Systematic review and meta-analysis of the effect of ABO blood group on the risk of COVID-19 infection

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1 Abstract

We have been experiencing a global pandemic with baleful consequences for mankind, since the Severe Acute Respiratory 2 Syndrome Coronavirus 2 (SARS-CoV-2) was first identified in Wuhan of China, in December 2019. So far, several potential 3 risk factors for SARS-CoV-2 infection have been identified. Among them, the role of ABO blood group polymorphisms has 4 been studied with results that are still unclear. The aim of this study was to collect and meta-analyze available studies on the 5 relationship between SARS-CoV-2 infection and different blood groups, as well as Rhesus state. We performed a systematic 6 search on PubMed/MEDLINE and Scopus databases for published articles and preprints. Twenty-two studies, after the removal 7 of duplicates, met the inclusion criteria for meta-analysis with ten of them also including information on Rhesus factor. The 8 odds ratios (OR) and 95% confidence intervals (CI) were calculated for the extracted data. Random-effects models were used 9 to obtain the overall pooled ORs. Publication bias and sensitivity analysis were also performed. Our results indicate that blood 10 groups A, B and AB have a higher risk for COVID-19 infection compared to blood group O, which appears to have a protective 11 effect. An association between Rhesus state and COVID-19 infection could not be established. 12

13 Introduction

¹⁴ Coronaviruses (COVs) are enveloped viruses with a single positive-stranded RNA genome. They belong

to the subfamily Orthocoronavirinae under the family Coronaviridae and are classified into four genera:

16 Alphacoronaviruses (α), Betacoronaviruses (β), Gammacoronaviruses (γ) and Deltacoronaviruses (δ).

¹⁷ The viral genome normally encodes four structural proteins, spike (S), envelope (E), membrane (M),

and nucleocapsid (N) (Ren et al. 2020). The term *coronavirus* refers to the appearance of CoV visions,

¹⁹ when observed under electron microscopy, in which spike projections from the virus membrane, give

the semblance of a crown, or corona in Latin (Su et al. 2016). To date, seven human CoVs (HCoVs) are

21 known. Among them, HCoV-229E and HCoV-NL63 are alpha-CoVs. The other five beta-CoVs include

HCoV-OC43, HCoV-HKU1, Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), Middle
 East Respiratory Syndrome Coronavirus (MERS-CoV) and Severe Acute Respiratory Syndrome Coro-

²⁴ navirus 2 (SARS-CoV-2) (Ye et al. 2020). In December 2019, a human outbreak of pneumonia, later

²⁵ named coronavirus disease (COVID-19), began spreading across the planet, infecting millions. The

causative agent of COVID-19 was quickly identified as a novel coronavirus, the Severe Acute Respira-

27 tory Syndrome Coronavirus 2 (SARS-CoV-2). Although close evolutionary relationships to bat CoVs

²⁸ suggest a bat origin for SARS-CoV-2, our understanding is notably limited by the scarcity of avail-

²⁹ able sequenced CoV genome (Banerjee et al. 2021). As a novel beta coronavirus, SARS-CoV-2 shares

³⁰ 79% genome sequence identity with SARS-CoV and 50% with MERS-CoV. Its genome organization is

³¹ shared with other beta coronaviruses (Hu et al. 2021).

The spike protein S appears to be critical for cellular entry because it guides the virus to attach to the 32 host cell. The receptor-binding domain (RBD) of the spike protein S binds to Angiotensin-Converting 33 Enzyme 2 (ACE2) to initiate cellular entry (Pillay 2020). The SARS-CoV-2 virus typically causes respi-34 ratory and gastrointestinal sickness. It can be transmitted through aerosols and direct or indirect contact, 35 as well as during medical cases and laboratory sample handling. The disease is characterized by symp-36 toms such as high fever, chills, cough, breathing difficulty, diarrhea, myalgia, fatigue and may occasion-37 ally lead to complications like pneumonia, severe acute respiratory syndrome (SARS) and eventually 38 death (Pal et al. 2020). 39

After the ABO blood group system was found by Karl Landsteiner in 1901, the search for the relationship between blood groups and various diseases has continued uninterrupted (Wu et al. 2020). Recently, several studies have reported an association between blood group and SARS-CoV-2 infection. However, results are conflicting, perhaps due to the potential effect of multiple confounding effects, and controversy remains with respect to the role of blood type on COVID-19 infection (Liu et al. 2020). We performed a meta-analysis to assess the association between ABO blood groups, Rhesus state and COVID-19 infection.

47 Materials and Methods

48 Search strategy

49 A systematic online search for published literature was carried out in PubMed/MEDLINE and Scopus

⁵⁰ databases, including unpublished articles, with the MESH (medical subject heading) terms 'ABO blood

⁵¹ groups' and 'COVID-19'. In order to expand our search scale, we also conducted a full-text search

⁵² with the relevant terms ('SARS-CoV-2 infection', '2019-nCoV infection', 'novel coronavirus infec-

tion' and 'ABO polymorphisms"). The searching time period was restricted between February 1st 2021

to March 7th 2021 and we limited the search language to English, with no restrictions on country or pub-

55 lication state.

56 Study selection

We included the studies that fulfilled the following inclusion criteria: i) studies that reported an association between COVID-19 infection and ABO blood groups and/or Rhesus state; ii) case-control and cohort studies; iii) provision of original data. Excluded studies included: (i) reviews, clinical guidelines, and expert consensus; (ii) animal or in vitro cell studies; (iii) studies for which the full text was not available; (iv) studies with insufficient data.

62 Data extraction

Data extraction included: first author's name, publication year, title and the link of the study, case def-63 inition, the distribution numbers of participants for each blood group (along with Rhesus state, when 64 there was a record) and for both, SARS-CoV-2 infected and uninfected subjects. For each study, a 65 numerical ID was used. Infection was confirmed by Polymerase Chain Reaction (PCR) and/or clini-66 cal diagnosis, although for several studies the confirmation method for SARS-CoV-2 infection was not 67 specified. Some studies included more than one group of controls, along with the corresponding pop-68 ulation of cases, while other studies reported more than one group of controls and cases. We included 69 in the analysis all the comparisons regarding different subgroups of controls and cases, in order to avoid 70 any overlapping. 71

72 Statistical analysis

For each study, we extracted the cross-classified frequencies between infection state and blood group. 73 We used logistic regression for deriving Odds Ratios (ORs) and their asymptotic standard errors, after 74 adjusting for multiplicity using the Benjamin-Hochberg procedure (Benjamini and Hochberg 1995). We 75 assessed heterogeneity using the I-squared statistic. Publication bias was assessed by visual inspection 76 of the funnel plots and further validated by Egger's test (Egger et al. 1997). Pooled ORs estimates and 77 95% confidence intervals (CIs) were obtained by performing meta-analysis using the inverse variance 78 method. Due to the amount of heterogeneity a random-effects model has been used for the ABO gene, by 79 applying the Hartung-Knapp-Sidik-Jonkman method (IntHout et al. 2014) for τ^2 . The 95% prediction 80 intervals (PIs) were also computed. The PIs present the heterogeneity in the same metric as the original 81

effect size measure, illustrating which range of true effects can be expected in future settings (IntHout

et al. 2016). We explored the robustness of our meta-analysis results using the leave-one-out method.

84 Software

⁸⁵ All models were run in R v4.0 (R Core Team 2020) using the meta package (Schwarzer and others ⁸⁶ 2007)

Results

88 Literature search

The literature search of the PubMed/MEDLINE and Scopus databases resulted in 589 potentially relevant studies (PubMed records=389 and Scopus records=200). The 351 of them were removed because they were duplicates. According to the inclusion criteria, we excluded the 216 irrelevant studies by screening abstract and title. Eventually, a total of 22 articles (GÖKER et al. 2020; Hoiland et al. 2020; Ad'hiah et al. 2020; Solmaz and Araç 2021; Taha et al. 2020; Dzik et al. 2020; Zalba et al. 2020; Chegni et al. 2020; Franchini et al. 2021; Gamal et al. 2021; Wu et al. 2020; Khalil et al. 2020; El-Shitany et al. 2021; Valenti et al. 2020; Muñiz-Diaz et al. 2021; Kibler et al. 2020; Barnkob et al. 2020; Bhandari et

⁹⁶ al. 2020; Rahim et al. 2021; Abdollahi et al. 2020; Fan et al. 2020; Boudin et al. 2020) were included in

⁹⁷ this systematic review and meta-analysis (Figure 1).

98 Study characteristics

Twenty-two studies were identified, meeting our inclusion criteria for meta-analysis, with the majority 99 of them being case-control studies. All studies were published in 2020, except for five studies that 100 were published in 2021. Half of the studies were carried out in Europe and North America while the 101 other half in Asia and Africa. A total of 84,659,546 subjects were included in this meta-analysis, with 102 21,462 COVID-19 infected subjects and 84,638,084 uninfected subjects. Among them, 147,302 subjects 103 were positive for Rhesus state and 20,313 negative. Most of the participants were adult males, forty to 104 seventy years old. In most of the studies, COVID-19 diagnosis was confirmed by a PCR test, using nasal 105 or pharyngeal swab specimens. The main characteristics of the studies are listed in Table 1. 106

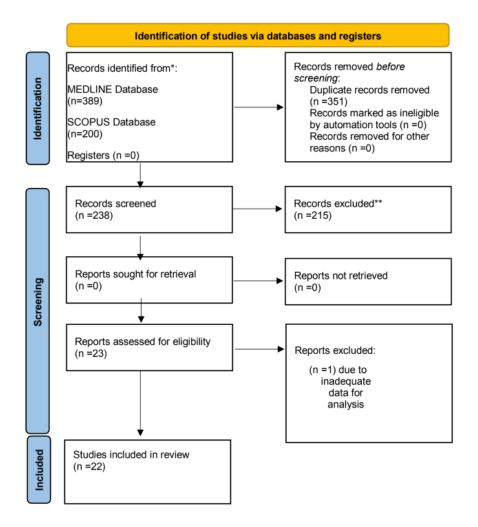
107 Association between blood groups and COVID-19 infection

Meta-analysis for the ABO group (Table 2 and Figures 2-7), revealed increased odds of COVID-19 infection in the (i) A group vs O (OR = 1.29, 95% Confidence Interval: 1.15 to 1.44), (ii) B vs O (OR = 1.15, 95% CI 1.06 to 1.25), and (iii) AB vs. O (OR = 1.32, 95% CI 1.10 to 1.57). Prediction intervals include the reference value of 1 for the OR in all pairwise comparisons. The visual inspection of the funnel plots (Fig. 8) and the results of Egger's test showed some evidence of publication bias for the

113 comparison between of A vs. O (p=0.013) and A vs. B (p=0.047). Sensitivity analysis by the leave-one-

¹¹⁴ out method provided similar estimates (Supplementary Files).

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

Figure 1: The PRISMA flow-chart

115 Association between Rhesus status and COVID-19 infection

¹¹⁶ Meta-analysis of the association between Rhesus state and COVID-19 infection (Figures 9 and 10) in

the 10 studies that included information on Rhesus, did not provide evidence of association with the

118 COVID-19 infection (Rh+ vs Rh- OR = 0.97, 95% CI 0.83 to 1.13). The 95% PI includes the reference

value of 1 for the OR in all pairwise comparisons. The leave-one-out sensitivity analysis provided

similar estimates (Supplementary Files). Visual inspection of the funnel plot (Figure 5) and the results

¹²¹ of Egger's test (p=0.618) showed no evidence of publication bias.

Study Year	Coun- try	Study Design	Sample Size (case/control)	Rhesus Status (posi-	Age. years	Male% (Case/Contr	Patients ol)	Controls
Boudin et al, 2020	France	Retro- spective Cohort	1263/406	tive/negative) 1439/230	Median Age (IQR): 28(23- 36)/27(23-33)	87/87	Patients with COVID-19 confirmed by RT-PCR or clinical symptoms suggestive to covid-19	Tested negative for COVID-19 or no clinical symptoms
Fan et al. 2020	China	Retro- spective Case- Control	105/103	ND	Mean Age±SD: (56.8±18.3)/(54.0±15.	52.4/54.4 (0)	Patients with COVID-19 confirmed by RT-PCR or clinically diagnostic cases	Tested negative for COVID-19 or no clinical symptoms
Abdol- lahi et al. 2020	Iran	Cross- Sectional	397/500	802/95	Mean Age (SD): 58.81 (15.4)/48.53 (17.9)	63.5/46.2	Patients with COVID-19 confirmed by RT-PCR	Healthy population
Rahim et al. 2021	Pak- istan	Cross- Sectional	1935/1935	ND	Mean Age ±SD: (39.73±15.26)/(32.36=	68.6/67.7 ±8.65)	Patients with COVID-19 confirmed by RT-PCR	Healthy blood donors
Bhan- dari et al. 2020	USA	Retro- spective Case- Control	825/396	1160/61	Mean Age ±SD: (57.64±18.17)/(54.21=	61/44 ±20.99)	Patients with COVID-19 confirmed by RT-PCR	Patients who were hospitalized without COVID-19
Barnkob et al. 2020	Den- mark	Retro- spective Cohort	7422/466232 7422/2204742	ND	Median Age (IQR): 52 (40-67)/50 (36-64)	32.9/32	Patients with COVID-19 confirmed by RT-PCR	Tested negative for COVID-19/ Healthy population
Kibler et al. 2020	France	Retro- spective Cohort	22/680	352/350	($(30-04)$) Mean Age ±SD: ($(82\pm8.4)/(82\pm6.9)$	31.8/45	Patients with COVID-19 confirmed by RT-PCR/ patients with typical symptoms and characteristic imaging findings on chest computed tomography (CT)	Patients who were hospitalized without COVID-19
Muniz- Diaz et al. 2021	Spain	Retro- spective Cohort	854/75870 965/52584	ND	Median Age (IQR): 45.0 (36.0-53.0)/45.0 (32.0-53.0)	39.5/51.5 59.07/49.85	COVID-19 blood donors confirmed by RT-PCR /transfused patients with COVID-19	Healthy blood donors/Patients transfused without COVID-19
Valenti et al. 2020	Italy	Case- Control	505/890 505/18097	ND	Median Age (IQR): 69.0 (59.0-77.0)/72.1 (58.2-82.5)	ND	COVID-19 patients. confirmation method was not specified	Healthy blood donors/transfused patients
El- Shitany et al. 2021	Saudi Arabia and Egypt	Retro- spective Cross- Sectional	726/707	1185/248	ND	15.2/16.5	COVID-19 recovered patients. confirmed by RT-PCR or biochemical and clinical symptoms	Healthy population
Khalil et al. 2020	Lebanon	Retro- spective Case- Control	146/6479	ND	Mean Age ±SD. (IQR): (41.9±18.52). (28-57) CO	66.4 CO	Patients with COVID-19 confirmed by RT-PCR	Patients who were hospitalized without COVID-19
Wu et al. 2020	China	Retro- spective Case- Control	187/1991	ND	[?]40: 63.1% CO	51.9 CO	Clinically diagnosed COVID-19 patients	Patients who were hospitalized without COVID-19
Gamal et al. 2020	Italy	Retro- spective Case- Control	1600/27715	25206/4104	ND	ND	Patients with COVID-19 confirmed by RT-PCR	Healthy blood donors
Fran- chini et al. 2021	Italy	Case- Control	447/16911	ND	Mean Age ±SD: (477±121)/(471±143)	86.1/61.0	Blood donors clinically recovered from COVID-19	Healthy blood donors
Chegni et al. 2020	Iran	Case- Control	76/80982137	ND	¿59: 53.2% CO	77.7 CO	COVID-19 patients. confirmation method was not specified	Healthy population
Zalba- Marcos et al.	Spain	Retro- spective Cohort	225/182384	ND	Mean Age (SD) of 44% 70.1(15.1) CO	64 CO	Patients with COVID-19 confirmed by RT-PCR	Healthy population
2020 Dzik et al. 2020	USA	Case- Control	957/5840	ND	ND	ND	Patients with COVID-19 confirmed by RT-PCR	Patients who were hospitalized without COVID-19
Taha et	Sudan	Case-	557/1000	1422/135	(26-35): 41.8%	42 CO	Patients with COVID-19 confirmed by RT-PCR	Healthy population
al. 2020 Solmaz et al.	Turkey	Control Cross- Sectional	1667/127091	113868/14980	CO ND	ND	Patients with COVID-19 confirmed by RT-PCR	Healthy population
2021 Ad'hiah et al.	Iraq	Case- Control	300/595	ND	Mean Age ±SD: (49.7±12.3/29.3±6.9)	59.7/49.7	Patients with COVID-19 confirmed by RT-PCR	Healthy blood donors
2020 Hoiland et al. 2020	Canada	Retro- spective Cohort	95/398671 95/62246	ND	Median Age (IQR) of 60%: 66 (58-73) CO	64.2 CO	Patients with COVID-19 confirmed by RT-PCR	Healthy blood donors
Goker et al. 2020	Turkey	Retro- spective Case- Control	186/1882	1868/200	(58-73) CO Median Age (IQR): 42 (19-92) CO	53.8 CO	Patients with COVID-19 confirmed by RT-PCR	Healthy blood donors

Table 1: Characteristics of the included studies

Comparison	OR	95% CI	95% PI	I2	95% CI
A - AB	0.98	(082 to 117)	(048 to 198)	0.25	(0 % to 56 %)
A - B	1.1	(098 to 123)	(067 to 179)	0.26	(0 % to 56 %)
A - O	1.29	(115 to 144)	(079 to 21)	0.54	(25 % to 71 %)
AB - B	1.11	(096 to 127)	(066 to 186)	0.03	(0 % to 48 %)
AB - O	1.32	(110 to 157)	(067 to 259)	0.41	(2 % to 65 %)
B - O	1.15	(106 to 125)	(087 to 153)	0	(0 % to 38 %)
Rh+ vs. Rh-	0.97	(083 to 113)	(061 to 154)	0.38	(0 % to 70 %)
	A - AB A - B A - O AB - B AB - O B - O	A - AB 0.98 A - B 1.1 A - O 1.29 AB - B 1.11 AB - O 1.32 B - O 1.15	A - AB 0.98 (082 to 117) A - B 1.1 (098 to 123) A - O 1.29 (115 to 144) AB - B 1.11 (096 to 127) AB - O 1.32 (110 to 157) B - O 1.15 (106 to 125)	A - AB 0.98 (082 to 117) (048 to 198) A - B 1.1 (098 to 123) (067 to 179) A - O 1.29 (115 to 144) (079 to 21) AB - B 1.11 (096 to 127) (066 to 186) AB - O 1.32 (110 to 157) (067 to 259) B - O 1.15 (106 to 125) (087 to 153)	A - AB 0.98 (082 to 117) (048 to 198) 0.25 A - B 1.1 (098 to 123) (067 to 179) 0.26 A - O 1.29 (115 to 144) (079 to 21) 0.54 AB - B 1.11 (096 to 127) (066 to 186) 0.03 AB - O 1.32 (110 to 157) (067 to 259) 0.41 B - O 1.15 (106 to 125) (087 to 153) 0

Table 2: Meta-analysis result	S
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Study	TE	seTE		Odds Ratio		OR	95	5%-CI	Weight
Ad'hiah et al. 2020	-0.72	0.3012				0.49	[0.27;	0.88]	5.1%
Valenti et al. 2020	-0.65	0.3533				0.52	[0.26;	1.04]	4.4%
Zalba-Marcos et al. 2020	-0.53	0.4471	-	-		0.59	[0.24;	1.41]	3.3%
Abdollahi et ai. 2020	-0.51	0.3779				0.60	[0.29;	1.26]	4.0%
Taha et al. 2020	-0.41	0.3512				0.66	[0.33;	1.32]	4.4%
Dzik et al. 2020	-0.19	0.2423		-		0.82	[0.51;	1.32]	6.1%
Franchini et al. 2021	-0.17	0.2951				0.85	[0.47;	1.51]	5.2%
Khalil et al. 2020	-0.11	0.4667				0.89	[0.36;	2.23	3.1%
Barnkob et al. 2020	-0.09	0.0738		-+-		0.91	[0.79;	1.05	9.0%
Muniz-Diaz et al. 2021	-0.07	0.2489		-		0.94	[0.57;	1.52]	6.0%
Solmaz et al. 2021	-0.02	0.1193		- ÷		0.98	[0.78;	1.24]	8.3%
Boudin et al. 2020	0.01	0.4026				1.01	[0.46;	2.22]	3.8%
Gamal et al. 2020	0.10	0.1862		- 		1.10	[0.77;	1.59]	7.1%
Rahim et al. 2021	0.12	0.1458		÷		1.13	[0.85;	1.51]	7.9%
El-Shitany et al. 2021	0.22	0.2427				1.25	[0.77;	2.01]	6.1%
Hoiland et al. 2020	0.28	0.8098			-	1.33	[0.27;	6.49]	1.3%
Kibler et al. 2020	0.47	1.4112				1.60	[0.10; 2	25.45]	0.5%
Wu et al. 2020	0.58	0.4100		-		1.79	[0.80;	4.00]	3.7%
Fan et al. 2020	0.61	0.6831			-	1.83	[0.48;	6.99]	1.8%
Goker et al. 2020	0.69	0.3983		-		1.99	[0.91;	4.34]	3.8%
Bhandari et al. 2020	0.77	0.4183		-		2.15	[0.95;	4.89]	3.6%
Chegni et al. 2020	0.79	0.7115			_	2.21	[0.55;	8.91]	1.6%
Random effects model						0.98	[0.82 :	1.171	100.0%
Prediction interval							[0.48;		
Heterogeneity: $I^2 = 25\%$, τ^2	= 0.10	71. p = 0.14					, ,		
		.,	0.1	0.5 1 2	10				

Figure 2: Forest pl	ots for the ABO gen	e comparison of A	vs. AB group
- Bare - Forest br		• • • • • • • • • • • • • • • • • • •	source group

Study	TE	seTE	(Odds Ratio	OF	8 9	5%-CI	Weight
Hoiland et al. 2020	-0.28	0.4063			0.70	6 [0.34;	1.68]	2.2%
Zalba-Marcos et al. 2020	-0.25	0.3374			0.78	3 [0.40]	1.51	2.9%
Dzik et al. 2020	-0.23	0.1483			0.79	0.59;	1.06	6.6%
Ad'hiah et al. 2020	-0.20	0.2573			0.8	2 [0.50;	1.36]	4.1%
Rahim et al. 2021	-0.18	0.1107			0.8	3 [0.67;	1.04]	7.5%
Franchini et al. 2021	-0.15	0.2090		<u> </u>	0.8			5.1%
Barnkob et al. 2020	-0.03	0.0511		+	0.9	0.88;	1.08	8.9%
Abdollahi et ai. 2020	0.05	0.2429		-	1.0	5 [0.65;	1.69]	4.4%
Muniz-Diaz et al. 2021	0.10	0.1810		÷	1.1	[0.78;	1.58]	5.7%
El-Shitany et al. 2021	0.12	0.1922		÷	1.1:	3 [0.77;	1.65	5.5%
Solmaz et al. 2021	0.13	0.0913		-+-	1.14	[0.95;	1.36]	8.0%
Boudin et al. 2020	0.19	0.2579		- <u>i</u> -	1.2	[0.73;	2.01]	4.1%
Gamal et al. 2020	0.20	0.1237			1.2	2 [0.95;	1.55]	7.2%
Taha et al. 2020	0.21	0.2097		<u>-</u>	1.24	[0.82;	1.87]	5.1%
Khalil et al. 2020	0.22	0.3247		- <u>i</u>	1.2	5 [0.66;	2.37]	3.1%
Wu et al. 2020	0.25	0.2473		-	1.2	0.79;	2.09]	4.3%
Valenti et al. 2020	0.28	0.2543		- <u>i</u>	1.3	3 [0.81;	2.19]	4.2%
Chegni et al. 2020	0.50	0.3998		<u>+</u>	1.6	5 [0.75;	3.61]	2.3%
Bhandari et al. 2020	0.53	0.2634		÷	1.69) [1.01;	2.84]	4.0%
Fan et al. 2020	0.54	0.4712		<u>+</u>	1.7	[0.68;	4.32]	1.8%
Goker et al. 2020	0.72	0.3417		<u>i — —</u>	2.0	5 [1.05;	4.01]	2.9%
Kibler et al. 2020	1.40	1.3956			4.04	[0.26; (62.21]	0.2%
Random effects model				þ	1.10	0.98;	1.23]	100.0%
Prediction interval						[0.67;	1.79]	
Heterogeneity: $I^2 = 26\%$, τ^2	= 0.05	22, <i>p</i> = 0.13						
			0.1	0.512	10			

Figure 3: Forest plots for the ABO gene comparison of A vs. B group

Study	TE	seTE		Odds Ratio		OR	95%-CI	Weight
Dzik et al. 2020	-0.16	0.1060		.		0.85	[0.69; 1.05]	6.4%
Rahim et al. 2021	-0.07	0.1189				0.93	[0.74; 1.18]	6.1%
Gamal et al. 2020	0.07	0.0745		-+-		1.07	[0.93; 1.24]	7.0%
Barnkob et al. 2020	0.12	0.0347		+		1.12	[1.05; 1.20]	7.6%
Zalba-Marcos et al. 2020	0.13	0.1924		- <u>H</u> -		1.14	[0.78; 1.66]	4.6%
Bhandari et al. 2020	0.14	0.2038				1.14	[0.77; 1.71]	4.4%
Boudin et al. 2020	0.15	0.1679				1.16	[0.84; 1.62]	5.1%
Hoiland et al. 2020	0.20	0.3098				1.22	[0.66; 2.24]	2.8%
Khalil et al. 2020	0.23	0.2589				1.26	[0.76; 2.09]	3.4%
Ad'hiah et al. 2020	0.23	0.2526		- 		1.26	[0.77; 2.07]	3.5%
Muniz-Diaz et al. 2021	0.25	0.0986				1.28	[1.06; 1.56]	6.6%
Franchini et al. 2021	0.27	0.1429		-		1.31	[0.99; 1.73]	5.6%
Taha et al. 2020	0.32	0.1669				1.38	[1.00; 1.92]	5.1%
Solmaz et al. 2021	0.36	0.0809		-+-		1.43	[1.22; 1.67]	6.9%
Valenti et al. 2020	0.37 (0.1652				1.45	[1.05; 2.01]	5.1%
Abdollahi et ai. 2020	0.42 (0.2174		<u> </u>		1.52	[0.99; 2.33]	4.1%
El-Shitany et al. 2021	0.44 (0.1784				1.55	[1.09; 2.19]	4.9%
Wu et al. 2020	0.61	0.2771		÷		1.85	[1.07; 3.18]	3.2%
Fan et al. 2020	0.67	0.4897				1.96	[0.75; 5.11]	1.4%
Chegni et al. 2020	0.70	0.3736		<u> </u>		2.02	[0.97; 4.21]	2.1%
Goker et al. 2020	0.81 (0.2482				2.26	[1.39; 3.67]	3.6%
Kibler et al. 2020	1.57 (0.8480				4.80	[0.91; 25.32]	0.5%
Random effects model				\$		1.29	[1.15; 1.44]	100.0%
Prediction interval					_		[0.79; 2.10]	
Heterogeneity: $I^2 = 54\%$, τ^2	= 0.052	6, <i>p</i> < 0.01			1			
			0.1	0.5 1 2	10			

Figure 4: Forest plots for the ABO gene comparison of A vs. O group

Study	TE	seTE	o	dds Ratio	D	OR	9	5%-CI	Weight
Hoiland et al. 2020	-0.56	0.8469				0.57	[0.11;	3.00]	1.0%
Wu et al. 2020	-0.33	0.4124				0.72	[0.32;	1.61]	3.4%
Rahim et al. 2021	-0.31	0.1417		-+-		0.74	[0.56;	0.97]	10.0%
Chegni et al. 2020	-0.29	0.7480	_			0.75	[0.17;	3.23]	1.3%
Bhandari et al. 2020	-0.24	0.4315				0.79	[0.34;	1.83]	3.2%
El-Shitany et al. 2021	-0.10	0.2536				0.91	[0.55;	1.49]	6.4%
Fan et al. 2020	-0.07	0.6981	-			0.94	[0.24;	3.67]	1.4%
Dzik et al. 2020	-0.04	0.2595		- ÷ -		0.96	[0.58;	1.60]	6.2%
Franchini et al. 2021	0.02	0.3357		- 		1.02	[0.53;	1.97]	4.6%
Goker et al. 2020	0.03	0.4860		_ 		1.03	[0.40;	2.67]	2.6%
Barnkob et al. 2020	0.07	0.0833		-+-		1.07	[0.91;	1.26]	12.1%
Gamal et al. 2020	0.10	0.2107		- 👘		1.10	[0.73;	1.67]	7.6%
Solmaz et al. 2021	0.15	0.1330				1.16	[0.89;	1.51]	10.4%
Muniz-Diaz et al. 2021	0.17	0.2925		- <u>+</u>		1.19	[0.67;	2.11]	5.4%
Boudin et al. 2020	0.18	0.4449		-		1.20	[0.50;	2.87]	3.0%
Zalba-Marcos et al. 2020	0.28	0.5264				1.33	[0.47;	3.72]	2.3%
Khalil et al. 2020	0.34	0.5102				1.40	[0.52;	3.81]	2.4%
Ad'hiah et al. 2020	0.52	0.3088		<u>-</u>		1.69	[0.92;	3.09]	5.1%
Abdollahi et ai. 2020	0.56	0.3988				1.75	[0.80;	3.82]	3.6%
Taha et al. 2020	0.63	0.3658				1.87	[0.91;	3.84]	4.1%
Kibler et al. 2020	0.92	1.9300				— 2.52	[0.06; 1	10.72]	0.2%
Valenti et al. 2020	0.94	0.4034		-	-	2.55	[1.16;	5.63]	3.5%
Random effects model				6		1.11	[0.96;	1.27]	100.0%
Prediction interval				_			[0.66;	1.861	
Heterogeneity: $I^2 = 3\%$, $\tau^2 =$	= 0.057	1, p = 0.42			I		-		
5 9		0.01	0.1	1	10	100			

Figure 5: Forest plots for the ABO gene comparison of B vs. AB group

Study	TE seTE	Odds Ratio	OR 95%-CI Weight	
Bhandari et al. 2020	-0.63 0.3979		0.53 [0.24; 1.16] 3.8%	
Rahim et al. 2021	-0.20 0.1482	=	0.82 [0.62; 1.10] 8.0%	
Chegni et al. 2020	-0.09 0.7343		0.92 [0.22; 3.86] 1.5%	
Hoiland et al. 2020	-0.09 0.8051		0.92 [0.19; 4.45] 1.3%	
Gamal et al. 2020	-0.03 0.1861	<u>+</u>	0.97 [0.68; 1.40] 7.3%	
Wu et al. 2020	0.03 0.4310		1.03 [0.44; 2.40] 3.4%	
Dzik et al. 2020	0.04 0.2379		1.04 [0.65; 1.65] 6.3%	
Fan et al. 2020	0.07 0.7108		1.07 [0.26; 4.30] 1.6%	
Goker et al. 2020	0.13 0.4255		1.13 [0.49; 2.61] 3.5%	
Boudin et al. 2020	0.14 0.3996	- <u>H</u> -	1.15 [0.53; 2.52] 3.8%	
Barnkob et al. 2020	0.21 0.0743	-+-	1.23 [1.07; 1.43] 9.3%	
El-Shitany et al. 2021	0.22 0.2433		1.24 [0.77; 2.00] 6.1%	
Muniz-Diaz et al. 2021	0.32 0.2501		1.37 [0.84; 2.24] 6.0%	
Khalil et al. 2020	0.34 0.4710		1.41 [0.56; 3.54] 3.0%	
Solmaz et al. 2021	0.38 0.1260		1.46 [1.14; 1.87] 8.5%	
Franchini et al. 2021	0.44 0.2991	+=-	1.55 [0.86; 2.78] 5.2%	
Zalba-Marcos et al. 2020			1.94 [0.81; 4.67] 3.2%	
Taha et al. 2020	0.74 0.3431	+ <u>+</u> -	2.09 [1.07; 4.09] 4.5%	
Abdollahi et ai. 2020	0.93 0.3838		2.53 [1.19; 5.38] 3.9%	
Ad'hiah et al. 2020	0.96 0.3048		2.60 [1.43; 4.73] 5.1%	
Valenti et al. 2020	1.03 0.3540		2.79 [1.40; 5.59] 4.3%	
Kibler et al. 2020	1.10 1.5800		— 3.00 [0.14; 66.37] 0.4%	
Random effects model		\$	1.32 [1.10; 1.57] 100.0%	
Prediction interval			[0.67; 2.59]	
Heterogeneity: $I^2 = 41\%$, τ^2	= 0.0984, p = 0.02			
		0.1 0.5 1 2 10		

Figure 6: Forest plots for the ABO gene comparison of O vs. AB group

Study	TE	seTE		Odds Ratio		OR	95	%-CI	Weight
Bhandari et al. 2020	-0.39	0.2298				0.68	[0.43;	1.06]	4.0%
Gamal et al. 2020	-0.12	0.1236		-		0.88	[0.69;	1.13	8.6%
Boudin et al. 2020	-0.04	0.2530		<u>+</u> ;		0.96	[0.59;	1.58	3.4%
Khalil et al. 2020	0.00	0.3309		-		1.00	[0.52;	1.92]	2.2%
Dzik et al. 2020	0.07	0.1410		÷		1.08	[0.82;	1.42]	7.5%
Valenti et al. 2020	0.09	0.2553		<u> </u>		1.09	[0.66;	1.81]	3.4%
Goker et al. 2020	0.10	0.3730		i		1.10	[0.53;	2.29]	1.8%
Taha et al. 2020	0.11	0.1959		- <u> </u>		1.11	[0.76;	1.64]	5.0%
Rahim et al. 2021	0.11	0.1139		÷		1.12	[0.89;	1.39]	9.2%
Fan et al. 2020	0.13	0.5104		ŧ		1.14	[0.42;	3.10]	1.0%
Barnkob et al. 2020	0.14	0.0520		+		1.15	[1.04;	1.28]	14.0%
Muniz-Diaz et al. 2021	0.14	0.1826		- -		1.16	[0.81;	1.65]	5.5%
Kibler et al. 2020	0.17	1.5661 ·				1.19	[0.06; 2	5.63]	0.1%
Chegni et al. 2020	0.21	0.4392				1.23	[0.52;	2.91]	1.3%
Solmaz et al. 2021	0.23	0.1000		֥		1.26	[1.03;	1.53]	10.2%
El-Shitany et al. 2021	0.31	0.1929		+ 12-		1.37	[0.94;	2.00]	5.1%
Wu et al. 2020	0.36	0.2807				1.43	[0.83;	2.49]	2.9%
Abdollahi et ai. 2020	0.37	0.2519		+ <u>+</u>		1.45	[0.89;	2.38]	3.4%
Zalba-Marcos et al. 2020	0.38	0.3380		- <u>+</u>		1.46			2.1%
Franchini et al. 2021	0.42	0.2147		÷=		1.52	[1.00;		4.4%
Ad'hiah et al. 2020	0.43	0.2615		÷		1.54	[0.92;	2.57]	3.2%
Hoiland et al. 2020	0.47	0.3968		- <u>+</u>		1.61	[0.74;	3.50]	1.6%
Random effects model				¢		1.15			100.0%
Prediction interval					_		[0.87;	1.53]	
Heterogeneity: $I^2 = 0\%$, $\tau^2 =$	0.017	0, <i>p</i> = 0.64	1		1				
			0.1	0.5 1 2	10				

Figure 7: Forest plots for the ABO gene comparison of B vs. O group

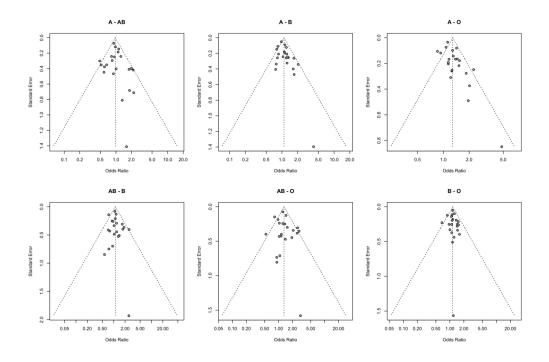


Figure 8: Funnel plots for the ABO gene

Study	TE seTE	Odds Ratio	OR	95%-CI Weight
Goker et al. 2020	-0.47 0.2259		0.63 [0	0.40; 0.98] 7.7%
Rahim et al. 2021	-0.29 0.1380		0.75 [0	0.57; 0.98] 12.2%
El-Shitany et al. 2021	-0.18 0.1401		0.83 [0	0.63; 1.10] 12.1%
Solmaz et al. 2021	0.02 0.0777	÷	1.02 [0	0.88; 1.19] 16.0%
Taha et al. 2020	0.08 0.1898		1.09 [0	0.75; 1.57] 9.3%
Boudin et al. 2020	0.08 0.1631		1.09 [0	0.79; 1.49] 10.7%
Bhandari et al. 2020	0.09 0.2767		1.10 [(0.64; 1.89] 5.9%
Abdollahi et ai. 2020	0.10 0.2196		1.10 [(0.72; 1.70] 8.0%
Gamal et al. 2020	0.11 0.0769		1.12 [(0.96; 1.30] 16.1%
Kibler et al. 2020	0.61 0.5629		— 1.83 [0	0.61; 5.52] 1.9%
Random effects mode	el	4	0.97 [0).83; 1.13] 100.0%
Prediction interval			[0).61; 1.54]
Heterogeneity: $I^2 = 38\%$,	$\tau^2 = 0.0355, p = 0.11$		I	
	0.2	0.5 1 2	5	

Figure 9: Forest plot for the Rhesus status

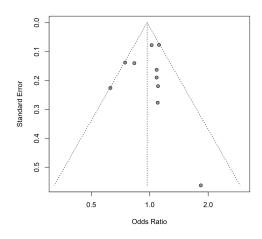


Figure 10: Funnel plot for the Rhesus status

122 Discussion

The aim of the study was to assess the relationship between COVID-19 infection and different blood 123 groups, as well as Rhesus state, using a meta-analysis method. Twenty-two studies were selected for 124 blood type and ten for the Rhesus factor. Our results revealed that the blood groups A, B and AB are 125 associated with an increase in the risk of COVID-19 infection in comparison with the O blood group, 126 which seems to be protective. A mild publication bias was observed for the A and O blood group pair, 127 through the visual inspection of the funnel plots and the results of Egger's test. Further, moderate to 128 substantial heterogeneity, has been observed for the blood groups A and AB in comparison with the O 129 blood group. Blood group B was characterized by the absence of heterogeneity. 130

Although the mechanisms that can explain the observed data have not yet been clarified, some assump-131 tions can be made. The main one assumes that the anti-A and anti-B natural antibodies being produced 132 in individuals with blood group O could potentially block viral adhesion to cells, which could explain 133 a lower risk of infection. Potential lack of such antibodies in blood groups A and B may explain the 134 higher risk of COVID-19 infection but further studies are needed to elucidate this hupothesis (Pourali 135 et al. 2020). Concerning the Rhesus status, there was not evidence of an association with COVID-19 136 infection. The visual inspection of the Rhesus factor funnel plot and the results of Egger's test showed 137 moderate heterogeneity but no evidence of publication bias. 138

The interpretation of the overall estimates should be done with caution because of the observed hetero-139 geneity between studies. There was variability in the design and sample size, while a considerable part 140 of the pooled control population comes mainly from a single study (Golinelli et al. 2020). Further, the 141 COVID-19 confirmation method was either genetic, clinical, or even unreported while potential con-142 founding factors such as age, gender, race, region, and underlying diseases that may influence the pre-143 disposition to COVID-19 infection could not be accounted for due to absence of relevant information. 144 Finally, the observed publication bias may be due to the study language chosen, which may have led to 145 the exclusion of other relevant studies, in other languages (Liu et al. 2020). Nevertheless, despite the 146 unexplained heterogeneity, subgroup and sensitivity analysis still confirmed our results. 147

In conclusion, this meta-analysis provides evidence for an increased risk of COVID-19 infection for

blood groups A, B and AB compared to blood group O, while an association between Rhesus state and

¹⁵⁰ COVID-19 infection could not be established.

151 Supplementary files

152 1. Leave-one-out method results for ABO blood group

153 Hosted file

- 154 supplementary data_ABO_leave_one_out.xlsx available at https://authorea.
- 155 com/users/155758/articles/518298-systematic-review-and-meta-

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156 analysis-of-the-effect-of-abo-blood-group-on-the-risk-of-covid-19-
157 infection
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158 2. Leave-one-out method results for Rhesus

159 Hosted file

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160 supplementary data_Rh_leave_one_out.xlsx available at https://authorea.
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161 com/users/155758/articles/518298-systematic-review-and-meta-
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162 analysis-of-the-effect-of-abo-blood-group-on-the-risk-of-covid-19-
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