# Microbes and Infectious Diseases

## Original article

# Association of blood groups with the clinical presentation of COVID-19 infection

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**A R T I C L E I N F O**

**Abbreviations:**
SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2
WHO: World Health Organization
CNS: Central nervous system
GIT: Gastrointestinal tract
ACE-2: Angiotensin-Converting Enzyme-2
CD: Cluster of differentiation
TMPRSS: Transmembrane serine protease-2
SARS-CoV: Severe acute respiratory syndrome
MERS-CoV: The Middle East respiratory syndrome-related coronavirus
HBGA: The histo-blood group antigens
ECRRM: Egypt Centre for Research and regenerative medicine

**A B S T R A C T**

**Background:** Blood groups' antigens, represent polymorphic traits inherited among populations, their expression differences, can increase or decrease the host susceptibility to infections. We aimed here to correlate the relation between the different blood groups and hosts' susceptibility towards COVID-19 infection. **Methods:** 355 samples, were analyzed for SARS-CoV-2 and blood groups typing. The candidates were then divided according to their results into; 210 positive-PCR (viral persistent, clearance and ICU admitted), and 145 negative-PCR contacts and then results were compared. **Results:** The highest frequency in control and viral clearance group was O-phenotype, followed by A-phenotype and the least was AB-phenotype. The highest frequency in the viral persistent group, was A-group, showed followed by B-group and the least was O-group. Lastly in ICU group, A-group was the highest frequency, followed by O-group and the least was B-group. Using Chi-square method, a statistically significant result was observed (*p-value= 0.034*). **Conclusions:** The blood group-O was the protective phenotype, controversy to the O-group, A-group was the risky phenotype, also AB-group was risky, as it showed the lowest frequency in both control and viral clearance group. Interestingly, the B-group was the least group susceptible to have bad prognosis and be admitted to the ICU. This can be a safety guideline for classifying healthcare workers, according to their ABO, to work with suspected cases with COVID-19 and also may help in developing specific anti- histo-blood group antibodies as an effective co-therapy for COVID-19.

## Introduction

Coronavirus disease-2019; COVID-19, is a syndrome of severe respiratory failure, caused by a new strain of coronavirus, known as the severe acute respiratory syndrome coronavirus-2; SARS-CoV-2. It firstly appeared in China, in Wuhan province, in 2019, and spread rapidly from China, to the whole world and

was announced to be a pandemic, by the World Health Organization; WHO; in March 2020 [1].

The cytokine storm, is one of its severe complications, which causes respiratory tract dysfunction and accumulation of fluid in the alveoli by intense inflammation. Also the presence of neurological disorders and gastrointestinal tract symptoms; GIT, vomiting and diarrhea, is due to the

presence of viral genetic materials, in the central nervous system; CNS and the GIT, respectively [2].

Multiple molecular studies have been done, to understand the pathogenesis of the viral entry and the process of viral infection and invasion in human cells. It was suggested that the virus spike-protein, bind to the angiotensin-converting enzyme-2; ACE-2; a receptor located at multiple sites such as the CNS, respiratory system, heart, pancreas, liver and kidney. Also, the presence of host cell receptor CD-147 and the transmembrane serine protease-2; TMPRSS-2, were suggested to bind to the virus spike-protein, thus help in the virus invasion [3,4].

Clinically, categorization of blood groups, according to the ABO-system, is the upper hand in the system of blood transfusion. It relays on the existence of two independent loci, which harmonize in action together, to generate the characteristic epitopes of this system. The first locus, exist at the last part of chromosome-9 arm and it is known as the ABO-locus. The second locus, is a protein coding gene, for the H-blood group and is found on the chromosome-19 and producing compounds attached to cell surfaces' lipids or proteins [5,6].

Many studies, linked the host susceptibility towards many pathogens, to this ABO-system. It was related to bacteria, such as *Helicobacter pylori* infection and viruses such as Norovirus, Hepatitis-B virus, rotavirus, and other members of Coronavirus, as the severe acute respiratory syndrome; SARS-CoV and the Middle-East respiratory syndrome-related coronavirus; MERS-CoV. For example, in the rotavirus gastroenteritis, the blood group-A and blood group-AB children, were more susceptible to infection than the children with blood group-O [7].

Other studies also correlated the ABO-system towards different viral infections. One study related the effect of the histo-blood group antigens; HBGA, to the susceptibility towards Norovirus, and another one stated that the worst outcome in West Nile virus infection was observed in blood groups-A and-D [8,9].

Accordingly due to the emerging of COVID-19 infection, some studies, related also the ABO-blood group to the host susceptibility towards this emerging SARS-CoV-2, its severity and its clearance [10].

**Objective of this work**

Our study, took in consideration all the backgrounds which correlated the association between the ABO-blood group system and the host susceptibility towards viral infections, to investigate the hosts' susceptibility to COVID-19 infections and its relation to the different blood group phenotypes, in Egypt.

**Material and Methods**

Compliance with the ethical standards: This study was conducted according to the principles expressed in the Helsinki Declaration of 1983. It was approved by the research and ethical committees of the contributing hospitals (IRB NO: 00012517). An informed consent was taken from study subjects.

All candidates involved in this study, were laboratory analyzed inside Egyptian fever hospitals, in the period of three months (May, June and July 2020). The study included both sexes, different ages, symptoms and outcomes. All the samples were analyzed in the Egypt Centre for Research and regenerative medicine; ECRRM.

**1. Sample collection**

- There were two types of samples, from each participated candidate; one whole blood for performing ABO grouping on EDTA (Ethylenediaminetetraacetic acid), and the other was either nasopharyngeal or oropharyngeal swab samples for PCR test for SARS-CoV-2.

- The whole blood samples, were withdrawn on coated tubes with EDTA; which act as an anticoagulant, binding the calcium ions and interrupting the clotting cascade, for the ABO-blood group typing. Samples were kept in refrigerators at 4° C until processed.

- The nasopharyngeal/ oropharyngeal swab samples, were collected in Copan Universal Transport Medium System (UTM-RT) or BD™ Universal Viral Transport System (UVT), then stored at -20°C for further processing for SARS-CoV-2 nucleic acid detection by Real-time PCR technique.

**2. Inclusion and exclusion criteria:**

Some criteria were applied to the collected samples from these candidates:

- Every sample with one type only of samples either EDTA or nasopharyngeal/ oropharyngeal was excluded.

- Control samples, were from healthy people, showing twice negative PCR result for SARS-CoV-2 test (to exclude false positive results) and they were in close contact to the confirmed positive cases to SARS-CoV-2.

- The positive cases were positive to PCR- SARS-CoV-2, at least two times, with time interval 4 days, (to exclude false negative). All positive samples were tested with PCR every 4-5 days until the end of our study or until viral clearance, with 2 PCR negative results.

- Every sample with one positive or one negative result only with no continuation was excluded.

- The samples to be tested with PCR, were kept at 2-4ºC (≤4 days) or frozen at -70 ºC or below if it will be tested after more than 4 days.

## 3. Grouping of patients and control

The number of samples, after applying the inclusion and exclusion criteria, were 355 samples, they were divided into two groups; group 1: 210 patients with positive PCR SARS-CoV-2 results and group 2 with 145 contacts with negative PCR SARS-CoV-2 results.

During the period of our work, group 1: was further subdivided into two subgroups according to their viral clearance and the persistence of the RNA of the virus in their blood by PCR method; group 1a: with 97 cases who showed viral clearance; changed from positive SARS-CoV-2 into negative, and group 1b: with 113 patients who showed persistent positive cases (still PCR positive till the end of our research). Group 1b, was further subdivided also, into 2 groups; group 1bi with 37 persistent positive SARS-CoV-2 patients whom were not admitted into the Intensive Care Unit; ICU and group 1bi: with 76 persistent positive SARS-CoV-2 patients but were admitted into the ICU.

## 4. Diagnostic Kits and procedures

### a-Diagnostic kits for blood pheno-typing agglutinating ABO kits

VITRO SCIENT, Murine monoclonal antibodies, it contains set of: Anti –A Monoclonal/ IgM antibodies Reagents (10 ml/vial)- Anti –B Monoclonal/ IgM antibodies Reagents (10 ml/vial)- Anti-D IgG/IgM Blend Reagent (10 ml/vial).

On clean glass slides, three drops of blood from each EDTA blood samples were added, then one drop of each reagent were added to each drop and mixed well to determine agglutination.

The interpretation results for ABO system were classified as the following:

- The agglutinated drops with the Anti-A Monoclonal reagents were considered as A-blood group. The agglutinated drops with Anti-B Monoclonal reagents were considered as B-blood group. The agglutinated drops with both Anti-A Monoclonal and Anti-B Monoclonal reagents were considered as AB-blood group. The non-agglutinated drops with both reagents were considered as O-blood group

- The agglutinated drops with Anti-D IgG/IgM blend reagents were considered as Rh-positive blood group. The non-agglutinated drops with were considered as Rh-negative blood group.

### b-Diagnostic system and kits for detection of SARS-CoV-2

700 µl of the stored nasopharyngeal/ oropharyngeal swab samples which were collected in the Copan UTM-RT or the BD™ UVT, were transported into sterile watherman tubes (cobas omni secondary tubes) and were bar-coded, then they were loaded in the sample rack of the fully automated molecular diagnostic system; Cobas 6800. The diagnostic reagents and kits used in our assay are Cobas Omni (Roche, USA) which are ready to use.

The results of the PCR test were classified into negative and positive PCR- SARS-CoV-2 and classified into groups, age, sex, statistical method.

### Statistical analysis

The statistical analysis was performed using SPSS 23 (SPSS Inc., Chicago). Quantitative variables were expressed as mean + SD. Chi-square test was used for qualitative variables. The data were considered significant if P values were $\leq 0.05$; highly significant if $P < 0.001$.

### Results

The present study included 210, COVID-19 positive patients (129 males and 81 females) subdivided into two groups (97 showed viral clearance, 113 with viral persistent). The 113 viral persistent group was further subdivided into 2 groups; 76 patients were admitted to ICU, and 37 patients were not admitted to the ICU, with male to female ratio of 8: 5. The control group included 145 individual (64 males and 81 females) with male to female ratio 4:5. As regard to gender, there was a significant difference between the patient group and control group ($p$-value= 0.001) and between the different patient groups ($p$-value= 0.012), as shown in **table (1,2).**

In the control group, there were 10 candidates under 20 years old, 73 candidates between the ages of 21-40, 62 candidates between the ages of 41-60, no candidates were above 60 years old. While, in the infected group, there were 16 patients under 20 years old, 69 patients between the age of 21-40 years old, 78

patients between the age of 41-60 years old and 47 patients above 60 years old.

Comparing the age among studied groups, using Student t-test, the mean age was 37.15± 13.475, in the control group, with the highest number between the ages of 21-40 years, while the mean age was 44.87 ±16.336, in the infected group, with the highest number of patients between 41-60 years, as shown in **table (3)**. The t-value of the age's equal variances assumed= -4.690. The t-test for equality of means was significant= 0.000, with $X^2$= 82.343, *p-value= 0.000* as shown in **table (4)**.

The most frequent blood group, in the control group was O-blood group, followed by A-blood group and the least one was AB-blood group (with percentage of 38.6 %, 32.4% and 7.6 % respectively). Same results were also discovered in the viral

clearance groups with O–blood group, to be the most frequent followed by A-blood group and the least was AB-blood group, with different ratios (37.1%, 32% and 9.3% respectively). Blood group-A showed the highest frequency in viral persistent groups followed by B-blood group and the lowest frequency was among blood group-O (48.6%, 27% and 10.8% respectively). Lastly in ICU group, the blood group-A was the highest frequent, followed by O-blood group and the least one was B-blood group (36.8%, 30.3% and 14.5% respectively). ($X^2$=18.060, p-*value= 0.034*), as shown in **table (5)**.

Most of the control group were Rh-positive with ratio of 93.8% and in the infected group also with ratio of 92.8% ($X^2$= 5.361, *p-value= 0.147*), as shown in **table (6)**.

**Table 1.** Gender status between control and infected group.

| Number and sex | Control | Infected | Total |
|---|---|---|---|
| **Female** | 81 | 81 | 162 |
| **Male** | 64 | 129 | 193 |
| **Total** | 145 | 210 | 355 |

On comparison of different studied groups regarding gender status groups, it was found statistically significant ($X2$= 10.336, *p-value= 0.001*).

**Table 2.** Distribution of gender in different groups of COVID-19 patients.

| Group | Control | Clearance | Persistent | ICU | Total |
|---|---|---|---|---|---|
| **female** | 81 (55.9%) | 40 (41.2%) | 13 (35.1%) | 28 (36.8%) | 162 (45.6%) |
| **male** | 64 (44.1%) | 57 (58.8%) | 24 (64.9%) | 48 (63.2%) | 193 (54.4%) |
| **Total** | 145 (100%) | 97 (100%) | 37 (100%) | 76 (100%) | 355 (100%) |

On comparison of different studied groups regarding gender groups, it was found statistically significant ($X^2$= 10.882, *p-value= 0.012*).

**Table 3.** Distribution of age in different groups of COVID-19 patients.

| Group | Control | Clearance | Persistent | ICU | Total |
|---|---|---|---|---|---|
| **<20** | 10 (6.9%) | 2 (2.1%) | 1 (2.7%) | 13 (17.1%) | 26 (7.3%) |
| **21-40** | 73 (50.3%) | 28 (28.9%) | 11 (29.7%) | 30 (39.5%) | 142 (40.0 %) |
| **41-60** | 62 (42.8%) | 35 (36.1%) | 14 (37.8%) | 29 (38.2%) | 140 (39.4%) |
| **>60** | 0 (0.0%) | 32 (33.0%) | 11 (29.7%) | 4 (5.3%) | 47 (13.2%) |
| **Total** | 145 (100%) | 97 (100%) | 37 (100%) | 76 (100%) | 355 (100%) |

On comparison of different studied groups regarding age groups, it was found statistically significant ($X^2$= 82.343, *p-value= 0.000).*

**Table 4.** Comparison of age among the control and COVID-19 patients.

| Status | Number | Mean | Std. Deviation | Std. Error mean |
|--------|--------|------|----------------|-----------------|
| **Control** | 145 | 37.15 | 13.475 | 1.119 |
| **infected** | 210 | 44.87 | 16.336 | 1.127 |

**Table 5.** ABO-groups in the control and different groups of COVID 19 patients.

| Group | Control | Clearance | Persistent | ICU | Total |
|-------|---------|-----------|------------|-----|-------|
| **A** | 47 (32.4%) | 31 (32.0%) | 18 (48.6%) | 28 (36.8%) | 124 (34.9%) |
| **B** | 31 (21.4%) | 21 (21.6%) | 10 (27.0%) | 11 (14.5%) | 73 (20.6%) |
| **AB** | 11 (7.6%) | 9 (9.3%) | 5 (13.5%) | 14 (18.4%) | 39 (11.0%) |
| **O** | 56 (38.6%) | 36 (37.1%) | 4 (10.8%) | 23 (30.3%) | 119 (33.5%) |
| **Total** | 15 (100%) | 97 (100%) | 37 (100%) | 76 (100%) | 355 (100%) |

On comparison of different studied groups regarding ABO-groups, it was found statistically significant ($X^2$= 18.060, *p-value= 0.034*).

**Table 6.** Rh-groups in the control and different groups of COVID-19 patients.

| | Control | Clearance | Persistent | ICU | Total |
|--|---------|-----------|------------|-----|-------|
| **Rh-Positive** | 136 (93.8%) | 94 (96.9%) | 34 (91.9%) | 67 (88.2%) | 331 (93.2%) |
| **Rh-Negative** | 9 (6.2%) | 3 (3.1%) | 3 (8.1%) | 9 (11.8%) | 24 (6.8%) |
| | 145 (100%) | 97 (100%) | 37 (100%) | 76 (100%) | 355 (100%) |

On comparison of different studied groups regarding Rh-groups, it was found statistically non-significant ($X^2$= 5.361, *p-value= 0.147*).

**Discussion**

In our study, 210 patients confirmed to be positive with COVID-19 and 145 healthy contact subjects in a case-control study, were involved. The blood group-O seemed to be the protective phenotype, being in high frequency within both the control group and the viral clearance group and at the least frequency, within the viral persistent group. Controversy to the O-group, was the A-group, having the highest frequency within both the persistent group and the ICU group. The AB-group also seemed to be a risky group, as it showed the lowest frequency in both control and viral clearance group controversy to the O-group. Interestingly, the B-group was the least group susceptible to have bad prognosis and to be admitted to the ICU.

Due to the limitation of our criteria in choosing of the control group, to be a contact with at least twice negative results, the number of males and the age in both control and infected groups were not exactly matched, but the number of females were matched. When different studied groups regarding gender groups was compared, the males were more susceptible to be admitted to the ICU.

The four genetic phenotypes of ABO-system are presented by the existence of A- and B-antigens on the surface of RBCs and their related antibodies in the blood, which are found on chromosome 9q34.1–34.2 [11,12].

Many researches have related the variability in host susceptibility, towards different pathogens, according to the variation in ABO-blood group system. This was interpreted to be due to blood group antigens, which act as receptors to different pathogens, helping different steps in their pathogenesis pathway in the host and /or by modifying his innate immunity [13].

Similar to our results, other studies observed that the highest risk group in SARS-CoV-2 infection, was among patients with blood group-A, while the lowest one was among blood group-O. They also observed the influence of blood type on the clinical symptoms of patients including fever, cough, dyspnea and others, but with no significant differences (*P > 0.05*) [10]. Also, in two studies in 2005 and 2008 on SARS-CoV, which is the same family of SARS-CoV-2, it was reported that the lowest infection susceptibility was in patients with blood group-O and

it was explained to be due to the presence and the absence of anti-A antibodies in blood group-O and A, respectively, as this antibodies may prevent the interaction between the virus and its receptors [14,15]. In addition, another study in 2020 on the SARS-CoV-2, reported that the sex and age of patients, were from the factors that influence susceptibility, and that the ABO-blood group variations, also were considered as COVID-19 susceptibility factor. The study suggested that blood group-AB, was susceptibility to COVID-19. On the contrary, the fatality in their study, was markedly accompanied with group-A. However, the lowest susceptibility and the protective evolution against COVID-19 was found in group-O [16].

The significance of group-O in decreasing the infection risk towards COVID-19 and groups A, B, or AB in increasing the probability of being infected, were also illustrated in many other studies [10, 17, 18].

In other studies, high rate of fatality, was found to be associated with group-A [16,18]. Accordingly, the ABO-antigens could influence the pathogenesis of COVID-19, but, the mechanisms of this interaction, are still under hypothesizing. Natural selection of specific alleles by the pathogens, is one of this hypothesis that could subject the people to the susceptibility of infection. The pathogens use the glycosylated cell-surface receptors to facilitate their attachment so, ABO-blood group variations, could influence the interactions between these pathogens and the population using the glycosylation [19]. In 2006, at the time of the discovery of SARS-CoV virus, the O-glycosylation was found to influence the viral pathogenesis [20]. The susceptibility of patients towards infection with SARS-CoV, was affected by the presence of anti-A and anti-B antibodies, which occur naturally in their bodies. In SARS-CoV infection, it has been hypothesized that these antibodies may decrease the rate of infection and the degree of protection may be influenced by the ABO-antibody titer, secretor status, and the incidence of group-O in the population [13].

Some speculations may help in explaining our results. There are mainly four theories or hypothesis for this explanation, the first one proposed that by modifying the allocation of the sialic acid-receptors formed by the antigens of blood groups via carbohydrate-carbohydrate interactivity, in the patients cell surface, this affect the spike-protein of the virus attaching to the host cell, either by increasing or decreasing this attachment, and thus explain that type-A individuals are more susceptible to infection than other types [1].

The second theory was supposed in 2008, and it was performed on the SARS-CoV and its receptor. It discussed that, this receptors could be blocked due to the human antibodies anti-A, thus provides the necessary protection against the virus, which clarify the high susceptibility of patients with blood group-A against this virus, and the contrary with blood group-O. This study also proposed also the third hypothesis. The study discovered that the inhibition of adhesion of the ACE-2 to the virus spike-protein by the presence of either a monoclonal or Anti-A-antibodies, can inhibit the virus-receptor adhesion, thus increase infectivity protection [15].

The fourth hypothesis could explain the bad prognosis and the high incidence for thrombosis in non-O blood group. The study was done in 2017. It discovered a significant increase in levels of plasma von Willebrand factor and increase in activity in Factor VIII in patients with non-O-blood type in comparison to patients with type O-blood [21]. Also, the clearance of this factor was powerfully related to the ABO-blood grouping system and this was also documented in 2008 [22].

## Conclusions

The blood group-O was the protective phenotype, controversy to the O-group, A-group was the risky phenotype, also AB-group was risky, as it showed the lowest frequency in both control and viral clearance group. Interestingly, the B-group was the least group susceptible to have bad prognosis and be admitted to the ICU.

This can be a safety guideline for classifying healthcare workers, according to their ABO, to work with suspected cases with COVID-19 and also may help in developing specific anti- histo-blood group antibodies as an effective co-therapy for COVID-19.

## Disclosure of potential conflicts of interest

The authors report that there are no conflicts of interest.

## Funding information

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