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Relationship between COVID-19 Infection and ABO Blood Groups Differences: A Tertiary Centre Experience in Al-Madinah, Saudi Arabia

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Abstract Controversial factors affecting COVID-19 infection include age, ethnicity, blood groups and Rh factor were investigated here. This study enrolled 2012 participants: COVID-19 cases (1006 patients), and control group (1006 subjects), 50.9% were Saudis and 49.1% were non-Saudis. Mean age for all participants was 36.0±12.7 years and ranged from 8 to 80 years. Mean age was 38.6+15.3 years for COVID-19+ve cases and 33.4±8.6 years for controls. Mean age significantly differed in COVID-19+ve cases from controls ($p<0.001$). COVID-19 infection was significant in Saudi participants compared to non-Saudi participants ($p<0.001$). In COVID-19 group, the frequencies of blood groups O, A, B and AB were 44.5%, 31.3%, 19.7% and 4.5%, respectively. The percentage of COVID-19 infection was higher in subjects having blood groups O and A. Regarding Rh factor, 94.0% of all participants were Rh+ve and 6.0% were Rh-ve. Among COVID+ve cases, 93.4% were Rh positive cases and 6.6% were Rh negative cases, while in the controls, 94.5% were Rh+ve and 5.5% were Rh-ve. The number of COVID-19+ve cases exceeded the number of healthy controls in A+ve subjects but not in O+ve and B+ve subjects. In multivariate analysis, people with blood groups B and AB were less likely to be infected ($p =0.049$) compared to those with groups O and A. In conclusion, older adults had greater risk of COVID-19 infection. Gatherings culture increased COVID-19 infection. Individuals with blood groups B and AB are less likely to get COVID-19 infection than O and A subjects. Rh+ve in O+ve and A+ve is associated with increased COVID-19 infection.

Keywords: *COVID-19, Rh+ve, Rh-ve, ABO blood groups, ethnicity, COVID-19 infection*

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1. Introduction

COVID-19 pandemic was reported to be more associated with certain blood groups. Blood groups may play a role in determining the infection with COVID-19 pandemic. Patients with blood group A were reported to have an increased risk for infection with SARS-CoV-2, whereas blood group O was associated with a decreased risk, indicating that certain ABO blood groups were correlated with SARS-CoV-2 susceptibility. [1] Testing results illustrate that people with blood group B are at the lowest risk of getting infected by SARS-COV-2 virus than those with other blood groups. Other factors associated with COVID-19 infection include age factor where elderly

individuals were at a higher risk of getting COVID-19 infections. Prophetic medicine remedies proved effective in both prevention and prophylaxis against COVID-19 infection where TaibUVID nutritional supplements were very promising. [2,3,4,5]

ABO blood groups are considered a risk factor for COVID-19 infection without causing deaths or hospitalization. There is a reported decrease in vulnerability among people from the O blood group. Similarly, the infection rate is also higher in males than females. Males are at a higher risk of being affected by COVID-19 infection. Variable distribution of blood groups among ethnic subgroups may cause variable infection susceptibility. [6] One published study suggested that increased susceptibility to COVID-19 infection results from anti-A antibodies that have the probability of inhibiting and interfering with the adhesion process of the virus-cell. Therefore, susceptibility to COVID-19 infection is enhanced by anti-A IgG in serum. Subjects with anti-A in serum (i.e. B and O blood groups) are significantly less represented in the COVID-19 group than those lacking anti-A antibodies. Therefore, most individuals with Anti-A, usually from O are more protected than those from B blood group (having Anti-A antibodies). [7]

Muñiz-Diaz et al. reported that blood group A had highest risk of COVID-19 infection while blood group O had a lower risk. Regarding severity, age was one of the most significant risk factors. ABO blood groups were important risk factors for COVID-19 severity and mortality. Mortality risk in group A individuals was significantly higher than in group O individuals. [8] Subjects having O blood group are less likely to develop any COVID-19 manifestations at earlier stages. Hence, they do not go for testing immediately. The predisposing factors for developing COVID-19 complications include prothrombic tendency and inflammatory process. [1] Another study illustrated that there is an increased likelihood for COVID-19 affecting blood group A individuals as HLA antigens may be essential in influencing this disease's occurrence and clinical evolution. [9] Epidemiological evidence also demonstrates that most of the females affected by this disease are of blood group A.

Boudin et al reported that ABO and Rh(D) blood groups are not associated with increased or decreased risk of infection by SARS-CoV-2. Boudin et al. did not compare the distribution of blood groups in hospitalized patients with SARS-CoV-2 infection and in the general population, but rather the distribution of SARS-CoV-2 infection according to blood groups in people exposed at the same time and in the same place to SARS-CoV-2. [10]

In another study, blood group A might have a role in increased susceptibility to COVID-19 infection, blood group O might be somewhat protective. However, once infected, blood group type does not seem to influence clinical outcome. [11]

The relationship of ABO blood groups to COVID-19 infection seem to be controversial. From a meta-analysis study, Blood group A increases the risk of positive COVID-19 infection compared to O blood group. Genetic polymorphism of ABO groups may contribute to the susceptibility of COVID-19 infection. [12]

2. Subjects and Methods

2.1. Ethical Committee Approval

This study was approved by the Institutional Review Board of the General Directorate of Health, Al-Madinah, Saudi Arabia. This study began on May 3, 2020, and ended on January 3, 2021. A total of 2012 subjects participated in this study. These participants were then divided into two groups: the COVID-19 cases cluster including 1006 participants and the control subjects with 1006 participants also.

2.2. Study Design

This study was conducted at Al-Madinah hospital, the main healthcare health center selected for treating COVID-19 patients in Al-Madinah region. Therefore, every participant was admitted to the hospital, where they were closely monitored. Furthermore, study's participants have different demographics, clinical structures, blood groups, and COVID-19 PCR reports. Study's demographics included age, blood grouping and nationality. Blood grouping and nationality data were important because the participants included both Saudi and non-Saudi participants. Clinical features included common symptoms of COVID-19 infection e.g. high fever, persistent cough, shortness of breath (dyspnea), acute chest pain, and diarrhea. All these symptoms were closely observed, and the data regarding their manifestations were recorded. This process was done for both groups of participants.

2.3. ABO and Rh Blood Grouping

The authors of this study withdrew blood samples of each participant and then conducted ABO and Rh blood grouping. This was done to help in showing which blood groups were more susceptible to COVID-19 infection and which blood groups may confer a resistance against SARS-COV-2 virus.

2.4. Statistical Analysis

All the data was acquired and critically examined with a standard Excel sheet. Data of eligible participants were collected for analysis. Statistical Package for Social Sciences (SPSS) version 21.0 was used to analyze the data collected during the study. Descriptive statistics were used to obtain frequency and percentage for categorical variables, and to obtain mean and SD for continuous variables. Student's t test was used to assess differences in mean. Chi square test and simple logistic regression were used to assess the association between the categorical variables. Multiple logistic regression was conducted to assess the association between COVID-19 infection and blood grouping. Chi-square test model and odds ratio (ORs) with 95% confidence interval (CIs) were used where $p<0.05$ was considered significant.

3. Results

3.1. Descriptive Statistics of Socio-demographic Variables and Blood Grouping

The present study included 2012 participants divided into two groups: COVID-19 cases group (1006 patients) and the control group (1006 subjects). Among all participants, 50.9% were Saudis and 49.1% were non-Saudis. About 33.3% of cases and 68.6% of controls were Saudis.

3.2. Effect of Age and Ethnicity of Participants on COVID-19 Infection

Age for all participants was 36.0±12.7 years and ranged from 18 to 80 years. Mean ±SD of ages was 38.6±15.3 years for cases and 33.4±8.6 years for the controls (Figure 1). COVID-19 cases were older in age than healthy controls (Table 1). Mean age significantly differed ($p<0.001$) in COVID-19 positive cases from healthy controls (Figure 1). Saudi participants were more protected from COVID-19 infection compared to non-Saudi participants. Saudi participants constituted the majority of healthy control group compared to non-Saudis who constituted the majority of COVID-19 cases (Figure 2).

3.3. Effects of ABO Blood Groups on COVID-19 Infection

Among all participants, blood group O subjects were the majority followed by group A, group B and finally group AB. The frequencies of blood types O, A, B and AB among all participants were 45.7%, 29.3%, 20.6% and 4.4%, respectively (Figure 3) and (Table 1). In the COVID-19 group, the frequencies of blood types O, A, B and AB were, 44.5%, 31.3%, 19.7% and 4.5%, respectively. In the control group, the frequencies of blood types O, A, B and AB were 46.8%, 27.2%, 21.6% and 4.4%, respectively (Figure 3) and (Table 1). The percentage of COVID-19 infection was higher compared to healthy controls in subjects having blood groups O and A. Subjects having blood group O had a higher percentage in acquiring COVID-19 infection than other blood groups. Percentage of COVID-19 positive cases followed the same order i.e. O>A>B>AB. Percentage of COVID-19 positive cases were less than healthy controls in subjects having blood group O ($p<0.05$) and B (Figure 3) and (Table 1).

3.4. Effects of Rh Factor on COVID-19 Infection

Regarding Rh factor, 94.0% of all participants were Rh positive and 6.0% were Rh negative. Among COVID +ve cases, 93.4% were Rh positive cases and 6.6% were Rh negative cases, while in the controls, 94.5% were Rh positive and 5.5% were Rh negative. No significant difference was found between the percentages of COVID-19 cases and healthy subjects regarding an effect of Rh factor on COVID-19 infection. With regard to Rh factor, the figure representing COVID-19 cases was comparable to that representing the healthy control group (Figure 4) and (Table 1). The order of frequencies of Rh+ve blood groups for COVID-19 cases was O+ve> A+ve > B+ve > AB+ve. That was the same order of frequency for healthy subjects (Figure 5) and Table 1. Regarding Rh-ve COVID-19 cases, the order of frequencies differed a little and it was: O-ve> B-ve > A-ve >AB-ve. That was the same order of frequency for healthy subjects (Figure 6) and Table 1. COVID-19 positive cases and healthy subjects followed the same frequency pattern with no significant differences as regard Rh factor. However, the number of COVID-19 positive cases exceeded the number of the healthy controls in subjects having group A+ve. The number of healthy controls exceeded the number of COVID-19 cases in subjects having blood groups O+ve and B+ve. Number of COVID-19 positive cases was almost equal to number of healthy controls in group AB+ve (Figure 5) and Table 1. Regarding Rh-ve subjects, the number of COVID-19 positive cases exceeded the number of healthy controls in subjects having group O-ve, A-ve and AB-ve. Number of COVID-19 positive cases were equal to numbers of healthy controls in subjects having B-ve (Figure 6 and Table 1).

3.5. Factors Associated with COVID-19 Infection

In univariate analysis, the risk of COVID-19 infection was higher among older people ($p<0.001$) and among non-Saudis (OR=4.1, 95. % CI 3.6-5.3) (Table 2). In multivariate analysis, people with blood groups B and AB were less likely to be infected (adj OR=0.8, 95%CI.6-0.99), ($p=0.049$) compared to those with groups O and A (Table 2).

Table 1. Descriptive statistics of the participants

	Total		Cases		Control	
Blood groups	n	%	n	%	n	%
O	919	45.7	448	44.5	471	46.8
A	589	29.3	315	31.3	274	27.2
B	415	20.6	198	19.7	217	21.6
AB	89	4.4	45	4.5	44	4.4
O+	857	42.6	415	41.3	442	43.9
A+	567	28.2	302	30.0	265	26.3
B+	381	18.9	181	18.0	200	19.9
AB+	86	4.3	42	4.2%	44	4.4
O-	62	3.1	33	3.3	29	2.9
A-	22	1.1	13	1.3	9	0.9
B-	34	1.7	17	1.7	17	1.7
AB-	3	.1	3	0.3	0	0.0
Rh						
Rh+ve	1891	94.0	940	93.4	951	94.5
Rh-ve	121	6.0	66	6.6	55	5.5
Nationality						
Saudi	1025	50.9	335	33.3	690	68.6
Non-Saudi	987	49.1	671	66.7	316	31.4
Age (Mean± SD)	36.0 ±12.7		38.6 ±15.3		33.5±8.6	

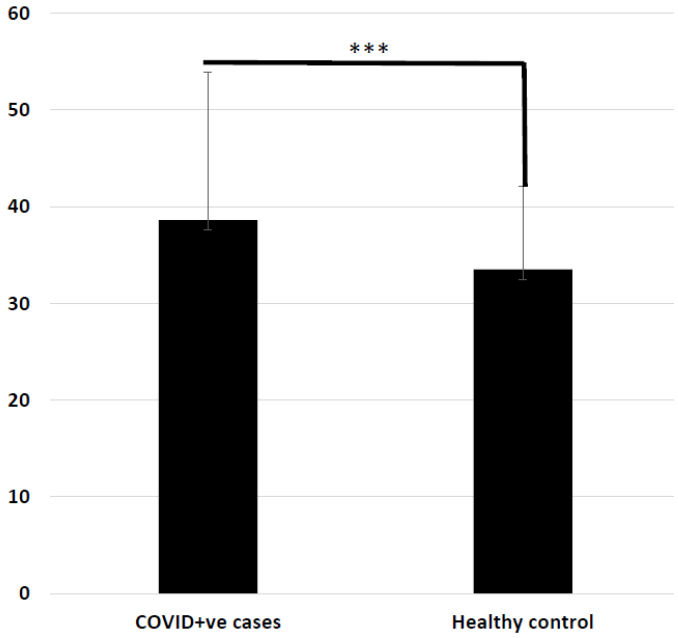

Figure 1. Effect of age on COVID-19 infection

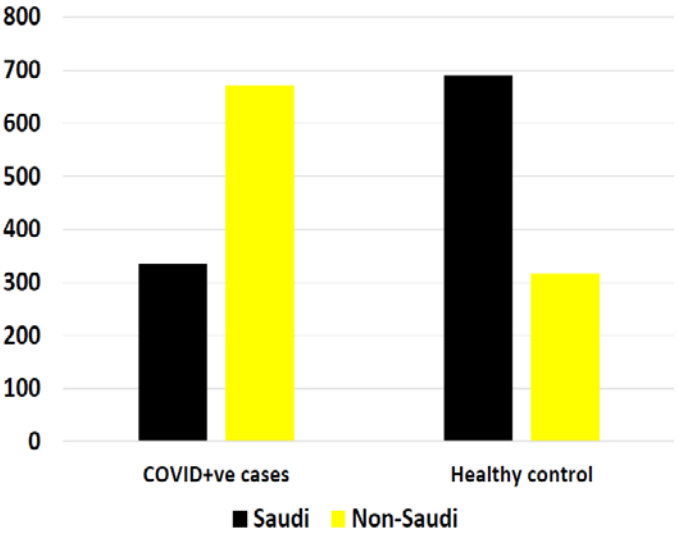

Figure 2. Effect of ethnicity on COVID-19 infection

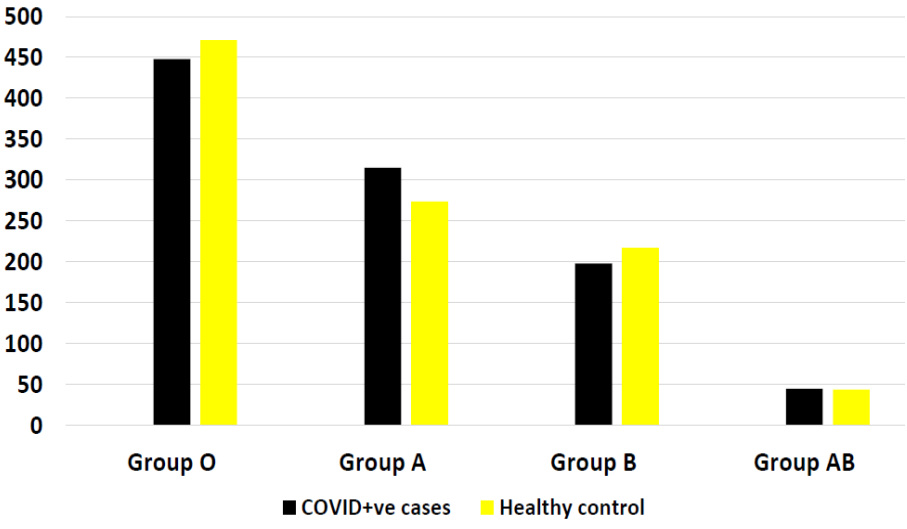

Figure 3. Effects of blood groups of participants in the study on COVID-19 infection

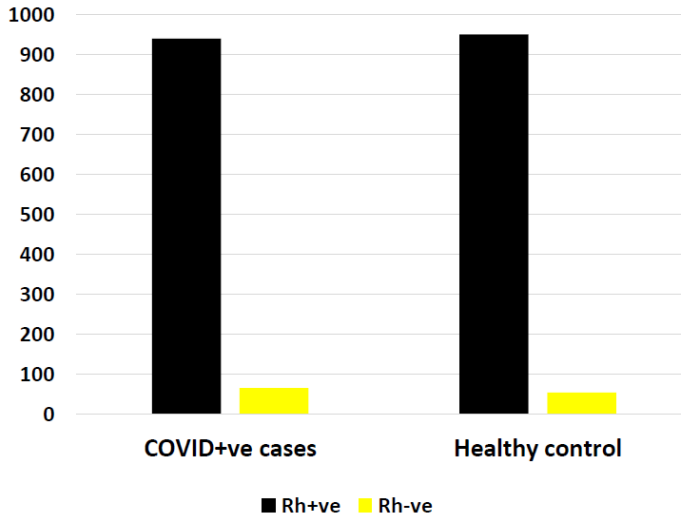

Figure 4. Effects of Rh factor of participants in the study on COVID-19 infection

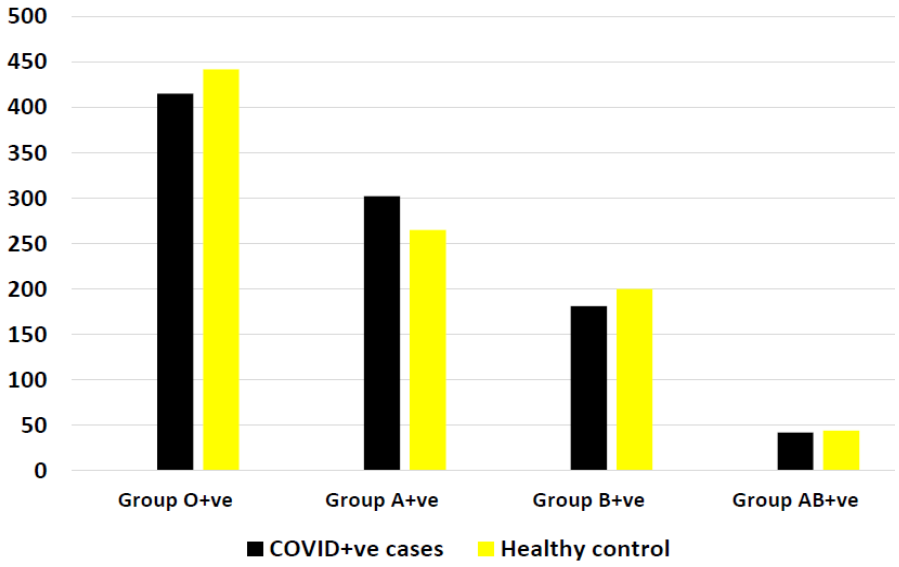

Figure 5. Effects of Rh+ve blood groups of participants in the study on COVID-19 infection

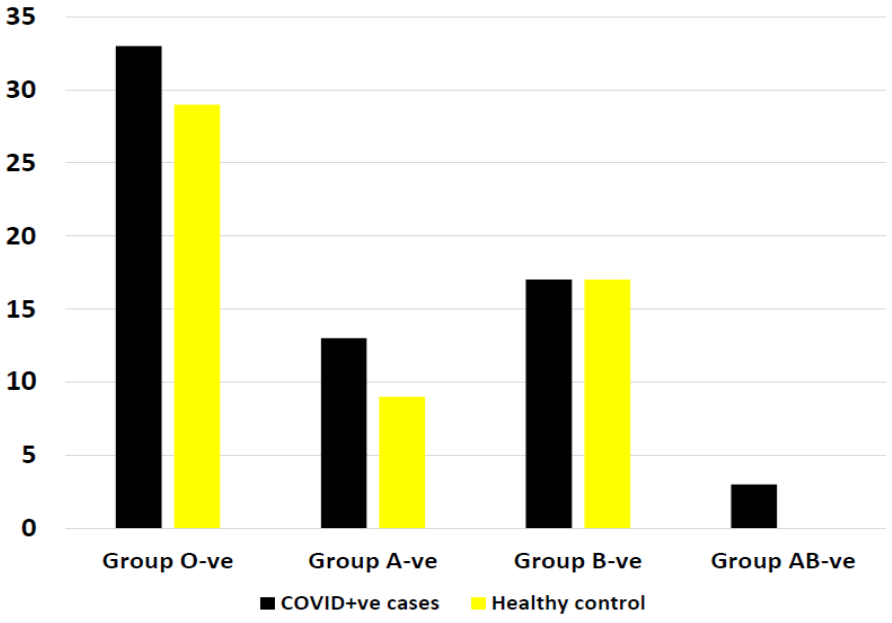

Figure 6. Effects of Rh-ve blood groups of participants in the study on COVID-19 infection

Table 2. Association between COVID-19 infection and ABO group adjusted for age and nationality

Grouping	Un adjusted OR	95.% CI.	P value	Adjusted OR	95.% CI.	P value
O	Reference			Reference		
A	1.2	.9-1.5	.073	1.0	.8-1.3	.734
B	.95	.8-1.2	.726	.8	.6-0.99	.049
AB	1.1	.7-1.7	.744	.8	.5-1.3	.462
Grouping						
O+	Reference			Reference		
A+	1.2	.9-1.5	.074	1.0	.8-1.3	.663
B+	.9	.8-1.2	.765	.8	.6-1.0	.053
AB+	1.0	.6-1.5	.942	.8	.5-1.2	.355
O-	1.2	.7-2.0	.466	1.4	.8-2.4	.262
A-	1.5	.6-3.6	.326	1.3	.5-3.4	.545
B-	1.0	.5-2.1	.857	1.1	.5-2.3	.858
AB-	-	-	-	-	-	-
Rh						
rh+	.8	.6-1.2	0.302	.7	.5-1.1	.108
rh-	Reference			Reference		
Nationality						
Saudi	Reference					
Non-Saudi	4.1	3.6-5.3	<0.001	-	-	-
	Cases	Controls				
Age mean (sd)	38.6 (15.3)	33.5 (8.6)	<0.001	-	-	-

4. Discussion

Various factors e.g. age and ethnicity are commonly investigated in an effort to illustrate a possible relationship between ABO blood groups and COVID-19 infection. Race and ethnicity depending on some cultural behaviors e.g. living in crowded populations and gatherings at food and habitat that may also influence COVID-19 infection. Most Hispanic females have blood group O than the black non-Hispanics. Similarly, non-Hispanics females who are non-white are more likely to be Rh+ve than another ethnicity. Therefore, most Hispanic females have the highest risk of getting COVID-19 infection. [13]

Our data revealed that mean age for COVID+ve patients is significantly higher ($p<0.001$) than the mean age for healthy controls (Figure 1). This is in agreement with previous reports [2,3,4,5] where older people may suffer from chronic debilitating diseases and comorbidities that may suppress the immunity and facilitate SARS-COV-2 infection. Saudi citizens were less susceptible to COVID-19 infection than non-Saudis (Figure 2). This is possibly due to the strict adherence done by Saudis to the health preventive measures decided by the ministry of health. Non-Saudi residents are adherent also but living in crowded dwelling places and gatherings at food times may not help strict obedience to the preventive measures. Non-Saudi residents may catch infection from their co-workers at living places that may facilitate COVID-19 infection. The Saudi government and authorities apply the preventive measures strictly on all and provide health services for free to all. Non-O individuals (i.e. people having blood groups A, B and AB) were said to have anti-A and anti-B antibodies that may help the prevention of viral entry using the angiotensin converting enzyme-2 (ACE-2) receptors. Similarly, many factors may increase the risk in these individuals e.g. hypercoagulability, autoimmunity, and dysbiosis (decreased microbial diversity with loss of beneficial bacteria) that result from vascular inflammatory sequelae. Many other risk factors are associated with development of COVID-19 infection. Elderly individuals are the most affected by SARS-COV-2 virus. Similarly, blood group O individuals are less likely to be affected by this virus than blood group B. [14]

Additionally, individuals having blood group A have higher infection possibility than healthy controls. Hypertension is another factor that places individuals at risk of being affected by COVID-19 infection. Hepatitis may also lead to increased COVID-19 infection. These factors may suppress immunity and facilitate disease occurrence. Because of differences in the rate of infection among individuals, the ABO blood type may be one of the biomarkers for predicting COVID-19 infection. [13] Number of COVID-19 positive cases was higher among all blood groups but group O blood was also prevalent in this huge study sample. The numbers of healthy controls exceeded the numbers of COVID-19 positive cases in subjects having blood group O and B. Numbers of COVID-19 positive cases were higher in subjects having blood group B (Figure 3 and Table 1). Our data revealed that COVID-19 infection is higher in patients having Rh+ factor than patients having Rh-ve factor (Figure 4 - Figure 6). However, the number of subjects in both the healthy group and the COVID-19 positive group was comparable to some extent. The percentage of COVID-19 infection was higher compared to healthy controls in subjects having blood group A. Blood group O subjects were the majority followed by group A, group B and finally group AB. Subjects having blood group O had a higher percentage in acquiring COVID-19 infection than other blood groups (Figure 4 - Figure 6 and Table 1).

With regard to Rh factor, the figure representing COVID-19 cases was comparable to that representing the healthy control group (Figure 4) and (Table 1). COVID-19 positive cases and healthy subjects followed the same frequency pattern with no significant differences as regard

Rh factor. However, the number of COVID-19 positive cases exceeded the number of the healthy controls in subjects having group A+ve. The number of healthy controls exceeded the number of COVID-19 cases in subjects having blood groups O+ve and B+ve. Number of COVID-19 positive cases was almost equal to the number of healthy controls in group AB+ve (Figure 5) and Table 1. Regarding Rh-ve subjects, the number of COVID-19 positive cases exceeded the number of healthy controls in subjects having group O-ve, A-ve and AB-ve. Number of COVID-19 positive cases were equal to numbers of healthy controls in subjects having B-ve (Figure 6 and Table 1).

Our data differed from some reported findings where blood group O patients have better results than other patients. Those reported findings were explained as effects of anti-B or anti-A antibodies from the donor that bind to the patient's cell surface, enhancing the formation of an immune complex soluble in the patients' plasma. [15] Further research is warranted to illustrate such relationships.

Our data differed from the report by Latz et al. where individuals from the O blood group had reduced the positivity of the disease. [16] However, our data agreed with Latz report in that individuals with Rh+ blood are likely to be COVID-19 positive. [16] In univariate analysis, the risk of COVID-19 infection was higher among older people ($p<0.001$) and among non-Saudis (OR=4.1, 95. % CI 3.6-5.3) (Table 2). In multivariate analysis, people with blood groups B and AB were less likely to be infected (adj OR=0.8, 95%CI.6-0.99), ($p=0.049$) compared to those with groups O and A (Table 2).

In conclusion, older age also plays a critical role in determining individual's susceptibility to COVID-19 infection. Older adults are at a greater risk of getting infected by the disease, and hence they should take preventive measures to protect their health. The culture of gathering at habitat and food intake helps increased COVID-19 infection and works against the preventive measures decided by the ministry of health. Blood groups may play a role in determining COVID-19 infection among individuals. Individuals with blood groups B and AB are less likely to get COVID-19 infection than those with blood group O and A. Rhesus factor is another factor that was associated with higher COVID-19 infection in blood groups O+ve and A+ve.

Conflict of Interest

The authors declare that there is no conflict of interest.

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