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ORIGINAL ARTICLE

# Abo Blood Group, Atherothrombotic Comorbidities, and COVID-19: A Case-Control Study of their Association in the Mexican Population

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*Background.* COVID-19 has been associated with negative results in patients with A blood group and with a better evolution in O blood group individuals.

*Aim.* Because the evidence regarding ABO blood groups and COVID was empirically not that clear in our country, we tested the association regarding COVID-19 and blood groups.

*Material and Methods.* Adult patients were enrolled in this prospective, case-control, observational multicenter study. Patients with a confirmed diagnosis of COVID-19 were assigned to one of three groups based on the clinical presentation of the infection. Age, gender, ABO and Rh blood groups, body mass index, history of diabetes mellitus or high blood pressure, and smoking were recorded directly or from their clinical charts. ABO blood group was obtained from 5,000 blood donors (50% each gender). Atherothrombotic variables were compared with a nation-wide data collection.

*Results.* A total of 2,416 patients with COVID-19 were included (women:39.6%; men:60.4%). There were no significant differences between cases and controls in terms of age. O blood group was the most frequently found in healthy donors and COVID-19 patients, but this blood group was significantly higher in COVID-19 patients vs. healthy donors. ABO blood group was not associated with the final health status in COVID-19 patients. Obesity, diabetes mellitus, hypertension and smoking were significantly more frequent among COVID-19 patients.

*Conclusion.* The proposed protective effect of the O blood group in COVID-19 patients could not be reproduced in the Mexican population while some atherothrombotic risk factors had a significant effect on the clinical evolution. 

*Key Words:* COVID-19, Blood Groups, SARS-CoV-2, Atherothrombotic Risk Factors.

## Introduction

Coronavirus disease (COVID-19), caused by the SARS-CoV-2 virus, is a pandemic which has rapidly spreading worldwide causing high numbers of infections and death (1). COVID-19 has variable clinical manifestations with most infected subjects experiencing only mild or even no symptoms (2). However, mortality is predominantly associated with the development of severe respiratory failure secondary to interstitial pneumonia and acute respiratory distress syndrome (3). Patients with the most aggressive variants of COVID-19 develop respiratory failure requiring support by mechanical ventilation (4). Although to date, no specific biological marker can confidently predict the evolution of the disease, several risk factors for COVID-19 infection, morbidity, and mortality have been described including age, sex, chronic diseases as well as laboratory findings (5). Two studies on COVID-19 patients in China found an association between ABO blood types and the presentation of the infection (6,7). Comparing the blood groups of hospitalized COVID-19 patients and the general population, the odds of testing positive for COVID-19 among individuals with A blood group were increased while among those with O blood group were decreased relative to the general population. Subsequent studies confirmed the associations between the ABO blood group and the clinical characteristics of patients with COVID-19 (8–12).

In our country, we noticed that the relationship between severity of COVID-19 and the ABO group was not quite as clear as suggested from the evidence published elsewhere. Long ago in Mexico, it is very well known that as high as 75–85% of the population carries the O blood group followed by A blood group. This distribution of ABO blood groups is quite regular across our whole country and the most accepted explanation for this distribution is the fact that Amerindians carried O blood groups in 100% of them. Indeed, the presence of the O group, either Rh+ or Rh–, has been considered a powerful genetic marker for the Mexican mestizo populations (13,14).

Having a population with such a high percentage of O blood group, may represent an attractive naturally occurring model to test the accepted associations between COVID-19 and the ABO blood group. Based on our observations suggesting a weak association between the ABO blood group and the clinical evolution of COVID-19 patients, we hypothesized that this evidence was perhaps not as significant as described in other populations. Therefore, our objective was to test the already accepted relationship between COVID-19 and blood groups in Mexico and its association with some of the most important atherothrombotic risk factors.

## Material and Methods

### *Patients*

For this case-control study, patients from 11 states from the Mexican Republic were enrolled in this prospective, observational, case-control study. Only adult patients, of both genders, with a confirmed test for SARS-CoV-2 virus infection were included. Patients were consecutively assigned to one of three groups based on the clinical presentation of the infection, namely: Group A. Patients treated at home after been diagnosed and who eventually survived the infection; Group B. Patients that required in-hospital treatment (including ventilation) because of a complicated evolution but who survived the viral disease; and Group C. Patients treated in-hospital who died.

### *Methods*

From all patients we collected their general characteristics namely age, gender, ABO blood group, and Rh blood group. General characteristics of the patients as well as their evolution and final health status were obtained were recorded directly or from their clinical charts. ABO blood group was obtained from 5,000 blood donors attended during the time of the pandemic to have a specific control group for this research. Blood groups were established using a semi-automatic technique that uses cards according to commercially available tests. Because our initial clinical observations strongly suggested a lack of association between ABO blood group and COVID-19 infection or evolution, we attempted to evaluate the likely impact of some atherothrombotic comorbidities on the COVID-19 evolution namely overweight and obesity, history of diabetes mellitus or high blood pressure, and smoking. Data obtained were compared with data collected at the 2018 ENSANUT, a strong, nation-wide collection of data which includes information regarding the atherothrombotic morbidities affecting our country (15).

### Statistical Analysis

Data analyses were made using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). For each blood group and comorbidity, results were reported as the total number and percentage. Age of healthy donors and COVID-19 patients is expressed as mean and ranges. On the other hand, we used the Fisherś exact test to evaluate whether the blood groups and comorbidities distributions differ between healthy donors and COVID-19 patients. For ABO blood groups frequencies, the statistical analysis was made based on a calculated sample size, assuming a decrease of as little as 5% in the frequency of 0 blood group in COVID-19 patients compared to the frequency in Mexican blood donors (75 %). Besides, a $\alpha = 0.5$ and 1-$\beta = 0.8$ were considered. In this way, the sample size was 2250 people per group. To analyze the likely association of blood groups and comorbidities with the final health status of the patients as well as the association of hospital death among COVID-19 patients with one or more comorbidities vs. patients without comorbidities, we calculated odds ratios with their confidence intervals, and $p$-values (Fisher's exact test). OR and CI were calculated with data of the event (Groups: A, B, or C) and the likely associated factors (blood group or comorbidity). As control group (no event), patients from groups B and C were controls for the group A; patients from the groups A and C as controls for the group B, while patients from the groups A and B as controls for the group C. $p$-values $\leq 0.05$ were considered significant.

### *Ethics*

The study protocol was accepted by the Ethics Local Committees of our institutions. In this study, we only required the data from the clinical charts of the patients. Therefore, patients were not informed about the study neither signed informed consent was obtained. To assure the confidentiality of the information, only the investigators had access to the complete data of the participants. The study fulfilled the national and international regulations for clinical research: Ley de General de Salud, the Helsinki Declaration, and the Code of Nuremberg.

## Results

ABO blood groups from 5,000 healthy donors (50% each gender), and 2,416 COVID-19 patients (women: 39.6%; men: 60.4%), were obtained. Mean age for healthy donors and COVID-19 patients was 40 years-old (ranges: 18–55 years-old), and 45.3 years-old (ranges = 18–63 years-old), respectively ($p = 0.59$).

### *ABO and Rh Blood Groups Distribution in Healthy Donors and COVID-19 Patients*

As expected for the Mexican population, the O blood group was the most frequently found in healthy donors and COVID-19 patients while AB blood group was very scarce among both study populations (Table 1). After including the Rh blood group, the 0+ group persisted as the most frequent among healthy donors and COVID-19 patients, while AB- group was found only in the 0.02% of healthy donors and was absent in patients with COVID-19. The Rh+ blood group was identified in 97.94% of healthy donors and in 97.72% of COVID-19 patients (Table 1).

The distribution of blood groups between healthy donors and COVID-19 patients showed some significant differences (Table 1). Both, O ($p = 0.0003$) and O+ ($p = 0.0004$) blood groups were identified in a significant higher percentage in COVID-19 patients than in healthy

**Table 1.** ABO and Rh blood groups in healthy donors and COVID-19 patients

| AB0–Rh | Healthy donors ($n$ = 5,000) | COVID-19 patients ($n$ = 2,416) | $p^*$ |
|---|---|---|---|
| 0/non-0; *n* (%) | 3,429 (68.58)/1,571 (31.42) | 1,757 (72.72)/659 (27.28) | 0.0003 |
| A/non-A; *n* (%) | 1,196 (23.92)/3,804 (76.08) | 490 (20.28)/1,926 (79.72) | 0.0004 |
| B/non-B; *n* (%) | 324 (6.48)/4,676 (93.52) | 159 (6.58)/2,257 (93.42) | 0.8803 |
| AB/non-AB; *n* (%) | 51 (1.02)/4,949 (98.98) | 10 (0.41)/2,406 (99.59) | 0.0058 |
| 0+/non-0+; *n* (%) | 3,366 (67.32)/1,634 (32.68) | 1,725 (71.40)/691 (28.60) | 0.0004 |
| A+/non-A+; *n* (%) | 1,161 (23.22)/3,839 (76.78) | 472 (19.50)/1,944 (80.50) | 0.0003 |
| B+/non-B+; *n* (%) | 320 (6.40)/4,680 (93.60) | 154 (6.37)/2,262 (93.63) | 1.000 |
| AB+/non-AB+; *n* (%) | 50 (1.00)/4,950 (99.00) | 10 (0.41)/2,406 (99.59) | 0.0081 |
| 0-/non-0-; *n* (%) | 63 (1.26)/4,937 (98.74) | 32 (1.33)/2,384 (98.67) | 0.8260 |
| A-/non-A-; *n* (%) | 35 (0.70)/4,965 (99.30) | 18 (0.75) 2,398 (99.25) | 0.8832 |
| B-/non-B-; *n* (%) | 4 (0.08)/4,996 (99.92) | 5 (0.21)/2,411 (99.79) | 0.1621 |
| AB-/non-AB-; *n* (%) | 1 (0.02)/4,999 (99.98) | 0 (0)/2,416 (100) | >0.99 |

*Direct comparisons between the total number of each blood group in healthy donors vs. total number of each blood group in COVID-19 patients.

**Table 2.** Association of blood group with health status in COVID-19 patients ($n$ = 2,416)

| Blood group | Groups | Non-Groups | $p$ | OR (95%CI) |
|---|---|---|---|---|
| | A ($n$ = 929) | A ($n$ = 1,487) | | |
| 0/non-0; *n* (%) | 670 (72.1)/259 (27.9) | 1087 (73.1)/400 (26.9) | 0.6058 | 0.952 (0.792–1.144) |
| A/non-A; *n* (%) | 197 (21.2)/732 (78.8) | 293 (19.7)/1194 (80.3) | 0.3770 | 1.097 (0.896–1.343) |
| B/non-B; *n* (%) | 57 (6.1)/872 (93.9) | 102 (6.9)/1385 (93.1) | 0.5012 | 0.888 (0.635–1.241) |
| AB/non-AB; *n* (%) | 5 (0.5)/924 (99.5) | 5 (0.3)/1482 (99.7) | 0.5214 | 1.604 (0.463–5.555) |
| | B ($n$ = 857) | B ($n$ = 1,559) | | |
| 0/non-0; *n* (%) | 615 (71.8)/242 (28.2) | 1142 (73.3)/417 (26.7) | 0.4451 | 0.928 (0.770–1.118) |
| A/non-A; *n* (%) | 181 (21.1)/676 (78.9) | 309 (19.8)/1250 (80.2) | 0.4593 | 1.083 (0.882–1.331) |
| B/non-B; *n* (%) | 59 (6.9)/798 (93.1) | 100 (6.4)/1459 (93.6) | 0.6685 | 1.079 (0.773–1.505) |
| AB/non-AB; *n* (%) | 2 (0.2)/855 (99.8) | 8 (0.5)/1551 (99.5) | 0.5096 | 0.454 (0.096–2.140) |
| | C ($n$ = 630) | C ($n$ = 1,786) | | |
| 0/non-0; *n* (%) | 472 (74.9)/158 (25.1) | 1285 (71.9)/501 (28.1) | 0.1602 | 1.165 (0.946–1.433) |
| A/non-A; *n* (%) | 112 (17.8)/518 (82.2) | 378 (21.2)/1408 (78.8) | 0.0740 | 0.805 (0.638–1.017) |
| B/non-B; *n* (%) | 43 (6.8)/587 (93.2) | 116 (6.5)/1670 (93.5) | 0.7795 | 1.055 (0.734–1.515) |
| AB/non-AB; *n* (%) | 3 (0.5)/627 (99.5) | 7 (0.4)/1779 (99.6) | 0.7267 | 1.216 (0.313–4.717) |

The analysis considered Group A as event and patients from groups B+C as comparative group; group B as event and patients from groups A+C as comparative group; and group C as event and patients from groups A+B as comparative group

donors. Contrary to this, the frequency of blood groups A ($p$ = 0.0004), A+ ($p$ = 0.0003), AB ($p$ = 0.0058), and AB+ ($p$ = 0.0081) was significantly higher in healthy donors (Table 1). No significant differences for the B blood group were found between the study groups.

### *Association of Bloods Groups with the Final Health Status of COVID-19 Patients*

We found that ABO blood group was not associated with the final health status in COVID-19 patients (Table 2). As shown in Table 2, none of the blood groups could be significantly associated neither with a non-complicated or complicated evolution of the disease nor with death. These results clearly contrast with previous evidence published in the literature showing a protective effect of O blood group.

### *Comorbidities and their Association with the Final Health Status of COVID-19 Patients*

Table 3 shows that obesity, diabetes mellitus, hypertension, and smoking were significantly more frequent among patients with COVID-19 as compared with the published data for the Mexican population (15). Among patients with COVID-19, only 3.0% were free of comorbidities while 45.9% had 3 or 4 comorbidities.

On the other hand, for COVID Group A, obesity and smoking were significantly associated with low possibility of surviving the infection at home. For COVID Group B, obesity and diabetes mellitus also showed a significant association with low possibility of surviving the infection when the patient was treated in the hospital (Table 4). For COVID Group C, obesity, diabetes mellitus, and smoking, showed a positive association with in-hospital death (Table 4). Regarding the number of deaths, COVID-19 patients without comorbidities represented only 0.25% of

**Table 3.** Comorbidities in healthy donors and COVID-19 patients

| Comorbidities | ENSANUT 2018 ($n = 82.7 \times 10^6$) | COVID-19 ($n = 1,200$) | $p$ |
|---|---|---|---|
| OW; *n* (%) | 32,335,700 (39.1) | 381 (31.75) | <0.00001 |
| OB; *n* (%) | 29,854,700 (36.1) | 542 (45.17) | <0.00001 |
| OW and OB; *n* (%) | 62,190,400 (75.2) | 923 (76.92) | 0.1707 |
| DM; *n* (%) | 8,518,100 (10.30) | 520 (43.33) | <0.00001 |
| H; *n* (%) | 15,216,800 (18.40) | 558 (46.50) | <0.00001 |
| S; *n* (%) | 9,427,800 (11.40) | 842 (70.17) | <0.00001 |

ENSANUT: Encuesta Nacional de Salud 2018; OW: overweight; OB: obesity; DM: diabetes mellitus; H: hypertension; S: smoking.

**Table 4.** Association of comorbidities with health status in COVID-19 patients (n = 1,200)

| Comorbidity | Groups | Non-Groups | $p$ | OR (95% CI) |
|---|---|---|---|---|
| | A ($n = 400$) | A ($n = 800$) | | |
| OB/No-OB; *n*, (%) | 274 (68.50)/126 (31.50) | 649 (81.1)/151 (18.9) | <0.00001 | 0.506 (0.384–0.666) |
| DM/No-DM; *n* (%) | 169 (42.25)/231 (57.75) | 351 (43.9)/449 (56.1) | 0.6212 | 0.936 (0.734–1.193) |
| H/No-H; *n* (%) | 182 (45.50)/218 (54.50) | 376 (47.0)/424 (53.0) | 0.6674 | 0.941 (0.740–1.198) |
| S/No-S; *n* (%) | 250 (62.50)/150 (37.50) | 592 (74.0)/208 (26.0) | 0.0001 | 0.586 (0.453–0.757) |
| | B ($n = 400$) | B ($n = 800$) | | |
| OB/No-OB; *n* (%) | 289 (72.25)/111 (27.75) | 634 (79.3)/166 (20.7) | 0.0072 | 0.682 (0.516–0.900) |
| DM/No-DM; *n* (%) | 157 (39.25)/243 (60.75) | 363 (45.4)/437 (54.6) | 0.0480 | 0.778 (0.609–0.993) |
| H/No-H; *n* (%) | 181 (45.25)/219 (54.75) | 377 (47.1)/423 (52.9) | 0.5806 | 0.927 (0.729–1.180) |
| S/No-S; *n* (%) | 283 (70.75)/117 (29.25) | 559 (69.9)/241 (30.1) | 0.7891 | 1.043 (0.802–1.357) |
| | C ($n = 400$) | C ($n = 800$) | | |
| OB/No-OB; *n* (%) | 360 (90.00)/40 (10.00) | 563 (70.4)/237 (29.6) | <0.00001 | 3.789 (2.643–5.431) |
| DM/No-DM; *n* (%) | 194 (48.50)/206 (51.50) | 326 (40.8)/474 (59.2) | 0.0113 | 1.369 (1.075–1.743) |
| H/No-H; *n* (%) | 195 (48.75)/205 (51.25) | 363 (45.4)/437 (54.6) | 0.270 | 1.145 (0.900–1.456) |
| S/No-S; *n* (%) | 309 (77.25)/91 (22.75) | 533 (66.6)/267 (33.4) | 0.0001 | 1.701 (1.291–2.242) |

OB: obesity; DM: diabetes mellitus; H: hypertension; S: smoking.
OR and CI were calculated as in the Table 2.

**Table 5.** Risk of death in COVID-19 patients with one or more comorbidities vs. patients without comorbidities

| Comorbidity | Dead patients *n* (%) | $p$ | OR (95% CI) |
|---|---|---|---|
| No comorbidities ($n = 36$) | 1 (2.78) | | |
| OB ($n = 66$) | 16 (24.24) | 0.0048 | 11.20 (1.419–88.39) |
| DM ($n = 25$) | 5 (20.00) | 0.0376 | 8.75 (0.954–80.26) |
| H ($n = 23$) | 5 (21.74) | 0.0291 | 9.72 (1.055–89.61) |
| S ($n = 59$) | 12 (20.34) | 0.0154 | 8.94 (1.109–71.99) |
| OB, DM; $n = 61$ | 19 (31.15) | 0.0006 | 15.83 (2.017–124.27) |
| OB, H ($n = 79$) | 23 (29.11) | 0.0009 | 14.37 (1.858–111.24) |
| OB, S; $n = 202$ | 72 (35.64) | 0.00001 | 19.38 (2.60–144.46) |
| DM, H ($n = 11$) | 2 (18.18) | 0.1323 | 7.78 (0.632–95.68) |
| DM, S ($n = 43$) | 7 (16.28) | 0.0649 | 6.80 (0.796–58.21) |
| H, S ($n = 41$) | 4 (9.76) | 0.3638 | 3.78 (0.403–35.52) |
| DM, H, S ($n = 34$) | 4 (11.76) | 0.1921 | 4.67 (0.494–44.051) |
| OB, DM, H ($n = 57$) | 21 (36.84) | 0.0001 | 20.42 (2.60–160.08) |
| OB, DM, S ($n = 155$) | 73 (47.10) | <0.00001 | 31.16 (4.164–233.16) |
| OB, H, S ($n = 167$) | 73 (43.71) | <0.00001 | 27.18 (3.638–203.09) |
| OB, DM, H, S ($n = 138$) | 63 (45.65) | <0.00001 | 29.40 (3.92–220.70) |

OB: obesity; DM: diabetes mellitus; H: hypertension; S: smoking

the fatalities while comorbidities were found in 99.75% of deaths.

Finally, Table 5 shows the impact of the number of comorbidities on the risk of death in COVID-19 patients, highlighting the fact that, the risk of death increased depending on the number of comorbidities associated. We found that the highest risk of death was for a COVID-19 patient with obesity, diabetes mellitus, and smoking history (OR = 31.16, 95% CI = 4.164–233.16; $p$ <0.00001), followed by patients with obesity, diabetes mellitus, hypertension, and smoking history (OR = 29.40, 95% CI = 3.92–220.70; $p$ <0.00001).

## Discusion

Long ago, it was described the association between viral and non-viral diseases with ABO blood groups (16–21). Since the SARS coronavirus pandemic, it was described that subjects with blood group O were less likely to become infected as compared with non-O blood group individuals (16). In the SARS-CoV-2 pandemic, the ABO blood group was again linked with COVID-19 (7). Indeed, for COVID-19, it has been described that there is a significant association between A blood group and a high number of positive cases (OR = 1.21; $p = 0.027$) while O blood group, on the other hand, has a lesser incidence of infection vs. other groups (OR = 0.67; $p = 0.001$) (7). In a study from a hospital system, COVID-19 positive cases had a high proportion of A blood group and a low proportion of O blood group (22).

A blood group has been linked to higher mortality risk in contrast to O blood group (OR 1.482; $p = 0.008$), and the latter was associated with a lower mortality risk compared with non-O blood groups (OR 0.660; $p = 0.014$) (7) however, such associations were found only in Rh-positive blood types (22). The effect of blood groups remained significant even after excluding other well known risk factors associated with worse prognosis, e. g. obesity, diabetes mellitus, and other comorbidities (7,22). Other studies also demonstrated that the O blood group has a negative predictive effect, and the A blood group was more frequent in patients who presented with severe pulmonary damage (6,7,22).

Several mechanisms are proposed to link ABO blood groups to infectious diseases all of them associated to the fact that blood groups are dictated by sugars and coronaviruses have surface proteins that bind sugars. Because A blood group cells have an extra sugar N-acetyl galactosamine on their surface it may allow more pathogen contact while this sugar is missing on O blood group cells (23). SARS-COV-2, a $\beta$ coronavirus closely related to SARS-CoV, requires the angiotensin-converting enzyme-related carboxypeptidase (ACE2) to enter the cell (24). The ABO blood group system has been associated with ACE activity (25,26). Indeed, the GATC haplotype of the four polymorphisms of ABO gene, which is prevalent among non-O blood type patients, is directly associated with ACE activity (25). Therefore, O blood type individuals show lower ACE levels and a higher protection against coronavirus infection. An association exists between the spike (S) protein of SARS-CoV-2 with ACE2 protein, its cellular receptor (27). Adhesion of S protein to the ACE2 receptor may be inhibited by the anti-A antibody as occurs in O blood group individuals thereby offering protection against SARS-CoV-2 infection (28). Another likely explanation for the protective effect of O blood group is that epitopes are exposed to the non-immune immunoglobulin IgM and its highly anti-glycan ABO isoagglutinin activities (29). Because such IgM activities are downregulated in the non-O groups, these immune characteristics may not be present in the O blood group (28). On the other hand, relationships between ABO blood groups and cardiovascular diseases have been described (30). The thrombotic risk is lower in O blood group vs. non-O individuals (30,31) and the A blood group is associated with an increased risk of cardiovascular diseases (29). The A antigen might protect P-selectin and intercellular cell adhesion molecule 1 from enzymatic cleavage thus promoting stronger and longer binding of leukocytes to the vascular wall. Adhesion molecules attached to the endothelium would increase adhesion, inflammation, and decreased circulation (32). These effects may predispose A blood group individuals to a higher risk for atherothrombotic disease. Therefore, O blood group individuals may be less likely to develop atherothrombotic diseases as well as severe COVID-19 and, on the contrary, A blood group subjects may be at higher risk to develop severe COVID-19, especially those with atherothrombotic risk factors such as obesity, diabetes mellitus or hypertension.

At the beginning of our research, two objectives were proposed. First, we attempted to evaluate the possible association between the frequency of COVID-19 and its severity and the ABO blood group. Second, because from the beginning of the study we doubt about this association, we planned to evaluate the impact of other risk factors on the possibility of infection and evolution of the patients.

Because the O blood group is found in 75–85% of the Mexican people, a country with such a homogeneous distribution of this biological variable represents a quite natural scenario to test the impact of ABO blood groups on COVID-19. Soon after the first publications informing about the negative relationship between O blood group and the possibility of infection as well as better prognosis, our immediate naive thought was that the impact of COVID-19 in Mexico would not be as severe as reported in other countries due to the high prevalence of O blood group. After a few weeks of the beginning of the epidemic in Mexico it was quite clear that such hopeful association was not working. Therefore, we challenged the hypothesis about the role of ABO blood groups and the possibility of being infected with the SARS-CoV-2 virus as well as the apparent prognostic value of some blood groups on the clinical fate of the COVID-19 disease. Indeed, because the high rate of O blood group in Mexico (an enormous and homogeneous control group), it would allow a more specifically investigation of the role of this biological characteristic on COVID-19 since less confounding variables are present.

Although the frequencies of the ABO blood groups were clearly established long ago in Mexico showing that the O blood group was highly present in the population, we decided to include patients from the North, Center, and

South regions of the country to have a wide view of the impact of the SARS-CoV-2 infection avoiding some likely confounding variables. Besides the number of patients included in this study, it must be underlined that their data were gathered from 11 out of 32 states conforming the Mexican Republic, a fact that allow us to state that the sample is representative of the Mexican population affected with COVID-19. On the other hand, although the ABO blood group frequencies were established in the past, we decided to create a new database with the blood groups of non-infected people in order strength our data by making direct comparisons with infected individuals. The ABO group distribution previously informed in our country was confirmed. Both, negative Rh blood groups as well as AB blood group, were almost absent in this research, a fact that reflects the frequencies of the ABO groups in our country. Based on these facts, we were unable to establish any association between Rh negative of AB blood groups and COVID-19. Therefore, our evidence is limited to the non-AB, Rh positive blood groups. Although it was demonstrated that blood groups would have predictive effects on the need for intubation, ICU hospitalization, or mortality (6,7), in our research, considering the ABO blood group frequencies occurring in our country as a control, we did not identify a relationship between a specific blood group and intubation or death due to COVID-19.

On the other hand, as previously demonstrated in other populations (33–41), we found that most atherothrombotic risk factors have a significant negative impact on the Mexican population with COVID-19. The frequencies of these risk factors were significantly associated with a worse prognosis in Mexican patients. These findings are not quite surprising considering the rates of obesity in our country, another gigantic epidemic which represents an enormous burden for the health system. As we showed, smoking is also another risk factor not been completely recognized in association with the complications and fatality rates in COVID-19 patients (40). Our population is a clear example of how the simultaneous occurrence of obesity and their surrogates (diabetes mellitus and hypertension) with smoking, imprints a very bad prognosis to our patients with COVID-19. Indeed, after decades of incontrollable and irresponsible growth of obesity in Mexico, it seems that COVID-19 truly represents a crisis within a crisis (40,41).

Our study has limitations. As the Mexican population is almost 130 million people, our sample size may be considered small however, we are sure that the information clearly reflects the behavior of our population and that no more individuals are needed to suspect that the relationship between the blood group and COVID-19 would change in the future. Another limitation was the power of test under the desired value when comparing the frequencies of B, B+, B–, AB, AB+, and AB– blood groups between study groups. However, this statistic limitation was innocuous and became irrelevant for our research since the frequency of these blood groups was so low for healthy donors and COVID-19 patients. On the other hand, data regarding dyslipidemias were not recorded. Accordingly, we may hypothesize that the results regarding the negative effect of the atherothrombotic risk factors could be even worse than described. Moreover, smoking was not stratified; therefore, we cannot build considerations about the intensity of this habit and the likely outcome of the patients. Moreover, although at the beginning of the study we considered to include a group of infected but asymptomatic patients, we discharged this idea because: a) Most of published evidence did not include these patients, b) In our country, at the time this research was conceived, almost 1.1 million people were infected but asymptomatic and there was no reason to believe that the frequency of blood groups would be different as compared with symptomatic individuals and; c) Being the purpose of this research to verify the relationship of the blood group with the severity of the disease in order to add evidence to explain the differences in the clinical presentation among ill individuals, to include a group of asymptomatic individuals was meaningless. However, the lack on infected but asymptomatic patients may be considered as a limitation of our study. Lastly, it must be underlined that we used blood donors as a control group and that, as previously suggested, these individuals may not totally reflect the healthy status of a specific population. Because blood donors may be considered healthier than the general population, this fact may influence the incidence of some diseases specially those likely associated with the blood group. However, we may argue that all evidence regarding the specific and quite characteristic frequencies of ABO and Rh blood groups in our country were built based precisely on blood donors. Therefore, although it is likely that our control group may not be completely equal to the healthy population in our country, our data quite closely reflects the reality.

## Conclusions

The proposed negative effect of A blood group as well as the protective effect of the O blood group on the prognosis of COVID-19 is not reproduced in the Mexican population. Perhaps, in our quite specific scenario characterized by a high proportion of individuals with the O blood group, the previously described associations between blood groups and the result of the COVID-19 were diluted. On the contrary, some well described atherothrombotic risk factors associated with endotelial dysfunction have a significant effect on the clinical evolution in our population. Of course, it is quite possible that other unknown immunological and/or endothelial ethnic-specific characteristics of our population may have a more decisive role determining the clinical fate of the Mexican patients with COVID-19.

## Conflict of Interests

None declared.

## Declaration of Funding

None declared.

## References

1. Coronavirus disease. (COVID-19) Situation Report –76World Health Organization WHO Coronavirus disease 2019 situation reports; 2019 https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200405-sitrep-76-covid-19.pdf?sfvrsn=6ecf0977_2 Accessed on April 5, 2020.
2. Wu Z, McGoogan JM. Characteristics of and important lessons from the Coronavirus Disease 2019 (COVID-19) outbreak in China: Summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020;323:1239–1242.
3. Berlin DA, Gulick RM, Martinez FJ. Severe Covid-19. N Engl J Med 2020;383:2451–2460.
4. Marini JJ, Gattinoni L. Management of COVID-19 Respiratory Distress. JAMA 2020;323:2329–2330.
5. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054–1062.
6. Li J, Wang X, Chen J, et al. Association between ABO blood groups and risk of SARS-CoV-2 pneumonia. Br J Haematol 2020;190:24–27.
7. Zhao J, Yang Y, Huang H, et al. Relationship between the ABO blood group and the COVID-19 susceptibility. medRxiv; 2020. https://doi.org/ggpn3d (Accessed on March 27).
8. Gerard C, Maggipinto G, Minon JM. COVID-19 and ABO blood group: Another viewpoint. Br J Haematol 2020;190:e93–e94.
9. Zaidi FZ, Zia AR, Abdullah SM, et al. COVID-19 and the ABO blood group connection. Transfus Apher Sci 2020;59:102838.
10. Goker H, Karakulak EA, Demiroglu H, et al. The effects of blood group types on the risk of COVID-19 infection and its clinical outcome. Turk J Med Sci 2020;50:679–683.
11. Dai X. ABO blood group predisposes to COVID-19 severity and cardiovascular diseases. Eur J Prev Cardiol 2020;27:1436–1437.
12. Bogetofte Barnkob M, Potteg A, Støvring H, et al. Reduced prevalence of SARS-CoV-2 infection in ABO blood group O. Blood Adv 2020;4:4990–4993.
13. Lisker R, Ramírez E, Babinsky V. Genetic structure of autochthonous populations of Meso-America: Mexico. Hum Biol 1996;68:395–404.
14. Majluf-Cruz A, Moreno-Hernandez M, Ruiz-de-Chavez-Ochoa A, et al. Activated protein C resistance and factor V Leiden in Mexico. Clin Appl Thromb Haemost 2008;14:428–437.
15. . Encuesta Nacional de Salud y Nutrición 2018 Ensanut: Presentación de resultados; 2019 https://www.inegi.org.mx/contenidos/programas/ensanut/2018/doc/ensanut_2018_presentacion_resultados.pdf Accessed on August 20, 2021.
16. Cheng Y, Cheng G, Chui CH, et al. ABO blood group and susceptibility to severe acute respiratory syndrome. JAMA 2005;293:1450–1451.
17. Loscertales MP, Owens S, O'Donnell J, al at. ABO blood group phenotypes and Plasmodium falciparum malaria: Unlocking a pivotal mechanism. Adv Parasitol 2007;65:1–50.
18. Boren T, Falk P, Roth KA, Larson G, Normark S. Attachment of Helicobacter pylori to human gastric epithelium mediated by blood group antigens. Science 1993;262:1892–1895.
19. Lindesmith L, Moe C, Marionneau S, et al. Human susceptibility and resistance to Norwalk virus infection. Nat Med 2003;9:548–553.
20. Wang DS, Zhang DS, Qiu MZ, et al. ABO blood group, hepatitis B viral infection and risk of pancreatic cancer. Int J Cancer 2012;131:461–469.
21. Foster MT, Labrum AH. Relation of infection with Neisseria gonorrhoeae to ABO blood groups. J Infect Dis 1976;133:329–330.
22. Zietz M, Tatonetti NP. Testing the association between blood type and COVID-19 infection, intubation, and death. medRxiv; 2020. https://doi.org/10.1101/2020.04.08.20058073. (Accessed on August 20, 2021.
23. Cooling L. Blood groups in infection and host susceptibility. Clin Microbiol Rev 2015;28:801–970.
24. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020;579:270–273.
25. Luo JQ, He FZ, Luo ZY, et al. Rs495828 polymorphism of the ABO gene is a predictor of enalapril-induced coughing Chinese patients with essential hypertension. Pharmacogenet Genom 2014;24:306–313.
26. Gasso P, Ritter MA, Mas S, et al. Influence of ABO genotype and phenotype on angiotensin-converting enzyme plasma activity. J Renin Angiotensin Aldosterone Syst 2014;15:580–584.
27. Walls A, Park Y, Tortorici M, et al. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell 2020;181:281–292.
28. Yamamoto F, Yamamoto M, Muñiz-Diaz E. Blood group ABO polymorphism inhibits SARS-CoV-2 infection and affects COVID-19 progression. Vox Sang 2021;116:15–17.
29. Arend P. Position of human blood group O (H) and phenotype-determining enzymes in growth and infectious disease. Ann N Y Acad Sci 2018;1425:5–18.
30. Wu O, Bayoumi N, Vickers MA, et al. ABO (H) blood groups and vascular disease: a systematic review and meta-analysis. J Thromb Haemost 2008;6:62–69.
31. Jenkins PV, O'Donnell JS. ABO blood group determines plasma von Willebrand factor levels: a biologic function after all? Transfusion 2006;46:1836–1844.
32. Pare G, Chasman DI, Kellogg M, et al. Novel association of ABO histo-blood group antigen with soluble ICAM-1: results of a genome-wide association study of 6,578 women. PLoS Genet 2008;4:e1000118.
33. Müller-Wieland D, Marx N, Dreher M, et al. COVID-19 and cardiovascular comorbidities. Exp Clin Endocrinol Diabetes 2020 doi:10.1055/a-1269-140.
34. Kim T, Roslin M, Wang JJ, et al. Body mass index as a risk factor for clinical outcomes in patients hospitalized with COVID-19 in New York. Obesity (Silver Spring) 2021;29:279–284.
35. Matsushita K, Ding N, Kou M, et al. The relationship of COVID-19 severity with cardiovascular disease and its traditional risk factors: A systematic review and meta-analysis. Glob Heart 2020;15:64.
36. Alamdari NM, Rahimi FS, Afaghi S, et al. The impact of metabolic syndrome on morbidity and mortality among intensive care unit admitted COVID-19 patients. Diabetes Metab Syndr 2020;14:1979–1986.
37. Tan E, Song J, Deane AM, et al. Global impact of COVID-19 infection requiring admission to the ICU: a systematic review and meta–analysis. Chest 2021;159:524–536.
38. Ahluwalia IB, Myers M, Cohen JE. COVID-19 pandemic: an opportunity for tobacco use cessation. Lancet Public Health 2020;5:e577 doi: 10.1016/S2468-2667 (20)30236-X.

39. Raines AM, Tock JL, McGrew SJ, et al. Correlates of death among SARS-CoV-2 positive veterans: The contribution of lifetime tobacco use. Addict Behav 2020;113:106692 doi:10.1016/j.addbeh.2020.106692.
40. Alla F, Berlin I, Nguyen-Thanh V, et al. Tobacco and COVID-19: A crisis within a crisis? Can J Public Health 2020;111:995–999.
41. Escobedo-de la Peña J, Rascón-Pacheco RA, Ascencio-Montiel IJ, et al. Hypertension, diabetes and obesity, major risk factors for death in patients with COVID-19 in Mexico. Arch Med Res 2021;52:443–449.