

## Coronavirus Pandemic

# ABO blood group influence COVID-19 infection: a meta-analysis

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### Abstract

**Introduction:** Previous studies have linked the relationship between ABO blood group and COVID-19 infection. However, existing evidence is preliminary and controversial. This meta-analysis sought to identify studies that describe COVID-19 and ABO blood group.

**Methodology:** A literature search was conducted from PubMed, Web of Science, MedRxiv, BioRxiv and Google Scholar databases. Members of cases and controls were extracted from collected studies. Pooled Odds ratio (OR) and 95% confidence interval (95%CI) were calculated and interpreted from extracted data. Publication bias and sensitivity analysis were also applied to confirm our discovery.

**Results:** Total 13,600 patients and 3,445,047 controls were included in the study. Compared to other ABO blood group, blood group O was associated with a lower risk of COVID-19 infection (OR = 0.76, 95%CI 0.66-0.84), while blood group A and AB was associated with a higher risk (OR = 1.25, 95%CI 1.10-1.41; OR = 1.13, 95%CI 1.04-1.23, respectively). In the subgroup analysis, the relationship between blood group A, O and COVID-19 infection remained stable among Chinese, European and Eastern Mediterranean populations. In American population, blood groups B was linked with increased risk of COVID-19 infection (OR = 1.21, 95%CI 1.09-1.35).

**Conclusions:** Our data suggested that individuals with blood types A and AB are more susceptible to COVID-19, while people with blood type O are less susceptible to infection. More research is needed to clarify the precise role of the ABO blood group in COVID-19 infection to address the global question.

**Key words:** ABO blood group; COVID-19; coronavirus disease 2019; meta-analysis.

*J Infect Dev Ctries* 2021; 15(12):1801-1807. doi:10.3855/jidc.13815

(Received 02 September 2020 – Accepted 02 August 2021)

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### Introduction

In December 2019, a novel coronavirus pneumonia outbreak appeared in Wuhan, Hubei province, P.R.C, and it quickly spread to other provinces in China, then became widespread around the world. This pathogen is a novel coronavirus (SARS-COV-2) that has never been found in humans before [1]. It was officially named Coronavirus Disease 2019 by World Health Organization (WHO) in February 2020, abbreviated as COVID-19 [2]. SARS-COV-2 is the third type of coronavirus that caused a worldwide pandemic after Middle East respiratory syndrome coronavirus (MERS-COV) and severe acute respiratory syndrome coronavirus (SARS-COV) [3]. As of 31 August 2020, a total of 25.1 million cases and over 884 thousand deaths were confirmed in more than 216 countries, areas or territories. In the United States, the number of infections has risen dramatically since the first week of March, and the U.S. now has confirmed 5.9 million cases [4].

The ABO blood group system is the first established human blood groups based upon antigens present on red cell membranes. Further research found ABO antigen not only exists on the surface of red blood cells, but also widely exists in some epithelial cells and various body fluids [5]. ABO blood group antigens can affect disease susceptibility through a variety of mechanisms, including acting as a receptor for pathogens and regulating immune responses in the form of antibodies [6]. Previous studies had linked the relationship between ABO blood groups and SARS-CoV infection, blood group O people have a lower infection rate [7]. Some recent studies have explored the relationship between the risk of SARS-CoV-2 infection and the ABO blood groups. Studies from China [8-10] and Europe [11-13] believe that the blood group O populations have lower risk of SARS-CoV-2 infection and blood group A have a higher risk. However, the results of studies conducted in the U.S. are different,

they found that people with blood group B have a higher risk of SARS-CoV-2 infection [14].

Therefore, we carried out a meta-analysis collected all possible studies from different nations to verify the presence and strength of the ABO blood group polymorphism association. The aim of this study is to determine SARS-CoV-2 positive individuals’ odds of having a specific blood group compared to controls, which may affect the kinetics of the pandemic according to the blood group distribution within the population.

## Methodology

### Literature search

The literature search was performed in PubMed, Web of Science, MedRxiv, BioRxiv and Google Scholar databases between January 1, 2020 and August 1, 2020. The following subject headings were employed: “blood group” or “blood type” or “blood groups” or “blood types”, “COVID-19” or “SARS-COV-2”.

### Study selection

Inclusion criteria were applied as: 1) study type: case-control study; 2) research objects: the patients and the controls came from the same area; 3) research method: the patients met the diagnostic criteria for COVID-19, and the detection method for ABO blood group was clear; 4) main indicators: number of

infections and controls in different blood groups. Studies were excluded if: 1) literature data was incomplete or original data could not be obtained; 2) small sample size research in the same area; 3) research without control group; 4) exclusion criteria included letters, reviews, meta-analysis and case reports.

### Data collection and quality assessment

Two researchers independently screened the literature according to the selection criteria, downloaded the full text of the literature that met the criteria, read it carefully, and extracted relevant data. When there was discrepancy, it was resolved by discussion or a third researcher. The extracted data include: 1) the first author; 2) time of the study; 3) country of the study conduction; 4) number of infections and controls in each blood group. The Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of the included research literature, it mainly involved three aspects, selection, comparability and exposure. The supreme score for each dimensions was 4 points, 2 points and 3 points, respectively. The assessment of article quality was based on the following scores: 0-3 points, 4-5 points and 6-9 points were regarded as poor quality, fair quality and high quality, respectively.

### Statistical analysis

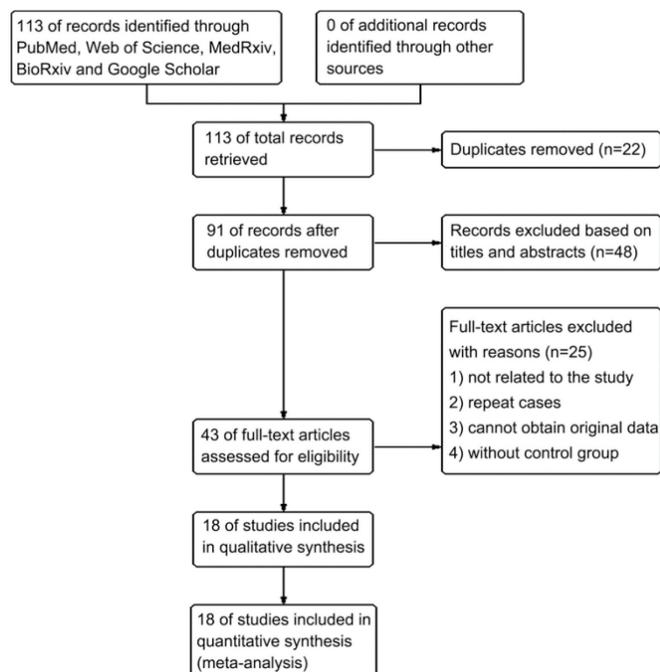
Meta-analysis was performed by RevMan version 5.3. The odds ratio (OR) of COVID-19 infection and the corresponding 95% confidence interval (95%CI) values across different blood groups were estimated. If Moran’s  $I^2 > 50\%$  or  $p > 0.05$ , it indicated the study was heterogeneous, and the random-effects model was used for analysis; otherwise, the fixed-effects model was used for analysis. The difference was statistically significant with  $p < 0.05$ . Besides, Begg’s funnel plot with visual inspection of asymmetry and Egg’s test were applied to evaluated publication bias, with a  $p < 0.05$  indicating potential bias (STATA version 11.0).

## Results

### Characteristics of eligible studies

A total of 113 potentially relevant articles were initially retrieved from four databases, and 18 articles were finally included according to the inclusion and exclusion criteria [8-25], as shown in Figure 1. All the selected articles were retrospective observational studies. The NOS scores ranged from 5 to 7 points. The clinical data of these patients was collected from January 2020 to June 2020, including 5 studies from China, 4 from America, 4 from Europe and 5 from

**Figure 1.** Flow diagram of the studies screening and selection process.



Eastern Mediterranean. The study included a total of 13,600 patients and 3,445,047 controls. The literature characteristics of the included studies are shown in Table 1.

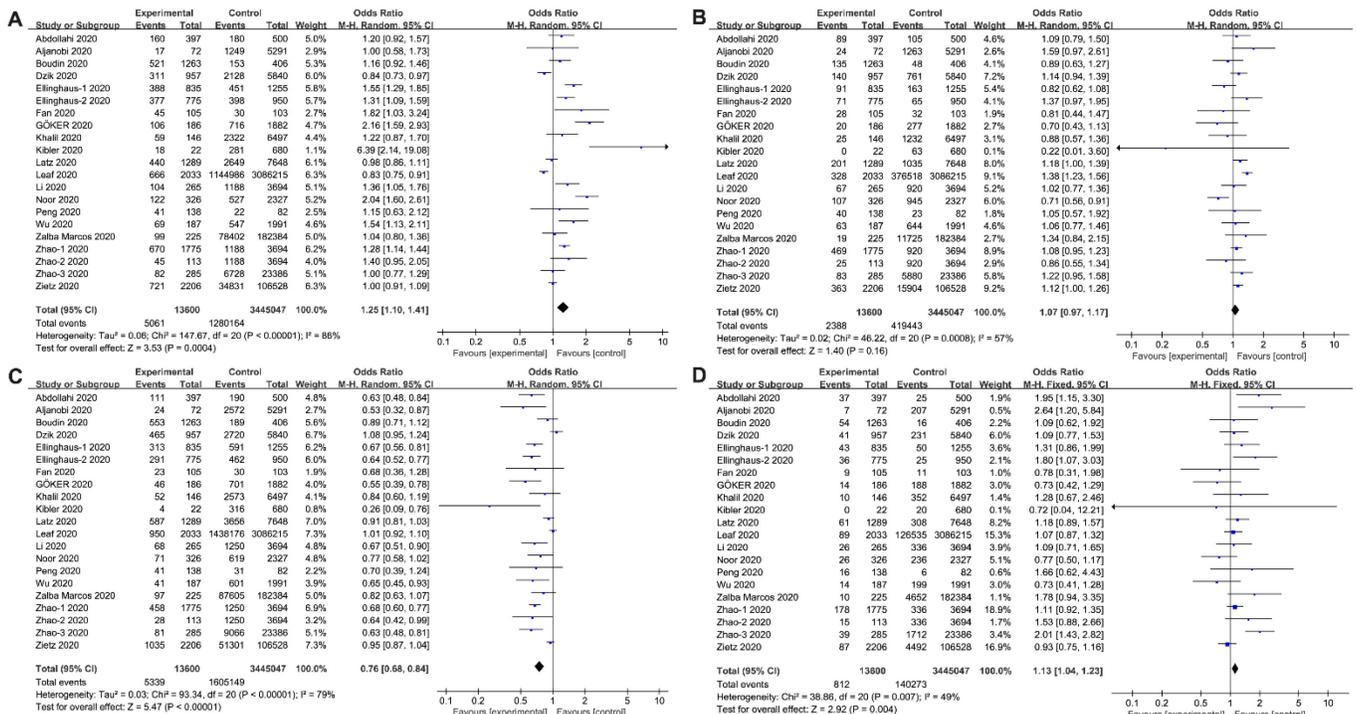
The relationship between ABO blood groups and COVID-19 infection

Results of the relationship between ABO blood groups and COVID-19 infection were recorded in Figure 2 and Table 2. The result of heterogeneity test

Table 1. Main characteristics of the included articles.

Author	Time	Country	Patients	Blood groups				Controls	Blood groups				NOS scores
				A	B	O	AB		A	B	O	AB	
Abdollahi [15]	2020.3	Iran	397	160	89	111	37	500	180	105	190	25	6
Aljanobi [16]	2020.3.15-2020.4.15	Saudi Arabia	72	17	24	24	7	5,291	1,249	1,263	2,572	207	6
Boudin [11]	2020.1.22-2020.4.13	France	1,263	521	135	553	54	406	153	48	189	16	6
Dzik [17]	2020.2.12-2020.5.13	America	957	311	140	465	41	5,840	2,128	761	2,720	231	5
Ellinghaus [12]	2020.2.17-2020.5.10	Italy	835	388	91	313	43	1,255	451	163	591	50	6
Fan [18]	2020.1.1-2020.3.5	China	775	377	71	291	36	950	398	65	462	25	6
Göker [19]	2020.1.1-2020.5.8	Turkey	105	45	28	23	9	103	30	32	30	11	7
Khalil [20]	2020.3.10-2020.5.5	Turkey	186	106	20	46	14	1,882	716	277	701	188	6
Kibler [13]	2020.2-2020.6	Lebanon	146	59	25	52	10	6,497	2,322	1,232	2,573	352	6
Kibler [13]	2020.1.1-2020.5.8	France	22	18	0	4	0	680	281	63	316	20	5
Latz [21]	2020.3.6-2020.4.16	America	1,289	440	201	587	61	7,648	2,649	1,035	3,656	308	5
Leaf [14]	2020.3.4-2020.4.11	America	2,033	666	328	950	89	3,086,215	1,144,986	376,518	1,438,176	126,535	5
Li [8]	2020.2.1-2020.3.25	China	265	104	67	68	26	3,694	1,188	920	1,250	336	6
Noor [22]	2020.3-2020.5	Pakistan	326	122	107	71	26	2,327	527	945	619	236	6
Peng [23]	2020.1.21-2020.2.20	China	138	41	40	41	16	82	22	23	31	6	5
Wu [9]	2020.1.20-2020.3.5	China	187	69	63	41	14	1,991	547	644	601	199	5
Zalba Marcos [24]	2020.4	Spain	225	99	19	97	10	182,384	78,402	11,725	87,605	4,652	6
Zhao [10]	NA.	China	1,775	670	469	458	178	3,694	1,188	920	1,250	336	6
Zhao [10]	NA.	China	113	45	25	28	15	3,694	1,188	920	1,250	336	6
Zhao [10]	NA.	China	285	82	83	81	39	23,386	6,728	5,880	9,066	1,712	6
Zietz [25]	-2020.6.15	America	2,206	721	363	1,035	87	106,528	34,831	15,904	51,301	4,492	5

Figure 2. Meta-analysis forest of blood groups in COVID-19 infection.



A: A vs non-A; B: B vs non-B; C: O vs non-O; D: AB vs non-AB.

between blood group A and non-A population was  $I^2 = 86\%$ . The random-effects model was applied to the analysis. Meta-analysis showed that the blood group A population was related to an increased risk of COVID infection (OR = 1.25, 95%CI 1.10-1.41).

The results of the heterogeneity test between the blood group B and non-B was  $I^2 = 57\%$ . Meta-analysis showed that the B blood group was unrelated with the incidence of COVID-19 by fixed-effects model (OR = 1.07, 95%CI 0.97-1.17).

The result of heterogeneity test between blood group O and non-O population was  $I^2 = 79\%$ . Meta-analysis showed that blood group O population was negatively correlated with COVID-19 infection by random-effects model (OR = 0.76, 95%CI 0.66-0.84).

The results of the heterogeneity test between the blood group AB and non-AB was  $I^2 = 49\%$ . Meta-analysis using a fixed-effects model showed that the blood group AB was positively correlated with the incidence of COVID-19, which was statistically significant (OR = 1.13, 95%CI 1.04-1.23).

*Subgroup and sensitivity analyses*

In the subgroup analysis, the relationship between blood group A, O and COVID-19 infection remained stable among Chinese, European and Eastern Mediterranean populations. However, this relationship was not found in American population. Blood groups B was linked with increased risk of COVID-19 infection in American population when compared with non-B group (OR = 1.21, 95%CI 1.09-1.35). In blood group AB, only European population showed an increased risk of COVID-19 infection compared with the non-AB (OR = 1.41, 95%CI 1.09-1.83), studies are shown in Table 2.

In the sensitivity analysis, when the studies by Leaf *et al.* [14] or Zietz *et al.* [25], two studies with the largest number of patients, were orderly removed or both removed at the same time, the pooled risk ratio were still stable, showing that blood O was associated with a lower risk of COVID-19 infection, while blood A and AB were associated with a higher risk of COVID-19 infection (Table 2).

*Publication bias analysis*

In the exploration for the plots of blood groups in COVID-19 infection, no obvious evidence of publication bias was present for blood group A vs non-A ( $p = 0.343$ ), blood group B vs non-B ( $p = 0.801$ ), and blood group AB vs non-AB ( $p = 0.843$ ), while a publication bias of blood group O vs group non-O was observed ( $p = 0.008$ ).

**Discussion**

Previous meta-analysis has shown that people with blood group A were more susceptible to COVID-19, while people with blood group O were less likely to be infected with COVID-19 [26]. But this study only summarized the data from two articles and enrolled 4379 patients. To further verify this relationship, our meta-analysis summarizes 18 studies from PubMed, Web of Science, MedRxiv, BioRxiv and Google Scholar databases to observe the relationship between ABO blood group and COVID-19 infection. Total 13,600 patients and 3,445,047 controls were included in our meta-analysis, the results suggested that blood group O was associated with a lower risk of COVID-19 infection, while blood group A and AB were associated with a higher risk.

The different expression of blood group antigens are determined by genes occupying the ABO locus on

**Table 2.** Meta-analysis results of different groups.

Group	No. of studies	Sample number (patient/control)	A vs. non-A		B vs. non-B		O vs. non-O		AB vs. non-AB	
			OR(95%CI)	P value	OR(95%CI)	P value	OR(95%CI)	P value	OR(95%CI)	P value
All studies	18	13,600/3,445,047	1.25 (1.10-1.41)	0.0004	1.07 (0.97-1.17)	0.16	0.76 (0.68-0.84)	<0.00001	1.13 (1.04-1.23)	0.004
<b>Subgroup</b>										
China	5	2,868/36,644	1.28 (1.17-1.40)	<0.00001	1.07 (0.97-1.18)	0.17	0.67 (0.61-0.74)	<0.00001	1.23 (0.94-1.62)	0.14
America	4	6,485/3,206,231	0.91 (0.82-1.01)	0.08	1.21 (1.09-1.35)	0.0006	0.98 (0.93-1.03)	0.40	1.04 (0.92-1.18)	0.51
Europe	4	3,120/185,675	1.34 (1.07-1.68)	0.01	1.03 (0.79-1.36)	0.81	0.72 (0.60-0.86)	0.0004	1.41 (1.09-1.83)	0.009
Eastern Mediterranean	5	1,127/16,497	1.57 (1.37-1.80)	<0.00001	0.93 (0.70-1.22)	0.59	0.68 (0.58-0.78)	<0.00001	1.25 (0.77-2.03)	0.37
<b>Sensitive analyse</b>										
Removed Leaf's study	17	11,567/358,832	1.28(1.13-1.44)	<0.00001	1.06 (1.00-1.12)	0.03	0.74 (0.67-0.82)	<0.00001	1.21 (1.05-1.40)	0.009
Removed Zietz's study	17	11,394/3,338,519	1.27(1.11-1.46)	0.0006	1.06 (0.95-1.17)	0.29	0.74 (0.66-0.83)	<0.00001	1.17 (1.07-1.28)	0.0005
Removed Leaf's and Zietz's study	16	9,361/252,304	1.31(1.15-1.49)	<0.00001	1.04 (0.98-1.11)	0.18	0.72 (0.65-0.81)	<0.00001	1.19 (1.08-1.32)	0.0004

chromosome 9 (9q34.1) [27]. The erythrocyte membrane is highly complex, the surface antigens on its surface interact with many other molecules which can affect the susceptibility to disease, by acting as receptors for pathogens. As an easily accessible factor in an individual's genetic makeup, ABO blood groups have been associated with many chronic diseases such as vascular disease, coronary heart disease and tumorigenesis [28]. Meanwhile, an increased association with specific risk and predisposing factors is present in infectious diseases. Guillon *et al.* revealed that blood group O was associated with a low risk of SARS-CoV infection [29]. Other infectious diseases, such as *Helicobacter pylori*, *Plasmodium falciparum*, Norovirus and Hepatitis B virus, have also been shown the association between ABO blood groups and host susceptibility [30]. Our meta-analysis found that the risk of infecting COVID-19 was also related to ABO blood group system. Based on existing studies, we speculate its possible mechanism. First, previous studies have found that SARS-CoV can use angiotensin-converting enzyme 2 (ACE2) receptor to promote virus entry into target cells, while anti-A antibodies can inhibit the SARS-CoV spike protein combine to ACE2 [29]. As the amino acid homology between SARS-CoV-2 and SARS-CoV spike protein reaches 76.5%, the protein has a high degree of homology [31]. We speculate that anti-A antibodies may also interfere with the binding of SARS-CoV-2 to ACE2 receptors, especially during the virus invasion stage. Second, in the study of the relationship between HIV infection and ABO blood type, it has been found that the polymorphic blood group antigens expressed on the surface of red blood cells, platelets and granulocytes can be used as attachment receptors by HIV, and natural anti-A and/or anti-B antibodies in the body can mediate the immune response and neutralize the virus [32-34]. There are similar findings in the process of malaria parasite infection. People with blood group O can reduce falciparum malaria infection through the mechanism of reducing red blood cell rosettes [35]. In view of these results, we speculate that the naturally occurring ABO antibody may be part of the innate immune response and may provide protection when people with blood group O are infected with SARS-CoV-2.

However, the results from the U.S. are inconsistent, they found blood group B have a higher risk of SARS-CoV-2 infection [14,21]. As an infectious disease, aside from genetic susceptibility factors, the chance of exposure to the source of infection is an important factor that can directly affect the risk of infection.

People living in higher endemic areas are at higher risk of exposure to COVID-19 infection, which might be the reason why the association between the ABO blood group and COVID-19 infection in American population was differ from that of other areas. Additionally, this difference might be partly attributed to the measures of prevention and control, regional health and economic development.

The potential clinical impact of the presented results deserve mention. Our study shed light on blood group O is less susceptible to COVID-19, and blood group A and AB is more susceptible to it, which suggest that individuals with blood group A and AB are supposed to do better personal protection to minimize the possibility of infection. Meanwhile, our finding provide supportive evidence that studying the association between ABO blood group and COVID-19 infection. Moreover, these insights may contribute to understand the kinetics of the epidemic at the local level, and to implement population-level health policies and interventions aimed to reducing the viral spread.

As SARS-CoV-2 is a novel virus, there are several limitations that should be considered in the present meta-analysis. First, the data available in the scientific literature to date were still preliminary. Bias may inevitably exist in the process of research design, data collection, data analysis and statistical processing. Second, it was difficult to obtain a uniform adjustment for confounders. This also influenced the intrinsic quality of the studies included in the meta-analysis. Third, although subgroup analyses were performed, analyses of previous studies have revealed that the heterogeneity cannot be ignored. Lastly, some controls populations were hospitalized patients, they may be deemed inadequately representative of the general populations.

## Conclusions

In the summary, this meta-analysis validated individuals with blood types A and AB are more susceptible to COVID-19, while people with blood type O are less susceptible to infection. This study may assists people realize the relationship between ABO blood groups and COVID-19 infection. Meanwhile, further studies are needed to support the association between ABO polymorphism and individual susceptibility to COVID-19 infection.

## Acknowledgements

We thank the anonymous referees and the editor for their comments and suggestions that helped improve the manuscript.

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**Conflict of interests:** No conflict of interests is declared.