ORIGINAL REPORT

Association between ABO blood group and COVID-19 infection: an updated systematic review and meta-analysis

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The relationship between ABO blood group and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 – coronavirus disease 19 [COVID-19]) infection has been investigated, and several studies have reported discordant findings. This systematic review and meta-analysis study were conducted to investigate the relationship between ABO blood group and COVID-19 infection. The international databases Institute for Scientific Information (ISI)/Web of Science, PubMed, and Scopus were systematically searched from 1 January 2020 through 14 June 2021. Twenty-seven studies met the inclusion criteria for meta-analysis including 23,285 COVID-19 case subjects and 590,593 control subjects. The odds of having each blood group among COVID-19 patients compared with control subjects were calculated. The random effects model was used to obtain the overall pooled odds ratio (OR). Publication bias and subgroup and sensitivity analyses were performed to explore the source of heterogeneity. According to the random effects model, the results indicated that the pooled estimates of OR (95% confidence interval) for blood groups A, O, B, and AB were 1.26 (1.13–1.40), 0.77 (0.71–0.82), 1.05 (0.99–1.12), and 1.11 (0.99–1.25), respectively. Therefore, individuals infected with COVID-19 have higher odds of having blood group A and lower odds of having blood group O. In conclusion, this study indicated that individuals with blood group A are more susceptible to COVID-19 infection, whereas those with blood group O are less susceptible to COVID-19 infection. However, further studies are warranted to support these findings.
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Key Words: COVID-19, ABO blood group, systematic review, meta-analysis

Coronaviruses have caused three global outbreaks of severe acute respiratory syndrome (SARS) (2002 and 2003), Middle East respiratory syndrome (MERS) (since 2012), and severe acute respiratory syndrome caused by SARS coronavirus 2 (SARS-CoV-2) (late 2019), leading to a pandemic.[1] SARS-CoV-2 appeared in Wuhan, China, on 31 December 2019. In February 2020, the World Health Organization named it COVID-19 (coronavirus disease 2019), and on 11 March 2020, the coronavirus outbreak was declared a pandemic.[2] The course of the disease varies from person to person and can range from a mild or even subclinical infection to a severe illness.[3] The main clinical symptoms of COVID-19 in humans include fever, cough, fatigue, anorexia, myalgia, and diarrhea. COVID-19 has shown heterogeneity of severity among patients, with shortness of breath being the most common symptom of the disease, often accompanied by hypoxemia.[4] Factors such as age, gender, and underlying diseases such as cardiovascular, respiratory, obesity, and diabetes predispose people to COVID-19.[5] Another factor that may be associated with COVID-19 is blood group. The ABO blood group system, consisting of four blood groups (A, B, AB, and O), is the most important blood group system in humans. The idea of using blood groups to measure a host's susceptibility to infectious diseases is not a new strategy and has already been proposed by Cooling.[6] ABO blood groups play an important role in infectious and noninfectious diseases, such as cardiovascular diseases and oncology. As receptors or coreceptors of microorganisms, parasites and viruses can play an important role in infection. Human histo-blood group antigens are one of the major antigens on the surface of human red blood cells that show polymorphic traits inherited among individuals and populations.[7] Some blood groups show an affiliation with susceptibility to various types of infection.[8] An association between group O and reduced risk of SARS-1 was reported in 2005 by Cheng et al.[9] Given the genomic similarity between SARS-CoV-2 and SARS-CoV, it has been hypothesized that anti-A and COVID-19 antibodies play a protective role. However, clinical evidence in this area is still controversial, and more comprehensive studies are needed.[10] Therefore, this systematic review and meta-analysis study was conducted to investigate the possible relationship between COVID-19 infection and ABO blood groups.

Methods

In this systematic review and meta-analysis, all observational articles published in English that examined the association between blood group and COVID-19 were reviewed

and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[11]

Search Strategy

The Web databases of Science, Scopus, and PubMed were searched by applying language (English) and document type (article) filters from 1 January 2020 through 14 June 2021. Key words were selected based on Medical Subject Headings (MeSH) terms for COVID-19; these key words included entry terms reported in PubMed (32 terms) and synonym terms from articles (22 terms) (Table 1). In addition, MeSH terms for blood group antigens, which included four entry terms and three synonym terms, were used to search the databases (Table 1).

Inclusion and Exclusion Criteria

Studies were included if they reported the prevalence of ABO blood groups among people with COVID-19 and those without COVID-19 and were published in English with access to full text; these studies included case-control studies and cohort studies having a control group i.e., individuals not infected with COVID-19. On the other hand, studies were excluded if they lacked sufficient information as well as being case series studies, letters to the editor, or commentaries.

Study Selection and Information Extraction

All observational studies published in English that reported the prevalence of ABO blood groups among people with COVID-19 and those without COVID-19 were analyzed. Review studies, letters to the editor, and case reports were excluded from analysis. The list of references of selected articles was also reviewed for access to more eligible studies. The process of searching and extracting articles was done by two independent authors.

Quality Assessment

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist was used to evaluate the methodologic quality of the included articles. Accordingly, all articles were reviewed for 10 selected items in this checklist: title and abstract, research objective/hypothesis, research setting, inclusion criteria, sample size, statistical methods, descriptive data, data

Table 1. MeSH terms used for the search strategy

MeSH term: COVID-19	
Entry term	**Synonym term**
1. COVID 19 Virus Disease	1. COVID-19 Virus Disease
2. COVID-19 Virus Diseases	2. COVID 19
3. Disease, COVID-19 Virus	3. 2019-nCoV
4. Virus Disease, COVID-19	4. Wuhan Coronavirus
5. COVID-19 Virus Infection	5. SARS-CoV-2
6. COVID 19 Virus Infection	6. 2019 Novel Coronavirus
7. COVID-19 Virus Infections	7. COVID-19 Virus
8. Infection, COVID-19 Virus	8. Coronavirus Disease 2019 Virus
9. Virus Infection, COVID-19	9. Wuhan Seafood Market Pneumonia Virus
10. 2019-nCoV Infection	10. covid19
11. 2019 nCoV Infection	11. covid 19
12. 2019-nCoV Infections	12. cov19
13. Infection, 2019-nCoV	13. covid-19
14. Coronavirus Disease-19	14. cov2
15. Coronavirus Disease 19	15. cov-2
16. 2019 Novel Coronavirus Disease	16. covid-sars
17. 2019 Novel Coronavirus Infection	17. cov-sars
18. 2019-nCoV Disease	18. coronavirus
19. 2019 nCoV Disease	19. coronavirus-sars
20. 2019-nCoV Diseases	20. cov sars
21. Disease, 2019-nCoV	21. coronavirus – sars
22. Coronavirus Disease 2019	22. coronavirus _ sars
23. Disease 2019, Coronavirus	
24. SARS Coronavirus 2 Infection	
25. SARS-CoV-2 Infection	
26. Infection, SARS-CoV-2	
27. SARS CoV 2 Infection	
28. SARS-CoV-2 Infections	
29. COVID-19 Pandemic	
30. COVID 19 Pandemic	
31. COVID-19 Pandemics	
32. Pandemic, COVID-19	

MeSH term: Blood group antigens	
Entry term	**Synonym term**
1. Antigens, Blood Group	1. Blood Group
2. Blood Group Antigen	2. Blood Type
3. Antigen, Blood Group	3. Blood Group Antigens
4. Group Antigen, Blood	

interpretation, limitations, and funding. If any of these items were mentioned in the article, the article was given a score of 1; otherwise, the article was given a score of 0. Therefore, the final score of the methodologic quality of each article was within the range of 0–10, with higher scores indicating higher methodologic quality. Scores within the range of 0–4, 5–7, and 8–10 were interpreted as low, moderate, and high quality, respectively.[12]

Data Analysis

To investigate the relationship between COVID-19 infection and ABO blood groups, the odds ratio (OR) and 95 percent confidence interval (CI) were calculated for each study; all selected studies were then combined to obtain a pooled OR. Heterogeneity between studies was assessed using the I^2 index; in studies with an I^2 index >30 percent, the random effects model was used; otherwise, the fixed effects model was used.[13,14] Subgroup analysis was also conducted to investigate the potential source of heterogeneity based on studies conducted on different continents. Sensitivity analysis was performed using the leave-one-out method. Accordingly, the sensitivity of the overall result for each blood group was determined by deleting one study each time and comparing the pooled OR resulting from the removal of that study with the overall pooled OR. The publication bias of the studies was also examined using Egger's regression test; values of $p < 0.1$ for this test were considered significant. All analysis were performed using R software version 4.3.2 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

In the initial search, 538 articles were identified. Of these articles, 84 duplicate articles were removed, and the titles and abstracts of the remaining 454 articles were reviewed. Non-observational articles (138 studies) and irrelevant studies (259 studies) were excluded, and the full text of the remaining 57 articles was reviewed again. Irrelevant studies refer to qualitative review studies and letters to the editor. An additional 28 studies were excluded due to lack of a control group, and two studies were published in Spanish. Thus, 27 eligible studies were included in the final analysis (Fig. 1).

In total, 27 articles with a sample size of 23,285 individuals were included in the final analysis. There were 16 studies from Asia,[1,2,7,15–27] four studies from Europe,[28–31] three studies from the United States,[32–34] and four studies from Africa.[35–38] There were four studies from Turkey[2,18,22,26] and three studies from China.[7,19,27] More details are provided in Table 2. Blood group A frequency varied from 19.5 to 63 percent in case subjects and from 21 to 65 percent in control subjects. Blood group B frequency varied from 8.5 to 36 percent in case subjects and from 5 to 32 percent in control subjects. Blood group AB frequency ranged from 1.5 to 20 percent in case subjects, and from 2 to 14 percent in control subjects, and blood group O frequency varied from 19.5 to 59 percent in case subjects and from 9.5 to 60.5 percent in control subjects. In terms of methodologic quality, all included articles met PRISMA/STROBE recommendations for methodologic quality.

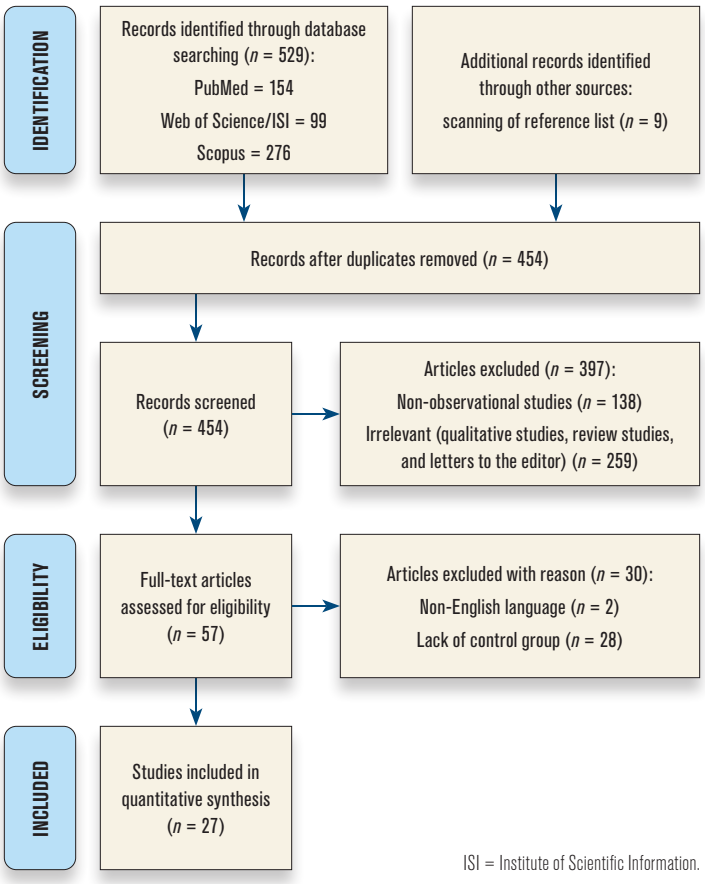

Fig. 1 Flow diagram for the literature search according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

A meta-analysis of the relationship between COVID-19 infection (positive SARS-CoV-2 infection) and blood group A (case) using a random effects model showed that the odds of COVID-19 in individuals with blood group A (case) were significantly higher than in individuals with blood group non-A (control) (OR 1.26, 95% CI 1.13–1.40, p <0.0001) (Fig. 2). In other words, individuals with blood group A had a

Table 2. Characteristics of selected papers included in the final analysis

					Blood group							
		Sample size			Patients with COVID-19 (%)				Patients without COVID-19 (%)			
First author	Year	Case	Control	Country	A	B	AB	O	A	B	AB	O
Abdollahi[1]	2020	397	500	Iran	40.30	22.42	9.32	27.96	36.00	21.00	5.00	38.00
Ad'hiah[15]	2020	1014	901	Iraq	35.50	21.79	10.75	31.95	32.74	21.53	8.99	36.74
Ad'hiah[16]	2020	300	595	Iraq	28.67	26.67	19.67	25.00	31.26	23.87	10.42	34.45
Aktimur[2]	2020	179	5200	Turkey	62.01	9.50	8.94	19.55	46.55	12.24	6.53	34.67
Almadhi[17]	2020	2334	4985	Bahrain	21.98	27.59	5.01	45.42	21.91	24.57	7.06	46.46
Barnkob[28]	2020	7422	466,232	Denmark	44.41	12.09	5.09	38.41	42.73	11.33	4.46	41.48
de Freitas Dutra[32]	2021	430	2212	Brazil	46.05	12.09	4.19	37.67	64.77	18.65	6.93	9.65
El-Shitany[35]	2021	726	707	Egypt	35.54	24.79	11.57	28.10	29.28	23.06	11.88	35.79
Fan[7]	2020	105	103	China	42.86	26.67	8.57	21.90	29.13	31.07	10.68	29.13
Garibaldi[33]	2021	72	158	Brazil	51.39	15.28	1.39	31.94	30.38	17.72	3.16	48.73
Goker[18]	2020	186	1882	Turkey	56.99	10.75	7.53	24.73	38.04	14.72	9.99	37.25
Higazy[19]	2021	1175	3694	China	38.03	25.97	9.97	26.03	32.00	24.99	9.01	34.00
Kahlout[20]	2021	361	2943	Qatar	35.73	18.84	5.82	39.61	32.31	20.46	5.57	41.66
Khalil[21]	2020	146	6479	Lebanon	40.41	17.12	6.85	35.62	35.84	19.02	5.43	39.71
Kirisci[22]	2021	455	7844	Turkey	44.40	19.34	6.59	29.67	40.85	16.57	6.97	35.61
Kotila[36]	2021	302	9138	Nigeria	19.53	25.93	5.72	48.82	22.96	19.38	3.36	54.30
Lehrer[34]	2021	720	11,855	USA	44.86	9.17	3.19	42.78	43.80	9.89	3.44	42.87
Mahallawi[23]	2021	234	978	Saudi Arabia	50.00	13.68	3.85	32.48	29.04	22.60	4.70	43.66
Muñoz-Culla[29]	2021	412	17,796	Spain	48.30	8.74	3.88	39.08	40.66	5.16	1.99	52.19
Nzoghe[37]	2021	127	1032	South Africa	21.26	18.11	1.57	59.06	20.83	15.70	2.81	60.66
Negro[30]	2021	167	891	Italy	46.11	8.98	3.59	41.32	39.17	13.02	4.94	42.87
Paleiron[31]	2021	1279	409	France	41.25	10.69	4.28	43.78	37.68	11.82	3.94	46.55
Rahim[24]	2021	1935	1935	Pakistan	27.03	35.87	11.78	25.32	28.79	31.89	14.21	25.12
Saify[25]	2021	301	1036	Afghanistan	37.21	20.27	9.97	32.56	31.85	23.46	8.30	36.39
Taha[38]	2020	557	1000	Sudan	32.32	18.31	6.10	43.27	27.20	19.10	3.40	50.30
Uyuklu[26]	2020	174	36,394	Turkey	42.53	19.54	8.05	29.89	40.30	19.34	8.48	31.88
Zhao[27]	2020	1775	3694	China	37.75	26.42	10.03	25.80	32.16	24.91	9.10	33.84

significantly increased risk of COVID-19 infection compared with individuals with blood group non-A. Heterogeneity (I^2 index) was high among these studies (I^2 = 78%, $p < 0.0001$). In the subgroup analysis, blood group A was compared with non–group A, and the findings showed that the grouping of studies by continents was heterogeneous (OR 1.27, 95% CI 1.13–1.43, for Asia; OR 1.27, 95% CI 1.97–1.65, for the United States; OR 1.26, 95% CI 1.07–1.49, for Europe; OR 1.02, 95% CI 0.64–1.62, for Africa; $p = 0.839$). Sensitivity analysis using the leave-one-out method showed the stability of the findings, and none of the studies alone had a significant effect on the pooled OR. Publication bias based on Egger's regression asymmetry test was also significant ($p = 0.0107$) (Fig. 3).

The results of the random effects model showed that the relationship between COVID-19 infection and blood group B individuals (OR 1.05, 95% CI 0.99–1.12) was not significant. According to the I^2 value, the distribution of blood group B individuals had a relatively heterogeneous structure (I^2 = 45%). The results of subgroup analysis showed homogeneity between studies conducted in the United States and those in other continents (I^2 = 0%), and most heterogeneity was related to studies conducted in Europe and Africa. In all subgroups, in accordance with the overall conclusion, there was no significant

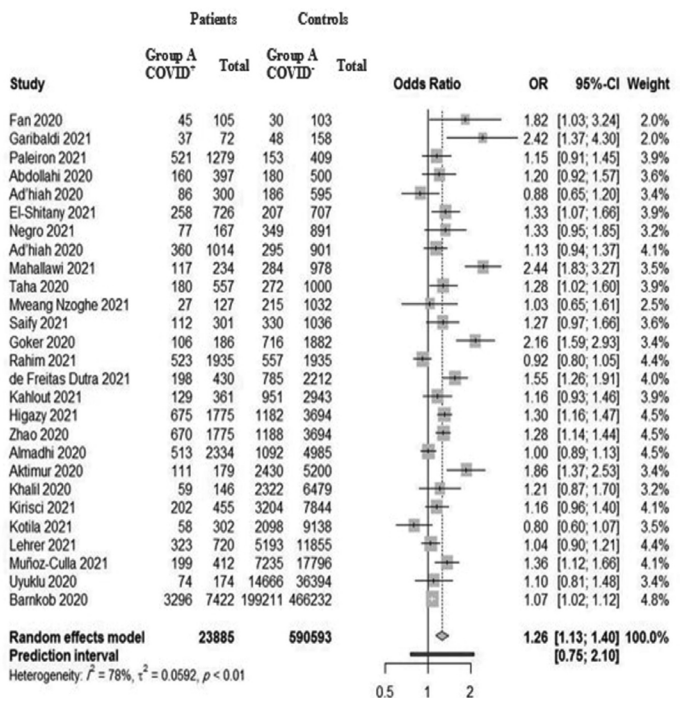

Fig. 2 Forest plot for the association between patients with blood group A and COVID-19 infection using random effects model with diamond representing pooled odds ratio (OR) estimate along with its corresponding 95 percent confidence interval (CI).

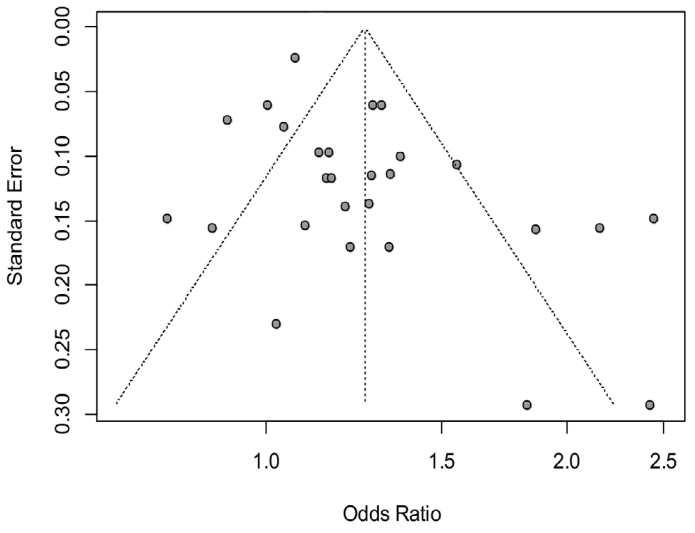

Fig. 3 Funnel plot to test publication bias for the association between blood group A and COVID-19 infection with no publication bias indicated by symmetry around the vertical line.

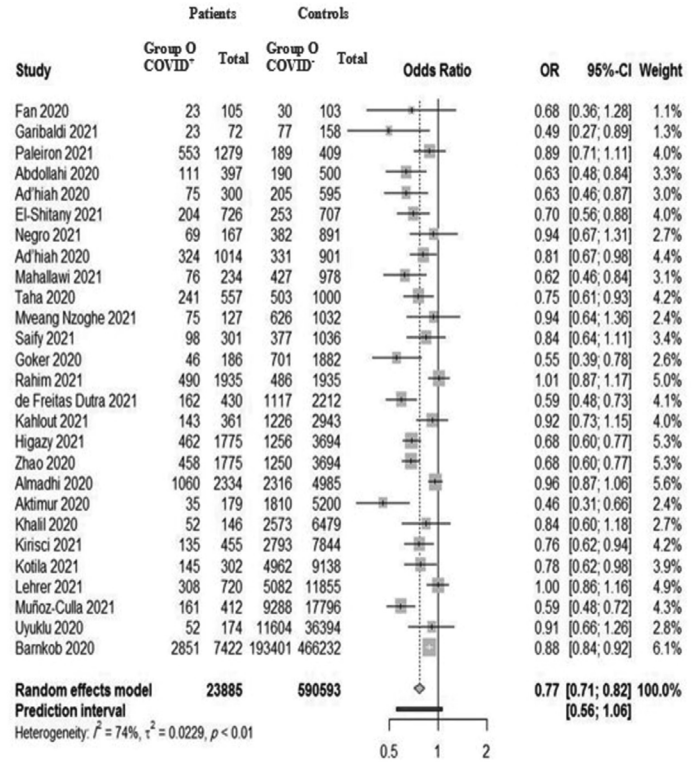

Fig. 4 Forest plot for the association between blood group O and COVID-19 infection using random effects model with diamond representing pooled odds ratio (OR) estimate along with its corresponding 95 percent confidence interval (CI).

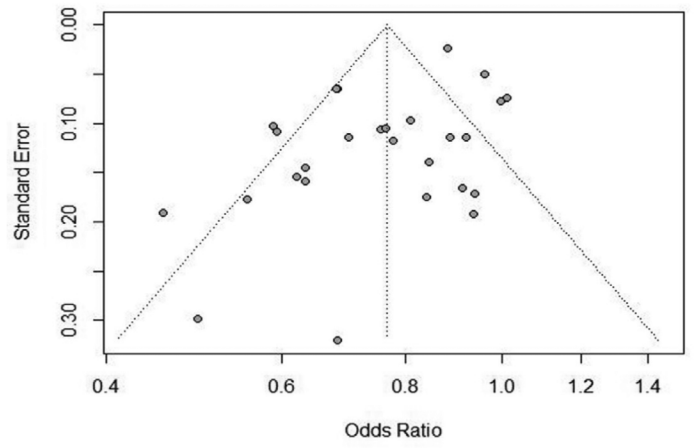

Fig. 5 Funnel plot to test publication bias for the association between blood group O and COVID-19 infection with no publication bias indicated by symmetry around the vertical line.

relationship between blood group B and COVID-19 infection. The publication bias of studies was also significant for blood group B (p = 0.096). The results of sensitivity analysis were also consistent with the main analysis.

Relatively high heterogeneity was observed also in the blood group AB individuals (I^2 = 61%). Using the random effects model, there was no significant relationship between COVID-19 infection and blood group AB (OR 1.11, 95% CI

0.99–1.25). The result of subgroup analysis also showed that across all continents, except for Africa, there was no significant relationship between COVID-19 infections and blood group AB individuals. According to subgroup analysis, there was a significant heterogeneity among studies conducted in Asia (I^2 = 67%) compared with other continents. The result of Egger's regression test based on funnel plot showed that publication bias in this blood group was not significant (p = 0.519). Although there was significant heterogeneity in individuals with blood group AB, the studies had comparable weights, and removing a study had no effect on the pooled OR.

According to the random effects model, the pooled estimate of OR for blood group O individuals compared with non–group O blood individuals was significantly associated with reduced COVID-19 risk (OR 0.77, 95% CI 0.71–0.82) (Fig. 4). In other words, patients with COVID-19 infection were less likely to have blood group O. There was a relatively high heterogeneity for this blood group (I^2 = 67%). The results of the subgroup analysis of continents to delineate this heterogeneity showed that there was a significant relationship between COVID-19 infection and blood group O individuals in all countries except the United States. Publication bias relates to the tendency to decide to publish a study based on its results (direction and strength) being significant or not but not based on its methodologic quality. The publication bias was significant for blood group O individuals (p = 0.014) (Fig. 5), and this result implies that some articles were published based on their findings, which may have had an impact on the pooled estimate. The result of sensitivity analysis was also in agreement with overall analysis, so that the removal of none of the studies alone had a significant effect on the pooled OR. Finally, according to meta-regression, our results revealed that year of publication (2020 vs. 2021) was not significant (p = 0.135).

Discussion

Our aim was to investigate the relationship between ABO blood groups and COVID-19 infection. The results of this study showed that the odds of infection in individuals with blood group A (case) was significantly higher than those with other blood groups (control). Also, individuals with blood group O compared with those with non–group O was significantly associated with a risk reduction in COVID-19 infection. The relationship between blood group and probability of SARS was reported for the first time in 2005 by Cheng et al.[9] Because of the genomic similarity between SARS-CoV-2 and SARS, the hypothesis of the protective role of anti-A and antibodies against COVID-19 has been raised, although clinical evidence in this field is still controversial.[10] The relationship between infections and diseases with blood groups has always been considered by researchers. Previous studies have shown that individuals with blood groups A and AB are susceptible to malaria, and blood group O provides resistance to several protozoal infections.[35] People with blood group A are vulnerable to neuroviruses and have a higher prevalence of *Helicobacter pylori,* but are less vulnerable to SARS and hepatitis B.[39] These individuals are susceptible to sepsis and acute respiratory distress syndrome (ARDS).[40] The results of Murugananthan et al.[41] showed that the risk of dengue hemorrhagic fever in people with blood group AB is about 2.5 times that in individuals with other blood groups. Also, the chance of developing rotavirus gastroenteritis in blood group A individuals is higher than in those with blood group B.[42] Individuals with blood groups A, B, and AB are more susceptible to thrombosis and myocardial infarction, while people with blood group O are more susceptible to high blood pressure.[43] Group A and AB individuals are more likely to be at risk for metabolic disorders such as hyperlipidemia and diabetes because of the presence of the A antigen.[44]

The results of a recent meta-analysis showed that most patients with SARS-CoV-2 have blood group A, and the chance of COVID-19 infection in individuals with blood group A was significantly higher than in individuals with other blood groups (OR 1.23),[45] which is in line with the results of the current study. Similar to the results of this study, results in a meta-analysis performed on 21 related articles revealed that the odds of COVID-19 infection in people with blood group O was less than in people with other blood groups (OR 0.81).[39] In the meta-analysis of Kabrah et al.,[46] performed on 16 studies, there was a significant correlation between COVID-19 infection and blood group; the rate of COVID-19 infection was reported in blood groups as follows: A > O > B > AB.[46] In the meta-analysis of Pourali et al.,[47] four studies were investigated, and the highest rate of COVID-19 infection was observed in those individuals with blood group A. To obtain the best estimates, a careful review of the selected studies was conducted to ensure that the studies selected for final analysis had control groups who were properly selected and were not blood donors.

The limitation of this study was exclusion of articles that did not report all the information needed for the full analysis. Another limitation of this study was that the association between the severity of COVID-19 disease and blood group

was not investigated. On the other hand, this study reports newer, more complete, and more updated studies compared with previous meta-analysis studies.

Conclusion

This study builds on the current literature establishing a link between ABO blood group and COVID-19 infection. The results of this study indicated a significant association between individuals with blood group A and COVID-19 infection, while blood group O individuals demonstrated lower incidence of infection. Because of the severity of COVID-19 and its unpredictable nature and severity, identifying risk factors associated with this infection, such as blood group, can help identify people at increased risk of infection.

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This study was not funded by any private or public sector.

Conflict of Interest

All authors declare that they have no conflict of interest.

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