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Review

ABO Blood Group is Associated with COVID-19 Susceptibility: a Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: Conflicting evidences exist that ABO blood groups correlate with the susceptibility to COVID-19 and its clinical outcomes. This study aimed to pool available articles that assessed a possible relationship between COVID-19 and ABO blood groups.
Materials and methods: A search was conducted in four databases comprising Pubmed/Medline, Google scholar, Journal storage (JSTOR) and African Journals Online (AJOL) for relevant studies available before 25th August 2020 and contained extractable data on ABO blood type distribution and COVID-19 disease. Search terms included a combination of "ABO blood group, and COVID-19, coronavirus, and SARS-COV-2".
Results: Fourteen articles that met study inclusion criteria were selected from a total of five hundred and eighty-five articles identified through database search. The fourteen articles reviewed comprised of a total of 73934 subjects (13189 SARS-COV-2 positive cases and 60745 controls). Overall, the risk of SARS-COV-2 infection was found to be significantly increased in patients with blood group A with ORs: 1.24 (95%Cl: 1.09-1.41, P = 0.001). Additionally, blood group O subjects were seen to have decreased odds of contracting COVID-19 infection (OR: 0.78, 95%Cl: 0.68 – 0.89, P=0.0003). No significant association was found between ABO blood groups and COVID -19 severity and mortality.
Conclusions: Blood group A was associated with a higher risk of SARS-COV-2 infection whereas risk of infection was lower in blood group O subjects. No statistical significant association was found between ABO blood groups and COVID-19 severity and mortality. The precise role of ABO blood group in COVID-19 susceptibility, severity and mortality requires further research for clarification.

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1. INTRODUCTION

SARS-COV-2 is the causative agent of COVID-19 and the seventh form of coronavirus which took its origin in Wuhan, Hubei province of China in December 2019. The disease has been declared as a pandemic on 11th March 2020 by WHO, and as on 24th August 2020, there were 23,616,858 positive cases, 813,068 deaths and 16,105,572 recoveries worldwide **[**1, 2**].** Clinical symptoms of COVID-19 include fever, cough, tiredness, and shortness of breath, sore throat, running nose and headache while the risk of morbidity and mortality include age, sex, and presence of co-morbidities such as cardiovascular diseases, diabetes, respiratory diseases, cancer, liver and kidney diseases [3, 4].

According to the International Society of Blood Transfusion, more than 30 blood groups exist and include the ABO and Rh blood groups [5]. The ABO and Rh blood group was discovered by Landsteiner in 1901 and 1941 respectively [6] and consists of the A, B, and H carbohydrate antigens and antibodies against these antigens [7]. The A, B and D blood antigens are found on the surface of the red blood cells and their presence or absence determines the ABO and Rh blood grouping of an individual [8]. The blood group antigens are glycoproteins and glycolipids and are genetically controlled and inherited in varying frequencies across human populations [8, 9]. Human ABO blood is located on chromosome 9 (9q34.2) [10] and are of four types: A, B, AB and O.

Though studies are currently ongoing to identify biological markers that can predict individual's susceptibility to SARS-COV-2, severity and COVID-19 clinical outcome have been associated with serum levels of some laboratory parameters [11-13]. Liver function tests have been used to assess the association between liver injury and COVID 19 [14].

The ABO blood group has been linked to diseases such as Norovirus [15], Influenza [16], *Plasmodium falciparum* infection and cancer [17]. Now there are growing evidences that showed the susceptibility to SARS-COV-2 is related to the ABO blood group of an individual **[**18-33**]**. Also, conflicting evidences exist on the relationship between ABO blood group and the severity and clinical outcome of COVID-19 disease. The aim of the current study was to carry out a systematic review and meta-analysis of all the studies that investigated the relationship between ABO blood group and COVID-19 for better understanding and guide.

2. MATERIALS AND METHODS

An electronic literature search was conducted by two

independent reviewers using the online databases of Pubmed/Medline, Google Scholar, Journal Storage (JSTOR) and African Journal OnLine (AJOL) from 2nd August, 2020 for relevant publications published up to 25th August, 2020. "ABO blood group" during the search protocol was combined with either "COVID-19", "SARS-COV-2" or "coronavirus" to identify studies published online. Eligible studies were further snowballed to identify additional articles.

Participants in this study were individuals with known ABO blood type who were documented to have SARS-COV-2 infection; whereas controls are individuals with known ABO blood group who were not SARS-COV-2 positive.

From this definition, studies were included if they:

1. Examined the association between ABO blood groups and either SARS-COV-2 infection or/and COVID-19 severity or/and death due to COVID-19,
2. Provided original data 3. Provided information on normal individuals with their ABO blood type known,
3. Were case-control, case series, cohort and cross-sectional in design (reports, correspondence and letters to the editors were also included if reporting original data).

Our exclusion criteria include:

1. Articles irrelevant to the subjects of the study (animal models, studies on COVID-19 that were not associated with ABO blood group and vice versa, studies on other strains of coronaviruses other than COVID-19),
2. Studies whose data are not extractable,
3. Duplicated studies (where we included articles once even when they were found in different databases),
4. Reviews and Figures,
5. Studies not retrievable in English language.

There were no restrictions on year, age, sex, gender, comorbidities, SARS-COV-2/blood type testing methods,

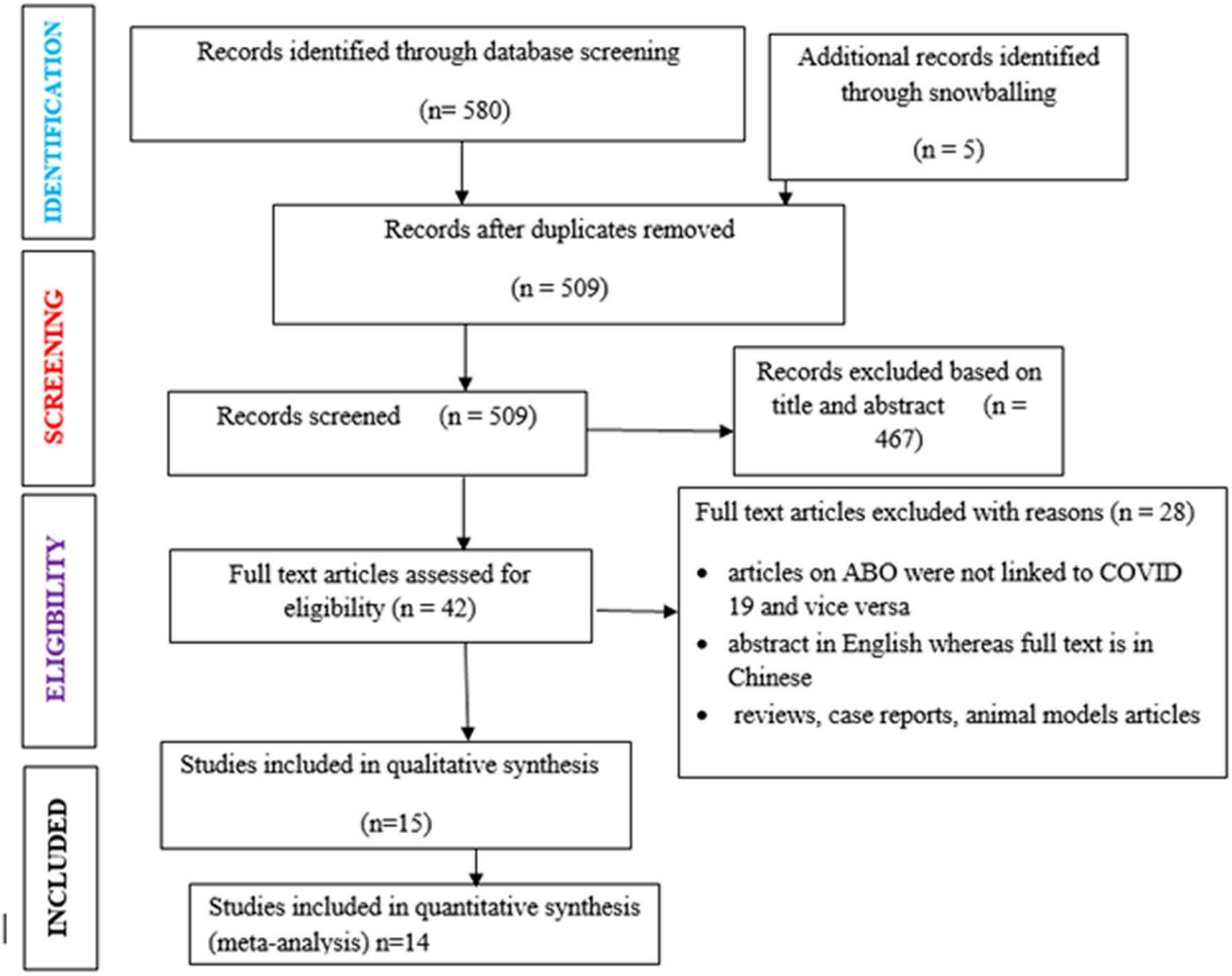

***Figure 1**: PRISMA flow chart showing study selection process.*

testing time, sample size, publication status, race, country/region and follow-up time.

Eligible articles using the inclusion and exclusion criteria were obtained by two independent reviewers through screening of the titles and abstracts whereas detailed information was obtained through careful review of the full-text. Any discrepancy was resolved through consensus. The data extraction format used in this study was similar to that reported by Wu et al. [18]**.** The following information were extracted: the first author and year of publication, country of participants, sample size and sample design, gender ratio, live controls and dead cases, non-severe controls and severe cases, asymptomatic controls and symptomatic cases. All the extracted data were transferred into an Excel spreadsheet. Any controversy to include or exclude any study was resolved through consensus and when it cannot be achieved, the main reviewer made the final decision. The data screening, selection and extraction processes were manually done and the entire process was done without blinding. The primary outcome measures were to investigate the association between ABO blood group and: 1. COVID-19 susceptibility; 2. COVID-19 severity; and 3. Mortality due to COVID-19. COVID-19 severity is defined as hospitalization with respiratory failure with subjects admitted in the intensive care unit of the hospitals. Figure 1 contains the flow chart of the study selection process.

In consultation with the other authors, the main reviewer carried out the quality appraisal of included studies using the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies recommended by National Institute for Health (NIH). The quality tool is comprised of 14 items/questions with a total score of 14. Each study was scored on a Yes (1) or No (0), and others [not applicable (NA), not reported (NR) or cannot determine (CD)]. Not applicable was used where some elements of the criteria did not apply as seen in Table 1.

Table 1. Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies

Criteria	Number of articles		
	Yes	No	Other
1. Was the research question or objective in this paper clearly stated?	15		
2. Was the study population clearly specified and defined?	14	1	
3. Was the participation rate of eligible persons at least 50%?	14	1	
4a. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? 4b. Were inclusion and exclusion criteria for being in the study pre-specified and applied uniformly to all participants?	14		1
5. Was a sample size justification, power description, or variance and effect estimates provided?			15
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	14		1
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	5		10
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?			15
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	15		
10. Was the exposure(s) assessed more than once over time?	2	2	11
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	15		
12. Were the outcome assessors blinded to the exposure status of participants?			15
13. Was loss to follow-up after baseline 20% or less?			15
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship	8	7	

Other includes not applicable, not reported and undetermined data.

2.1. STATISTICAL ANALYSIS

Data analysis for included studies was performed using Review Manager Software (version 5.3.5). The random-effect model was used to obtain the pooled odds ratios (ORs) and 95% confidence interval (CIs) and was used to measure the association between SARS-COV-2 infection, COVID-19 severity, COVID-19 related deaths and ABO

Table 2. Characteristics of included studies and subgroups

Ref.	Country	Study design	Sample size	Age (years)	Gender (M/F)	COVID-19 (symptomatic)	Control	Severe cases	Non-severe cases	Died cases	Alive cases	Quality score
[20]	Iran	Cross-sectional	897	Cases: 58.81±15.4 Control: 48.53±17.9	483/414	397	500	127	270	NR	NR	7
[21]	China	Retrospective	106	45(3-90)	52/54	80	26	17	63	NR	NR	8
[22]	France	Retrospective Cohorts	1688	28.0 (23-35)	1466/222	1279	409	3	1276	0	1279	7
[23]	China	Retrospective case control	208	Cases: 56.8 ± 18.3 Control: 54.0 ± 15.0	Cases: 55/50 Control: 56/47	105	103	NR	NR	NR	NR	8
[24]	USA	Retrospective	7648	> 18.0	Cases : 417/872 Control: NR	1289	6359	123	1166	89	34	8
[25]	USA	Retrospective cohort	6797	NR	NR	957	5840	NR	NR	135	822	9
[26]	USA	Retrospective cohort	2033	62.0 (52–71)	1297/736	2033	NR	2033	0	799	1234	9
[27]	Italy and Spain	Retrospective Cohort	3815	66.5 (54-79)	Cases : 1096/514 Control : NR	1610	2205	1610	0	NR	NR	8
[28]	China	Retrospective case - control	2178	Not clear	Cases : 97/90 Control : NR	187	1991	NR	NR	NR	NR	7
[29]	Turkey	Retrospective	2067	Cases: 42.0 (19-92) Control: NR	Cases : 100/86 Control: NR	186	1881	31	155	NR	NR	7
[30]	China (Central hospital of Wuhan)	Retrospective cohort	3959	Not clear	Cases: 113/152 Control: NR	265	3694	NR	NR	57	208	8
[31]	China	Retrospective cohort	234	> 13.0	133/101	234	NR	97	137	21	76	9
[32]	USA	Retrospective cohort	13051	54.0 (36-72)	5024/8027	2394	10657	399	1995	331	68	10
[33]	China (Wuhan Jinyintan Hospital)	Retrospective	5469	NR	NR	1775	3694	NR	NR	206	1569	8
{33}	China (Renmin Hospital of Wuhan University)	Retrospective	3807	NR	NR	113	3694	NR	NR	NR	NR	8
|33|	China (Shenzhen Third People's Hospital)	Retrospective	23671	NR	NR	285	23386	NR	NR	NR	NR	8

M: Male; F: Female; NR: Not reported. Zhao et al. [33] in one (1) manuscript presented three (3) studies in 3 different areas in China and presented differently here. Also, all control participants are COVID-19 negative subjects apart from those reported by Zhou et al [21] which are asymptomatic carriers.

blood group. Increased or decreased risk of COVID-19 infection, severity or death was indicated when the OR was greater or less than 1 respectively. Test of heterogeneity between studies was assessed using the chi-squared test and I-squared (I^2) statistic. Results of the meta-analysis were presented graphically using forest plots. In the forest plots, the weight of each study and the 95% CIs determined the size of the squares and the lines beside it respectively. The level of statistical significance was set at $P < 0.05$.

3. RESULTS

A total of 585 articles were initially identified after search of the databases and were reduced to 509 articles following duplicates removal as shown in Figure 1. After a thorough scan of the abstracts using the study inclusion criteria another set of 467 articles were removed. The full texts of the remaining forty-two articles were critically evaluated resulting in twenty-eight articles being excluded using the study exclusion criteria. One study that met inclusion criteria for qualitative synthesis was later dropped for meta-analysis due to low quality (quality score of 3) as seen in Table 1 and data on ABO blood group and COVID-19 were not clearly extractable [19]. Finally, a total of 14 [20-33] studies were included in this systematic review and meta-analysis.

3.1. CHARACTERISTICS OF INCLUDED STUDIES FOR META-ANALYSIS

The basic characteristics of included studies are shown in Table 2. Fourteen eligible studies including 13189 SARS-COV-2 positive cases and 60745 controls were included in our meta-analysis. The studies were all published in year 2020 (Table 2). On study location, six of the studies were carried out in China [21, 23, 28, 30, 31, 33], four in US [24-26, 32], one each in France [22], Turkey [29] and Iran [20]. One of the studies was multi-country in nature (involving Spain and Italy) [27]. There were 13

Table 3. Studies showing results for COVID-19 susceptibility and blood group distribution

Ref.	Blood group A				Blood group B				Blood group AB				Blood group O			
	COVID n (%)	Total	Control n (%)	Total	COVID n (%)	Total	Control n (%)	Total	COVID n (%)	Total	Control n (%)	Total	COVID n (%)	Total	Control n (%)	Total
[20]	160 (40.3)	397	180 (36.0)	500	89 (22.4)	397	105 (21.0)	500	37 (9.3)	397	25 (5.0)	500	111 (28.0)	397	190 (38.0)	500
[21]	31 (38.8)	80	5 (19.2)	26	16 (20.0)	80	13 (50.0)	26	5 (6.3)	80	1 (3.8)	26	28 (35.0)	80	7 (26.9)	26
[22]	521 (40.7)	1279	153 (37.4)	409	135 (10.6)	1279	48 (11.7)	409	54 (4.2)	1279	16 (3.9)	409	553 (43.2)	1279	189 (46.2)	409
[23]	45 (42.9)	105	30 (29.1)	103	28 (26.7)	105	32 (31.1)	103	9 (8.6)	105	30 (29.1)	103	23 (21.9)	105	11 (10.7)	103
[24]	440 (34.1)	1289	2209 (34.7)	6359	201 (15.6)	1289	834 (13.1)	6359	61 (4.7)	1289	247 (3.9)	6359	587 (45.5)	1289	3069 (48.3)	6359
[25]	311 (32.5)	957	2128 (36.4)	5840	140 (14.6)	957	761 (13.0)	5840	41 (4.3)	957	231 (4.0)	5840	465 (48.6)	957	2720 (46.6)	5840
[27]	765 (47.5)	1610	849 (38.5)	2205	162 (10.1)	1610	228 (10.3)	2205	79 (4.9)	1610	75 (3.4)	2205	604 (37.5)	1610	1053 (47.8)	2205
[28]	69 (36.9)	187	547 (27.5)	1991	63 (33.7)	187	644 (32.3)	1991	14 (7.5)	187	199 (10.0)	1991	41 (21.9)	187	601 (30.2)	1991
[29]	106 (57.0)	186	716 (38.1)	1881	20 (10.8)	186	277 (14.7)	1881	14 (7.5)	186	188 (10.0)	1881	46 (24.7)	186	701 (37.3)	1881
[30]	104 (39.2)	265	1188 (32.2)	3694	67 (25.3)	265	920 (24.9)	3694	26 (9.8)	265	336 (9.1)	3694	68 (25.7)	265	1250 (33.8)	3694
[32]	786 (32.8)	2394	3512 (33.0)	10657	392 (16.4)	2394	1641 (15.4)	10657	94 (3.9)	2394	465 (4.4)	10657	1122 (46.9)	2394	5039 (47.3)	10657
[33]	670 (37.7)	1775	1188 (32.2)	3694	469 (26.4)	1775	920 (24.9)	3694	178 (10.0)	1775	336 (9.1)	3694	458 (25.8)	1775	1250 (33.8)	3694
{33}	45 (39.8)	113	1188 (32.2)	3694	25 (22.1)	113	920 (24.9)	3694	15 (13.3)	113	336 (9.1)	3694	28 (24.8)	113	1250 (33.8)	3694
|33|	82 (28.8)	285	6728 (28.8)	23386	83 (29.1)	285	5880 (25.1)	23386	39 (13.7)	285	1712 (7.3)	23386	81 (28.4)	285	9066 (38.8)	23386

Leaf et al. [26] and Zeng et al. [31] were excluded because there are no control data provided for comparison and Zhao et al., in one (1) manuscript presented three (3) studies in 3 different areas referenced as [33]. {33} and |33|.

Table 4. Results of subgroup analysis of ABO blood group association with SARS-COV-2 infection

Subgroup	Studies (n)	Sample size	B versus non-B			O versus non-O			A versus non-A			AB versus non-AB		
			OR (95% CI)	P value	I^2 %	OR	P value	I^2 %	OR (95% CI)	P value	I^2 %	OR (95% CI)	P value	I^2 %
All studies	12	75361	1.05 (0.97-1.14)	0.25	35 (P=0.10)	0.78 (0.68-0.89)	0.0003	84 (P<0.00001)	1.24 (1.09-1.41)	0.001	83 (P<0.00001)	1.12 (0.92-1.36)	0.27	70 (P<0.0001)
Studies divided per country														
USA	3	27496	1.13 (1.03-1.23)	0.007	0 (P = 0.46)	0.98 (0.89 -1.08)	0.69	53 (P=0.12)	0.95 (0.89 -1.02)	0.17	47 (P = 0.15)	1.03 (0.88-1.20)	0.74	34 (P =0.22)
China	5	39398	1.00 (0.84-1.19)	0.98	50 (P=0.06)	0.72 (0.60–0.86)	0.0003	52 (P=0.05)	1.29 (1.18-1.42)	P<0.00001	29 (P = 0.20)	1.03 (0.69-1.53)	0.89	80 (P<0.0001)
Iran	1	897	1.09 (0.79-1.50)	0.61	NA	0.63 (0.48–0.84)	0.002	NA	1.20 (0.92-1.57)	0.19	NA	1.95 (1.15-3.30)	0.01	NA
Europe (France + Italy + Spain + Turkey)	3	7570	0.91 (0.77-1.08)	0.29	0 (P=0.46)	0.70 (0.55-0.89)	0.003	71 (P=0.03)	1.50 (1.13-1.99)	0.005	81 (P=0.005)	1.11 (0.73-1.67)	0.63	56 (P=0.10)
Studies divided per sample size														
>2000	8	72462	1.09(1.02-1.16)	0.009	0 (P=0.47)	0.75(0.65-0.87)	0.0002	87 (P<0.00001)	1.22 (1.05-1.42)	0.010	87 (P<0.00001)	1.16 (0.97-1.38)	0.10	62 (P=0.005)
<2000	4	2899	0.79 (0.53-1.19)	0.26	65 (P=0.04)	1.00 (0.65-1.54)	1.00	75 (P = 0.008)	1.24 (1.05-1.46)	0.010	28 (P=0.25)	0.90 (0.33-2.42)	0.83	85 (P=0.0002)

Leaf et al. [26] and Zeng et al. [31] were not included in the subgroup analysis because they were not part of studies included for susceptibility testing (Table 2).
NA: Not applicable.

retrospective studies and one cross-sectional study. The NIH quality assessment score of selected studies ranged from 7 to 10 points (the highest possible score is 14), with mean and median of 8 each (Table 2). Of all the studies, 12 were original articles while one each was a correspondence [26] and a letter to an editor [25]. The case groups were COVID-19 infected individuals admitted in the hospital. Meanwhile, for the control subjects, three studies used data from blood donor populations/databases [20, 27, 29], three studies used data from the general population [30, 32, 33]

Table 5. Studies showing case results for COVID-19 severity

Ref.	Blood group A				Blood group B				Blood group AB				Blood group O			
	Severe COVID n (%)	Total	Non-severe COVID n (%)	Total	Severe COVID n (%)	Total	Non-severe COVID n (%)	Total	Severe COVID n (%)	Total	Non-severe COVID n (%)	Total	Severe COVID n (%)	Total	Non-severe COVID n (%)	Total
[20]	51 (40.2)	127	109 (40.4)	270	28 (22.0)	127	61 (22.6)	270	10 (7.9)	127	27 (10.0)	270	38 (29.9)	127	73 (27.0)	270
[21]	11 (64.7)	17	20 (31.7)	63	0 (0)	17	16 (25.4)	63	1 (5.9)	17	4 (6.3)	63	5 (29.4)	17	23 (36.5)	63
[22]	0 (0)	3	521 (40.8)	1276	1 (33.3)	3	134 (10.5)	1276	0 (0)	3	54 (4.2)	1276	2 (66.7)	3	551 (43.2)	1276
[24]	41 (33.3)	123	399 (34.2)	1166	18 (14.6)	123	183 (15.7)	1166	7 (5.7)	123	54 (4.6)	1166	57 (46.4)	123	530 (45.5)	1166
[26]	666 (32.8)	2033	0 (0)	0	328 (16.1)	2033	0 (0)	0	89 (4.4)	2033	0 (0)	0	950 (46.7)	2033	0 (0)	0
[27]	765 (47.5)	1610	0 (0)	0	162 (10.1)	1610	0 (0)	0	79 (4.9)	1610	0 (0)	0	604 (37.5)	1610	0 (0)	0
[29]	17 (54.8)	31	89 (57.4)	155	3 (9.7)	31	17 (10.9)	155	4 (12.9)	31	10 (6.5)	155	7 (22.6)	31	39 (25.2)	155
[31]	40 (41.2)	97	54 (39.4)	137	30 (30.9)	97	34 (24.8)	137	0 (0)	97	0 (0)	137	27 (27.8)	97	49 (35.8)	137
[32]	111 (27.8)	399	675 (33.8)	1995	78 (19.5)	399	314 (15.7)	1995	17 (4.3)	399	77 (3.9)	1995	193 (48.4)	399	929 (46.6)	1995

while in one [22], and in four other studies [23-25, 28] control data were obtained from populations with same level of exposure and hospitalized patients who were in admission before COVID-19 episode, respectively. Control data was obtained from asymptomatic COVID-19 carriers in one study [21] while two studies [26, 31] did not use control.

Table 6. Studies showing case results for COVID-19 mortality

Ref.	Blood group A				Blood group B				Blood group AB				Blood group O			
	Died n (%)	Total	Alive n (%)	Total	Died n (%)	Total	Alive n (%)	Total	Died n (%)	Total	Alive n (%)	Total	Died n (%)	Total	Alive n (%)	Total
[22]	0 (0)	0	521 (40.7)	1279	0 (0)	0	135 (10.6)	1279	0 (0)	0	54 (4.2)	1279	0 (0)	0	553 (43.2)	1279
[24]	36 (40.4)	89	5 (14.7)	34	14 (15.7)	89	4 (11.8)	34	5 (5.6)	89	2 (5.9)	34	34 (38.2)	89	23 (67.6)	34
[25]	45 (33.3)	135	266 (32.4)	822	17 (12.6)	135	123 (15.0)	822	8 (5.9)	135	33 (2.8)	822	65 (48.1)	135	400 (48.7)	822
[26]	268 (33.6)	799	398 (32.3)	1234	129 (16.1)	799	199 (16.1)	1234	41 (5.1)	799	48 (3.9)	1234	361 (45.2)	799	589 (47.7)	1234
[30]	20 (35.1)	57	84 (40.4)	208	15 (26.3)	57	52 (25.0)	208	8 (14.0)	57	18 (8.7)	208	14 (24.6)	57	54 (26.0)	208
[31]	8 (38.1)	21	32 (42.1)	76	7 (33.3)	21	23 (30.3)	76	0 (0)	21	0 (0)	76	6 (28.6)	21	21 (27.6)	76
[32]	104 (31.4)	331	7 (10.3)	68	46 (13.9)	331	32 (47.1)	68	15 (4.5)	331	2 (2.9)	68	166 (50.2)	331	27 (39.7)	68
[33]	85 (41.3)	206	585 (37.3)	1569	50 (24.3)	206	419 (26.7)	1569	19 (9.2)	206	159 (10.1)	1569	52 (25.2)	206	406 (25.9)	1569

From Table 3, twelve evidences reported data on the association between ABO blood group and SARS-COV-2 susceptibility. As shown in Figure 2, the risk of contracting SARS-COV-2 infection was found to be significantly higher among individuals of blood group A (OR: 1.24, 95%Cl: 1.09 - 1.41, P = 0.001). The heterogeneity among the studies was found to be significantly high (I-squared = 83%, P < 0.00001) using the random-effect model. However, the risk of SARS-COV-2 infection was found to be significantly decreased among blood group O individuals (OR: 0.78, 95% Cl: 0.68 - 0.89, P = 0.0003); a significant heterogeneity (I-squared = 84%, P < 0.00001) was also observed between studies using the random-effect model. When compared with other ABO blood groups and applying random-effects models (for B: I-squared = 35%, P = 0.10; for AB: I- squared = 70%, P < 0.0001), the odds of SARS-COV-2 infection seemed to be increased among individuals with blood group B (OR: 1.05, 95%Cl: 0.97 – 1.14, P = 0.25) and blood group AB (OR: 1.12, 95%Cl: 0.92 - 1.36, P = 0.27). However, the findings were of no statistical significance. Table 4 contains the result of the subgroup analysis. The observed association between blood group A and SARS-COV-2 infection remained stable in studies carried out in China, Europe, and across all sample sizes. Meanwhile, the inverse relationship between blood group O and SARS-COV-2 infection was unchanged among studies carried out in Europe, Iran, China and studies with sample sizes > 2000 (Table 4). However, increased risk of SARS-COV-2 infection in blood group B subjects was found to be statistically significant among studies carried out in USA (OR: 1.13, 95CI: 1.03 – 1.23) and those with sample sizes > 2000 (OR: 1.09, 95CI: 1.02 – 1.16) but remained unchanged and non-significant in studies done in China, Europe, Iran and those with sample sizes < 2000 (Table 4). Furthermore, significant risk of SARS-COV-2 infection in blood group AB subjects was only found among Iranians (OR: 1.95, 95CI: 1.15 – 3.30) (Table 4). In sensitivity analysis as shown in Table 7 using Sensitivity analysis (leave-one-out approach), the high heterogeneity observed in blood groups A, AB and O (Figure 2) could not be accounted for by the individual studies as the I^2 and the pooled estimate remained unchanged. Besides, low heterogeneity was observed among studies carried out in USA while remaining high among studies done in China and Europe with the exception of blood group A and AB respectively (Table 4).

Table 7. Results from sensitivity analysis leave-one-out method: pooled/ OR and 95% confidence interval calculated omitting each study in turn

Studies omitted	B versus non-B			O versus non-O			A versus non-A			AB versus non-AB		
	OR (95% CI)	P value	I^2 %	OR	P value	I^2 %	OR (95% CI)	P value	I^2 %	OR (95% CI)	P value	I^2 %
[20]	1.25	1.08-1.43	84	1.05	0.96-1.14	40	1.08	1.88-1.31	69	0.79	0.69-0.91	84
[21]	1.23	1.08-1.40	84	1.08	1.01-1.14	0	1.11	0.91-1.36	72	0.77	0.67-0.88	85
[22]	1.25	1.09-1.44	84	1.06	0.97-1.15	36	1.12	0.91-1.37	72	0.77	0.67-0.89	85
[23]	1.22	1.07-1.40	84	1.05	0.97-1.15	37	1.19	1.01-1.40	56	0.76	0.67-0.87	83
[24]	1.28	1.11-1.47	83	1.03	0.95-1.12	30	1.10	0.89-1.37	72	0.77	0.66-0.90	84
[25]	1.28	1.13-1.46	79	1.04	0.95-1.14	38	1.12	0.90-1.38	72	0.75	0.66-0.86	81
[27]	1.22	1.07-1.39	80	1.06	0.97-1.16	37	1.09	0.88-1.34	70	0.80	0.69-0.91	81
[28]	1.22	1.07-1.40	84	1.05	0.96-1.14	40	1.15	0.94-1.40	70	0.79	0.69-0.91	84
[29]	1.19	1.05-1.34	80	1.07	0.99-1.15	29	1.15	0.94-1.40	70	0.80	0.70-0.93	84
[30]	1.23	1.07-1.47	84	1.05	0.96-1.15	40	1.12	0.91-1.38	72	0.79	0.69-0.91	84
[32]	1.28	1.10-1.48	82	1.04	0.94-1.15	40	1.14	0.93-1.41	68	0.76	0.66-0.88	80
[33]	1.24	1.07-1.44	83	1.04	0.94-1.14	40	1.11	0.88-1.39	72	0.79	0.69-0.91	83
{33}	1.23	1.08-1.41	84	1.06	0.97-1.15	37	1.09	0.89-1.34	71	0.79	0.69-0.91	85
|33|	1.26	1.10-1.45	84	1.04	0.95-1.13	36	1.06	0.88-1.28	62	0.79	0.69-0.91	84
Expected value	**1.24**	**1.09-1.41**	**83**	**1.05**	**0.97-1.14**	**35**	**1.12**	**0.92-1.36**	**70**	**0.78**	**0.68-0.89**	**84**

Leaf et al. [26] and Zeng et al. [31] were not included in the subgroup analysis because they were not part of studies included for susceptibility testing (Table 2).

A total of nine studies reported data on the association between COVID-19 severity and ABO blood group, as were shown in Table 5. Using the random-effects model, we observed from our meta-analysis as shown in Figure 3 an increased risk of COVID-19 severity among individuals of blood group B (OR: 1.15, 95%Cl: 0.90 - 1.45, P = 0.26), those of blood group AB (OR: 1.12, 95%Cl: 0.78 - 1.60, P = 0.55) and blood group O (OR: 1.03, 95%Cl: 0.88 - 1.21, P = 0.73). Observed also was a decreased risk of COVID-19 severity among individuals of blood group A (OR: 0.96, 95%Cl: 0.74 - 1.26, P = 0.78). However, none of the observed results were of statistical significance. Meanwhile, heterogeneity between the studies were generally low (Figure 3).

Eight studies reported data on the association between COVID-19 mortality and ABO blood group, out of which, complete data on blood group AB was seen in seven of the studies as were shown in Table 6. From Figure 4 using random-effects model, our meta-analysis showed a non-statistically significant increased risk of death among people with A blood group (OR: 1.26, 95%Cl: 0.93 – 1.70, P=0.13) and blood group AB (OR: 1.23, 95%Cl: 0.93 – 1.62, P=0.15). However, individuals with O blood group and blood group B were found to have a non-statistically significant decreased risk of death [blood group O: OR: 0.93 (95%Cl: 0.75 – 1.17) , P=0.55; blood group B : OR: 0.77, 95%Cl: 0.49 – 1.21, P=0.25) (Figure 4).

4. DISCUSSION

From the analysis of 14 observational studies, we concluded the existence of potential relationship between COVID-19 susceptibility and ABO blood group of individuals. Also, from the study we found that individuals with blood group A were at more risk of being infected with SARS-COV-2 than those of non–A blood group whereas blood group O individuals were seen to have a decreased risk of infection than non-O blood type. The findings of this meta-analysis are similar to an earlier review and meta-analysis study by Pourali and colleagues [34] and a recent work done by Wu and colleagues [18]. In

another meta-analysis, the risk of SARS-COV-2 infection was also reported to be increased among A blood type individuals (OR: 1.23, 95%CI: 1.09 – 1.40) and decreased in those with O blood type (OR: 0.77, 95% Cl: 0.67-0.88) [35]. The finding of increased odds of SARS-COV-2 infection among A blood group individuals in this study means that such individuals might need stringent measures like strengthened personal protection and vigilant surveillance to reduce the chance of infection.

The finding of no significant association between ABO blood group and COVID-19 severity in this study (Figure 3) which is similar to that reported in a previous review [18]. However, considering individual studies, significant increased risk of severity among blood group A was seen in Zhou et al. [21].

On the association between death due to COVID-19 and ABO blood group, we did not find any significant relationship in all the ABO blood groups (Figure 4). Our finding corroborates that reported in two previous studies [18, 35]. However, in Latz et al., studies [24], the odds of death were significantly high with A blood group and low with O blood group.

The association of ABO blood groups and susceptibility to several infectious diseases has been a matter of debate for decades now. ABO blood group had been associated with increased risk of hepatitis B infection, pancreatic cancer and other cancers [36, 37]. A blood type was associated with pancreatic cancer [OR (95% CI): 1.425 (1.071–1.894)] and also was found to significantly modify the risk of pancreatic cancer among subjects with anti-hepatitis B core antibody (anti-HBc) (OR = 1.882, 95% CI, 1.284–2.760) [37]. In another study, the risk of hepatitis B

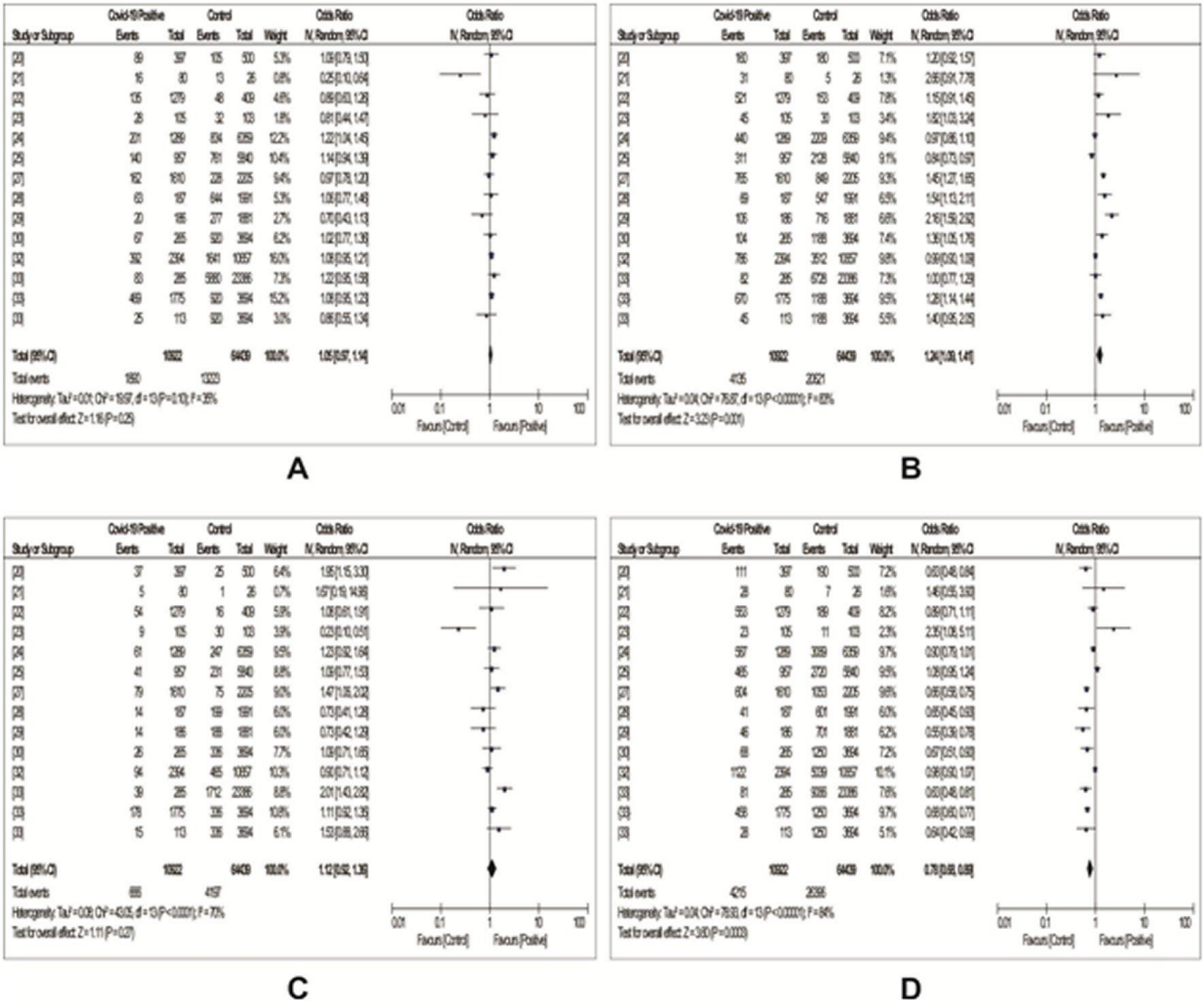

***Figure 2**: Forest plots with odd ratios showing the association between ABO blood groups and COVID-19 susceptibility. A: A blood group; B: B blood group; C: AB blood group; D: O blood group.*

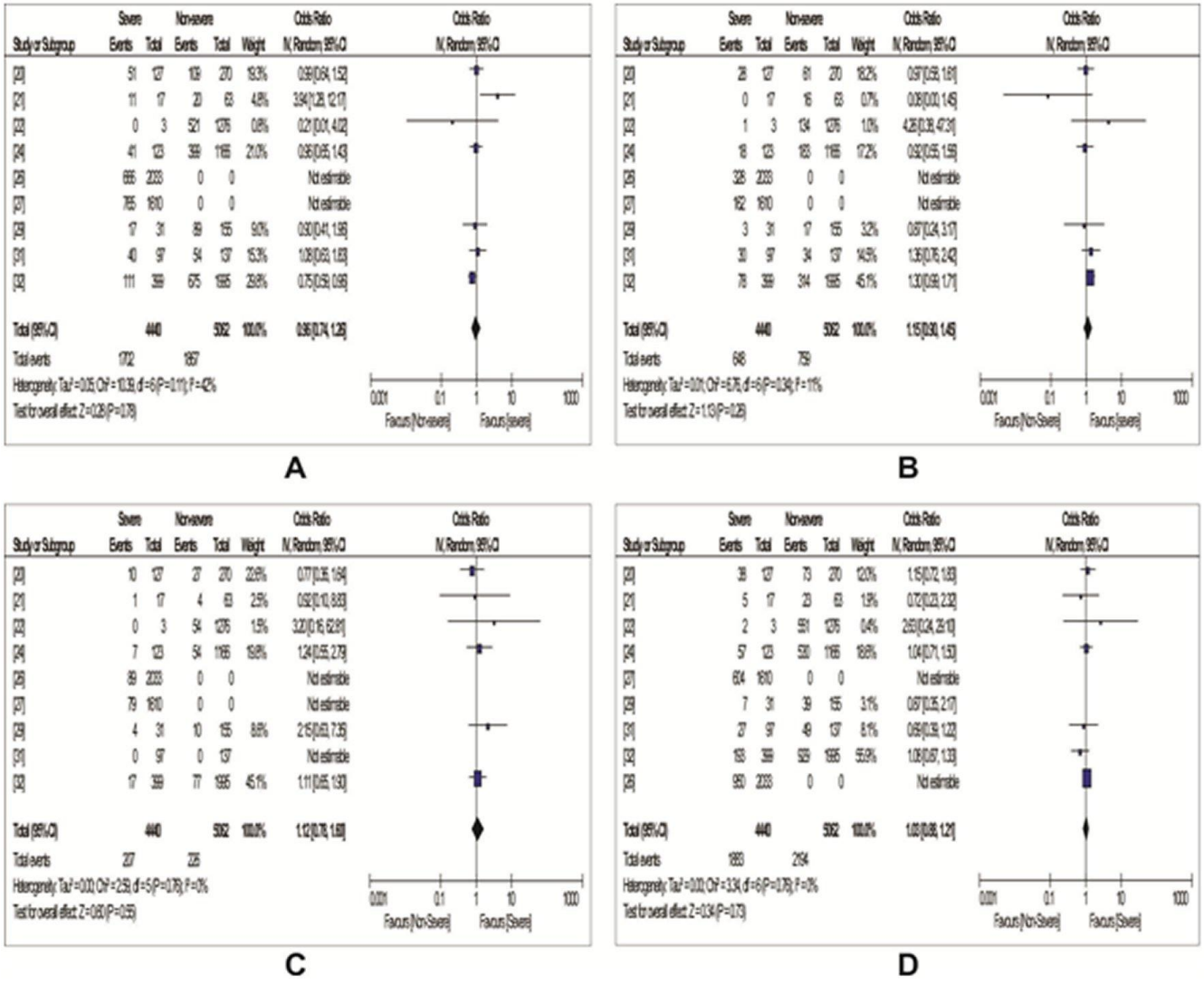

***Figure 3**: Forest plots with odd ratios showing the association between ABO blood groups and COVID-19 severity. A: A blood group; B: B blood group; C: AB blood group; D: O blood group.*

infection was reported to be decreased and increased among B blood type and blood group O individuals respectively [38]. Meanwhile, other studies reported no correlation between HBV, HIV infection and ABO blood group and even identified risk of infection to be higher in blood group O donors than those of AB group [39, 40].

A review study identified studies that postulated correlations between ABO blood group and different infections like Norovirus, Rotavirus, HIV, Influenza virus, severe acute respiratory syndrome coronavirus (SARS-COV) and malaria [41]. According to these studies, the risk of infection was reported to be increased with blood groups O, A, and B. Additionally, the study trying to explain the association between SARS and ABO type reported that among hospital workers who contracted SARS after exposure to a single index patient, resistance to infection were seen among group O individuals whereas about 23/34 of infected individuals were non-O group (groups A, B and AB) [41]. ABO blood group has also been related to the transmission of SARS following the outbreak in Honk Kong [42].

It is still unclear the exact mechanism that explains the association of ABO blood groups with viral infection [37]**.** The clinical significance of blood group antigens beyond compatible blood transfusion could be due to their being expressed on many tissues in addition to their presence on the surface of human red blood cells [31, 43]. A recent genomic study identified a 3p21.31 gene cluster as a genetic susceptibility locus in patients with Covid-19 with respiratory failure and reported a potential involvement of the ABO blood-group system [27]. ABO antibody titer, secretor status, and incidence of blood group O in the population have also been identified to be some factors that influence the protective role of blood group O to SARS-COV infection [41]. The possibility of natural antibodies to protect against certain viral infection could be associated with the ability of anti-A and anti-B natural antibodies which are found in individuals of blood group O to recognize A and B antigens on virus glycoproteins [44]. Guillon and colleagues explained the ability of anti-A antibodies either in its monoclonal or natural forms blocked the interaction between the angiotensin converting enzyme 2 (ACE2) receptor and the SARS (S) spike protein [44]. Besides, SARS-COV has been shown to bind to ABO carbohydrates and enter cells through the ACE2 receptors found in virtually all cells of major organs in the body [45]. The absence of anti-A and anti-B natural antibodies in O blood type carriers was reported to limit the SARS-COV binding with ABO carbohydrates and ACE2 [34]. In addition to low ACE2 among the O blood type carriers, they have also been found to have a higher interleukin 6 (IL-6) levels than non-type O carriers [45]. Meanwhile, cytokine storm has been associated with severe COVID-19

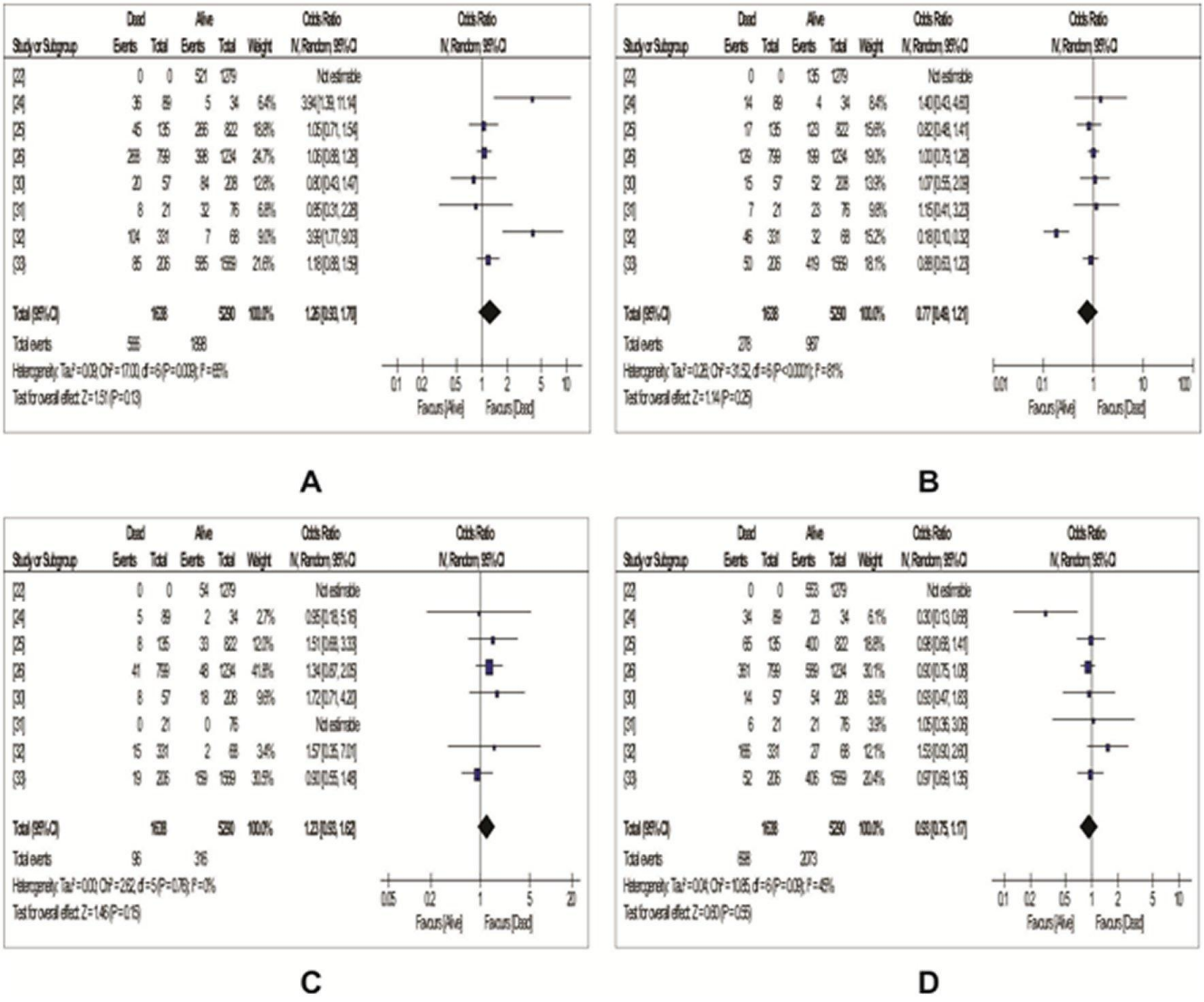

Figure 4*: Forest plots with odd ratios showing the association between ABO blood groups and COVID-19 mortality. A: A blood group; B: B blood group; C: AB blood group; D: O blood group.*

disease and have been shown to worsen the condition leading to high mortality associated with the disease [46, 47]. Interleukin-6 plays an important role in moderating the inflammation processes, thus, the high level of IL-6 in O blood type individuals could explain their lesser chances of developing severe COVID-19 disease and even death.

The high levels of Willebrand factor and factor III found in subjects of blood group A, B, or AB have also been reported to increase the susceptibility of these individuals to arterial and venous thromboembolism when compared to those of O blood group [37, 48]. Besides, the risk of developing cardiovascular diseases and aggregate disease situations have been linked to the A allele of the ABO blood group [49]. Meanwhile, the identified mechanism of ABO blood group action on infection needs further investigations and confirmations.

The limitations of the study include:

1. The publication bias was not determined,
2. We also did not account for other blood groups such as Rhesus and Duffy groups,
3. There was also possibility of missing out some studies that should have been included despite thorough literature search,
4. Despite our robust search strategy no study was identified in Africa.

Meanwhile, the strength of our study is derived from being most recent, employed a larger sample size with more regional coverage compared to other published review reports. None of the included studies were of low quality. However, more large scale confirmatory multi-country studies are needed.

5. CONCLUSIONS

Blood group A is associated with a higher risk of SARS-COV-2 infection whereas risk of infection was lower in blood group O subjects. No statistically significant association was found between ABO blood groups and COVID-19 severity and mortality. The precise role of ABO blood group in COVID-19 susceptibility, severity and mortality requires further research for clarification.

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