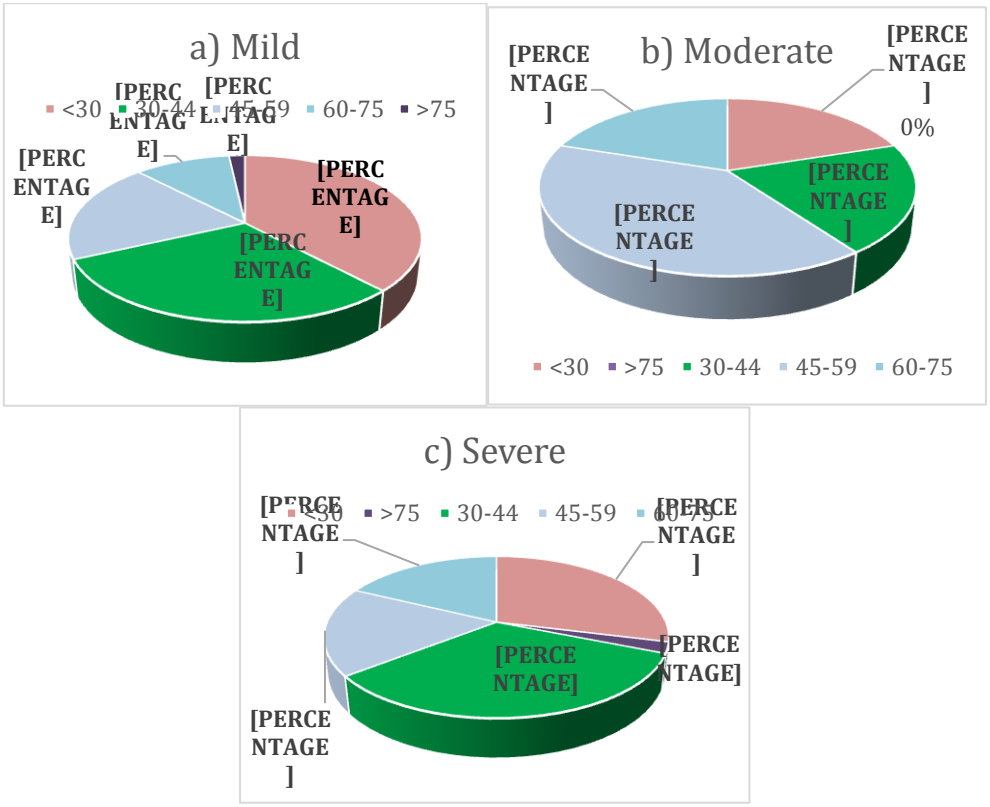

Figure 3. a) Mild severity cases with age wise distribution b) Moderate severity cases with age wise distribution c) Severe severity cases with age wise distribution

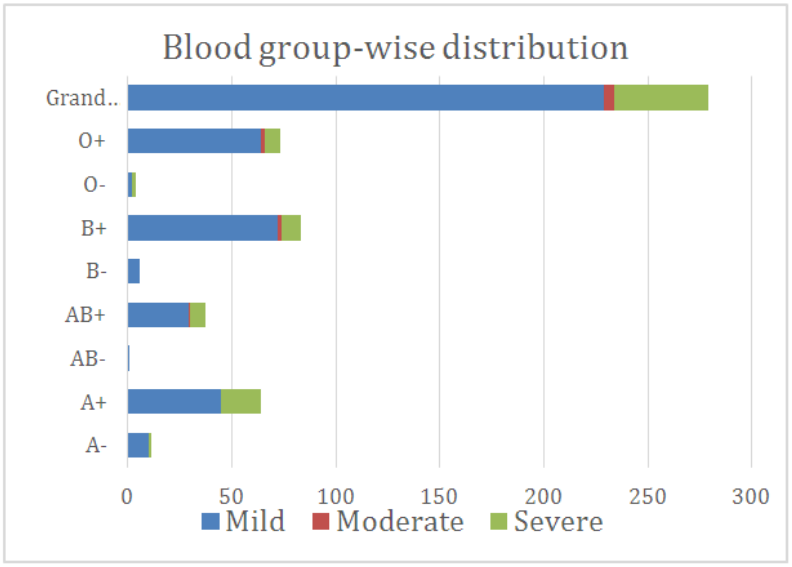

Figure 4 Distribution of ABO blood groups in our study population**:** This graph has the different blood groups on the Y-axis and the number of patients on X-axis. Furthermore, within each blood group line is subdivided, based on the severity of infection, as mild, moderate and severe infections represented in different color codes.

	A +	**A -**	**AB +**	**AB -**	**B +**	**B -**	**O +**	**O -**	**Grand Total**
Mild	45	10	29	1	**72**	6	64	2	**229**
Moderate	-	-	1	-	2	-	2	-	5
Severe	**19**	1	7	-	9	-	7	2	45
Grand Total	64	11	37	1	**83**	6	73	4	**279**

Table 1. ABO blood group & Rh antigen distribution in our study sample. Each blood group is further categorized based on severity, as mild, moderate and severe.

Blood Group types	Patidar et al., 2020	Shani et al. 2018	Agrawal et al., 2014	Das et al. 2001
A (%)	23.16	22.91	22.88	18.85
B (%)	34.1	38.5	32.26	32.69
O (%)	34.56	30.12	37.12	38.75
AB (%)	8.18	8.45	7.74	5.27
Rh(D) +ve	94.13	95.14	94.61	94.53
Rh(D) -ve	5.87	4.85	5.39	5.47

Table 2. Distribution of ABO Blood groups & Rh (D+) Antigen in the Indian population. Values are taken from epidemiological data and expressed in percentage form

Blood Group types	Our study	Average Prevalence in General population	Mild	Moderate	Severe
A (%)	26.88%	21.95%	24.01%	0%	44.44%
B (%)	31.89%	34.38%	34.06%	40%	20%
O (%)	27.59%	35.13%	28.82%	40%	20%
AB (%)	13.62%	7.41%	13.10%	20%	15.55%
Rh(D) +ve	92.11%	94.60%	91.70%	100%	92.11%
Rh(D) -ve	7.88%	5.395%	8.29%	0%	7.88%

Table 3. Distribution of ABO blood groups & Rh (D) antigen in our study sample, compared to the average prevalence in the general population. Furthermore, each blood group distribution in various severities of infection is also shown.

V. Discussion

This study elucidates the epidemiological correlation between the severity of COVID-19 infection with factors such as age, gender, and ABO blood group types in the Indian population. Our sample size consisted of 279 patients who tested positive for the COVID-19 infection and were admitted to Dr. R.N. Cooper Hospital. Analysis of our data showed nearly similar infection rates in males and females. In contrast to expected trends, younger individuals <45yrs made up majority of the mild as well as severe infection groups with older individuals showing mainly mild infection. Our data **(Table 1)** suggested that most of the severe infections occurred in individuals with A (+) blood group, whereas the majority of mild cases consisted of individuals with the B (+) and O (+) groups. As a limitation of our study, due to a lack of a large sample size, the data on patients with moderate severity was limited and equally distributed in all three groups of severity.

The highly infectious coronavirus disease, so called "COVID-19" struck the city of Wuhan in China in December 2019, not taking much time to spread rapidly across the world, resulting in one of the deadliest pandemics. The first confirmed case of COVID-19 was reported on January 27, 2020 in Kerala (8) and from there on, spread fast enough to result in a nationwide lockdown in March 2020. Since then, many studies have been conducted to find any link or association between the ABO blood group and COVID-19 infection all over the world (9-11). One study (14) conducted on 11412 individuals in the NYP hospital stated that the blood groups A & B conferred a greater risk of severe infection and that O had a somewhat protective effect. Gullion et al.'s (12) study of 265 patients saw the highest frequency of blood group A in its severe patient category. Most of these inferences are reflected in our studies of the Indian population as well.

When talking about the Indian population, there is not enough epidemiological data available on the relationship between ABO blood group and COVID-19 infection. Based on the severity of infection, we divided our patients into three groups: mild, moderate, and severe. While we did not have enough patients to be categorized into moderate severity, we found out that the A (+) *[44.44%]* blood group was the most prevalent in the severe infection group, similar to the observations reported in cohort studies by Garg I et al. (13) and Guillon P. et al. (12), of 383 and 265 COVID-19 patients respectively, where individuals with the A (+) blood group were more prone to severe infection than the others. The studies conducted by H. Goker et al. (15) and Bhandari et al. (7) groups have reported that those with blood group A had a higher risk of severe disease, whereas those with O+ had a somewhat protective factor. The link between A blood group and increased severity of infection is supported by our data, which indicates that severe infection was seen mainly in the A (+) blood group and that mild infection was seen mainly in the B (+) and O (+) blood groups, resembling the results of the abovementioned studies.

Furthermore, the Guillon P. et al. (12) study suggests that anti-A-antibodies can block the adhesion of SARS-CoV S-protein to ACE2-expressing cell lines. Considering the similarity between the genomic structures of SARS-COV 2 and SARS-CoV, Bhattacharjee S et al. (16) have addressed the possibility of hypothesizing a protective role of anti-A-antibodies against COVID-19 severity. However, the role of ABO antibodies in altering the interaction between the spike protein of SARS-CoV-2 and the ACE-2 receptor is still unknown.

There was near equal representation of Rh (+) antigen across all the grades of severity studies. However due to the very low prevalence of Rh (-) in the study, 22 or 7.8%, and the whole Indian population in general, there is not enough data to establish an association between Rh (–) antigen and the severity of COVID-19 infection. One contrasting feature we found in our study data was that the majority of individuals with the B (+) blood group reported mild cases, similar to those with the O (+) blood group. This is in stark contrast to other studies which suggest that the B+ blood group has a propensity for showing severe infection.

While there are only a few quantitative epidemiological studies reporting the correlation of the ABO blood group system with COVID-19 infection, there are some limitations to our study. Firstly, the sample size of COVID-19 patients is smaller and the data is collected from a single hospital center. Secondly, there was not enough data available on patients with moderate severity of infection as well as Rh (-) antigen expression. One important limitation is that this study did not consider underlying pre-existing conditions or comorbidities that might modify the outcome of the study.

VI. Conclusion

All of this information points to a possible link between ABO blood group and COVID-19 infection susceptibility and severity in the Indian population. This study confirms that people with the A blood group are more likely to get a severe illness, but people with the B and O blood groups usually only get a mild infection. To validate this link, more meta-analytic analyses and research with larger sample sizes are needed. If verified by future studies, the findings of the present study would have several potential clinical implications.

1) People with a susceptible blood group may require enhanced personal protection to reduce the risk of infection.
2) SARS-CoV-2-infected patients with susceptible blood groups might need to receive more vigilant surveillance and aggressive treatment.
3) It might be helpful to introduce ABO blood typing in the management of SARS-CoV-2 infection and COVID-19.

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