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EXPLORING THE ASSOCIATION OF ABO BLOOD GROUP WITH THE SEVERITY OF COVID-19: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

Background and aims: The rapid spread of COVID-19 across the globe has resulted in an unprecedented global health crisis. The causative agent of COVID-19 is the SARS-CoV-2 virus. Previous studies have suggested a potential relationship between ABO blood groups and susceptibility to coronavirus infection. In this study, we aim to investigate the association between ABO blood groups and COVID-19 severity. Our research will focus on populations in Pakistan and its neighboring countries.

Methods: Search Engines Google Scholar, PubMed, Embase, and Web of Science databases from January to December 2022. Using MeSH/Emtree terms and free-text words like ABO blood types (groups), blood group antigens, novel coronavirus-infected pneumonia, COVID-19, and SARS-CoV-2.The search was limited to English, with no restrictions on country or publication status.

Results: A total of 26,332 subjects were studied. The majority of the studies included between 14 and 80 years of age. Individuals with blood group A seem to link a higher risk to COVID-19 severity (Odds ratio of 1.2 with 95% confidence interval [0.691, 2.084]). Meanwhile, individuals with O blood group might had a lower risk of COVID-19 severity (the odds ratio was found to be 0.981 having 95% confidence interval of [0.784, 1.228]), and individuals with B and AB blood groups were likely to relate a lower risk to COVID-19.

Conclusions: This evidence-based meta-analysis found no significant association between ABO blood groups and the severity of COVID-19 outcomes, but Individuals with blood group A had a higher risk of COVID-19 severity as compared to other blood groups. Our study shows there are varied outcomes across different populations and demographic areas. Factors such as male gender, age, and comorbidities were more critical in disease progression and outcomes.

Keywords: ABO blood types (groups), blood group antigens, novel coronavirus-infected pneumonia, COVID-19, and SARS-CoV-2

Introduction

The end of 2019 marked the beginning of a new human challenge as the world had never faced a health crisis of this magnitude eliciting mass hysteria among people. SARS-COV2, an entity that could kill thousands in no time is a hazard of enormous potential. There was a huge global impact with this novel virus changing the history of the human population and dealing with pandemics forever. (1)

In developing countries like Pakistan where the health system is not well established, it was a bigger challenge. The uneducated masses were not able to figure out what was going on, where some of these people believed it to be part of a taboo and some denied the existence of such a crisis until a member of their family got affected by the virus. The authorities got exhausted with the behavior of the masses and they continually struggled to provide the correct information, hence the standard operating procedures were to be followed. (2) (3, 4)

Like every other country that has reported cases to the World Health Organization (WHO), Pakistan also reported 1,527,956 cases that were confirmed and 30,369 deaths caused by COVID-19 from 3rd January 2020 up to 6th May 2022. Also, 252,931,485 doses of the vaccine were administered by 4th May 2022. However, it was also seen that compared to rural areas, the urban areas remained most affected by the pandemic. (https://covid19.who.int/region/emro/country/pk) This research question also had an investigative potential focusing on the susceptibility factors.

To determine risk factors for viral susceptibility and severe illness, enormous research efforts have been undertaken. (5) For triage and prognosis, it is crucial to understand the risk factors associated with COVID-19. Numerous population-based studies have identified several characteristics, such as gender, race, ethnicity, age, obesity, and co-morbidities that are linked to worse outcomes following COVID-19.(6) Blood type has been examined as a risk factor for COVID-19 in several research papers. (7, 8) Blood group antigens contribute to infection directly through a number of mechanisms. They have the potential to act as pathogen receptors, co-receptors, and signaling proteins, and they can also facilitate viral particles to enter intracellularly. (9) The ABO phenotype has also been linked with stomach ulcers (more common in group O individuals) and gastric cancer (more common in group A individuals). (10) The ABO blood group antigens also appear to have been significant throughout our evolution. The frequencies of various ABO blood types differ among populations, suggesting that a particular blood group conferred a selection advantage (for example, resistance against infectious disease) or relationship with various infectious diseases as well as syndromes. (11) Clinical studies have associated certain blood types with bacterial, parasite, and viral illnesses. Blood group O individuals were more likely to contract the Norwalk virus and had greater rates of Helicobacter pylori infection. Numerous earlier research revealed a connection between hepatitis B and Norwalk virus infection with blood groups. (12) The interaction of organisms like bacteria, viruses, parasites, and fungi with the carbohydrate moieties on the surface of erythrocytes and other tissues has been discovered. (13)

Landsteiner's ABO blood classifications are polysaccharide epitopes that are embedded in the outer layer of human cells. The antigenic determinants of A and B blood categories are trisaccharide moieties GalNAcα1-3-(Fucα1,2)- Galβ-and Galα1-3-(Fucα1,2)- Galβ-, while O blood antigen is Fucα1, ABO blood group was found. All blood had formerly been taken for granted to be the same, and the frequently tragic consequences of blood transfusions were not known. The ABO blood group antigens continue to be crucial for transfusion medicine, and they swiftly gained attention as COVID-19 was declared a pandemic. This is because ABO antigens are thought to be the most immunogenic blood group antigens. (14)

The ABO blood groups framework was laid out in 1901 and it contains 3-alleles A, B, and O, all coded by the ABO gene. The blend of these 3 alleles on red platelets (RBCs) achieves six genotypes and four phenotypes, determining antigens on Red Blood Cells with counter antibodies circulating in plasma. Since then many studies have been conducted to concentrate on the expected linkage of the ABO blood group framework with different diseases either communicable or non-communicable. (14)

The sequence distribution of the ABO blood groups in the Pakistani population is B with frequency (33.37%), followed by O (33.14%), then A (33.09%), and AB (9.74%). The relative prevalence of blood groups O, A, B, and AB in Western Europe is 46%, 42%, 9%, and 3%, respectively. Thus the susceptibility to COVID-19 varies amongst populations. (15) At this rate, we can assume that the ABO distribution of any population can affect the risk of developing COVID 19 and it may vary from one demographic region to another**.** (16)

Numerous studies have linked specific ABO phenotypes to a risk of developing COVID-19 as well as some blood groups were associated with more complications and severe outcomes. ABO has four fundamental phenotypes: O, A, B, and AB.(17) The immune system develops antibodies against any ABO blood group antigens that are absent from the person's RBCs. As a result, a person in group A will have anti-B antibodies and a person in group B will have anti-A antibodies. People with blood type O in their serum will include both anti-A and anti-B antibodies.(18) Blood group AB is the least common, and these individuals will have neither anti-A nor anti-B in their serum. A multi-centric retrospective analysis showed critically ill patients with COVID-19 in ICUs predominantly had blood type A Up till now research suggests the most common involved blood type remains A for reasons unknown.(19) It was observed that severity of COVID-19 varied with different age groups, co morbidities, and gender. Blood Group was also in debate to be associated with different outcomes. To find out this association of Severity of COVID -19 with Blood groups we conducted this study.

2. Methods

Meta-analysis Of Observational Studies in Epidemiology (MOOSE) recommendations were used to guide this review.

3. Data sources and search strategy

Two independent reviewers LA (Investigator) and SM (Research Associate) searched the databases of the Google scholar, PubMed, Embase, and Web of Science from January 2022 to December 2022. We used MeSH/Emtree terms combining free-text words, such as ABO blood types (groups), blood group antigens, novel coronavirus-infected pneumonia, COVID-19, and SARS-CoV-2, which were properly adjusted for the different databases. We limited the search language to English, with no restrictions on country or publication status. To ensure a comprehensive search, the latest research references were manually screened to identify studies qualified. The studies were scrutinized by the third reviewer MA (Internee).

4. Inclusion and exclusion criteria

Inclusion criteria: 1) Cross-sectional studies, cohort studies and case-control studies were included 2) All the data regarding ABO blood group distribution, the number of COVID-19 infected and uninfected subjects, and deaths were extracted. Exclusion criteria: 1) results that could not be gathered from articles; 2) case reports, case series, duplicate reports and in vitro and animal studies; 3) the full text of the study was not be available; 4) the study was not relevant to the subject.

5. Study selection

Studies were independently identified by two reviewers (MA and LA). After removal of the duplicates, the two reviewers assessed the studies according to the eligibility criteria by reading the title and abstract. Controversial literature was confirmed by discussion of the two reviewers. A third reviewer (TM) assisted if they were unable to reach an agreement.

6. Data extraction and quality assessment

To ensure the completeness and consistency of the data, two independent reviewers (FA and AK) extracted data from the eligible studies using a predesigned template. The template included the following items: general information (first author, year of publication, country/region, characteristics of participants (age, gender, race, and education level and disease stage), and characteristics of the

study (Sample size, study design, follow-up time), exposure factor (ABO blood group distribution), and outcomes (severity, morbidity and mortality). Disagreements were resolved by consensus or through consultation with the third reviewer (TM). Quality assessments were performed by two researchers (AK and FA) by using Newcastle Ottawa Scale (NOS) checklist. The NOS is a 9 – point scale that allocates points based on the selection process of observational studies. For each study, a score of 1 was assigned to each item, except for comparability, which has 2 points. It results in maximum score of 9. The studies scored from 0-2 considered poor quality, 3–5 deemed fair quality, and 6–9 regarded as good/high quality. If any discrepancies existed, the two authors resolved the issue through discussion to reach a consensus.

7. Statistical analysis

Variables from all the included studies were matched according to the criteria of severity defined by WHO. The primary outcome measure i.e. Severity was pooled across the studies by using odds ratio as an effect measure with 95% confidence intervals. Random effects model was applied, based on the assessment of heterogeneity. To assess the heterogeneity by I^2 statistic, the Cochran's Q test was applied. The publication bias was assessed by using the funnel plot and for the asymmetry of funnel plot Egger's test was applied. The statistical significance was considered at a two-tailed significance level of 0.05. All the statistical analyses were conducted using Medcalc software v20.215 and the forest plots were generated to visually represent the combined effect estimates. The overall findings were interpreted in the context of the study objectives and the quality of evidence was assessed by Newcastle Ottawa Scale.

8. Results

8-a. Literature search

A comprehensive search yielded 1069 potentially relevant studies from all databases, of which 150 were excluded after removal of the duplicates. The remaining 919 studies were screened by title, out of which 848 studies were excluded as they were not aligned to the research question. Out of the remaining 71 records, 37 studies were filtered based on the abstract. We reviewed the full text of these remaining 37 studies and 17 studies were finalized for the systematic review and identified 6 studies that met the inclusion criteria of the meta-analysis. The detailed search process is demonstrated in Fig. 1.

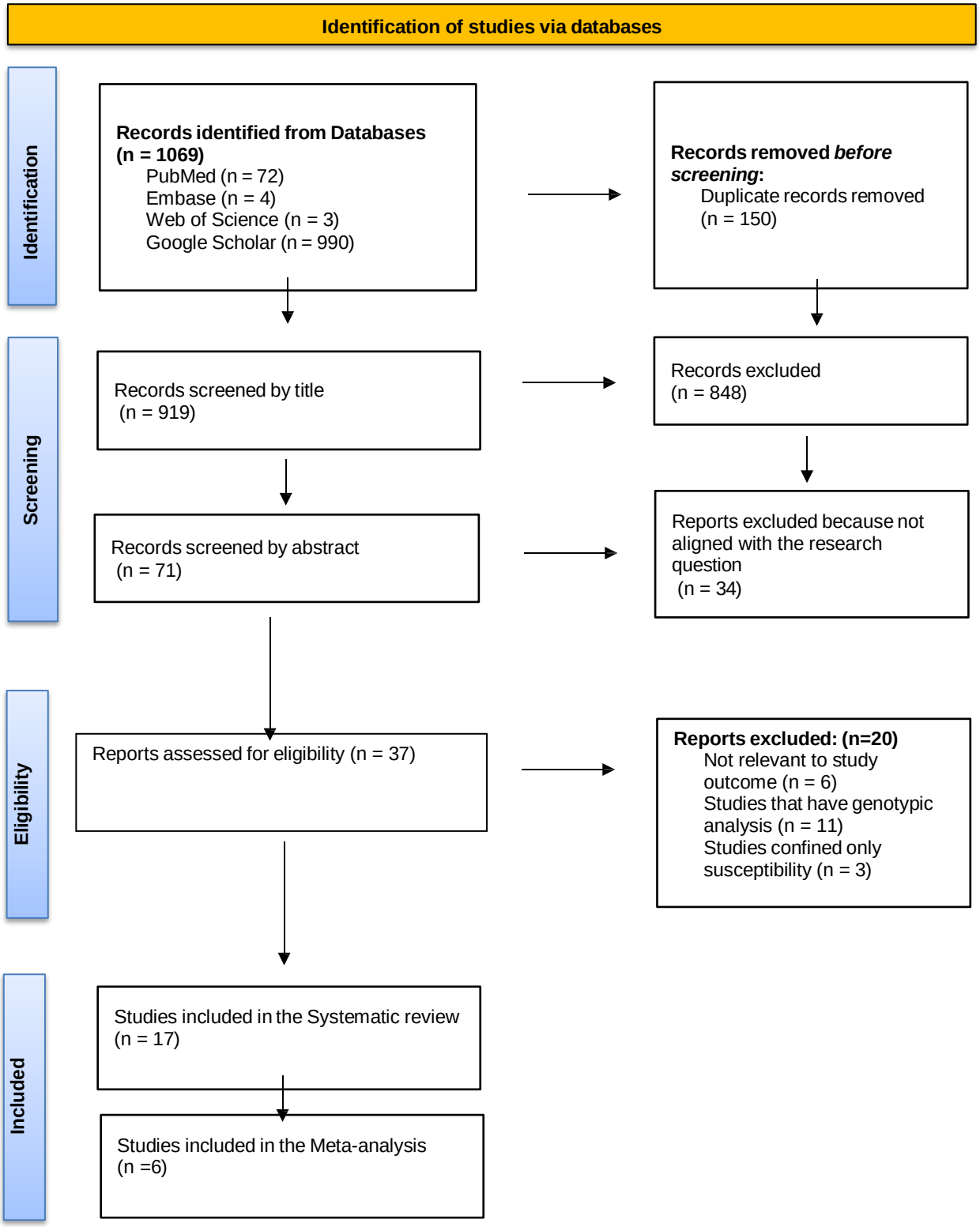

Fig: 1 Flow diagram for study Selection process in Systematic review and Meta-analysis

8-b. Study characteristics and quality assessment

We selected 17 studies for systemic review. Out of them 2 were published in 2020, 11 were published in 2021, 4 in 2022. A total of 26,332 subjects were studied. The majority of the studies included between 14 and 80 years of age. Most of the COVID-19 diagnoses were confirmed by a positive RT-PCR test using nasal and pharyngeal swab specimens. The details characteristics and outcomes are given in the table below

Table – 1: Basic characteristics and main findings of the included studies

Study Year	Country	Study Design	Sample Size	Age (years)	Gender	Patients	Rhesus	ABO blood group prevalence				Main findings
								Blood group "A"	Blood group "B"	Blood group "O"	Blood group "AB"	
Syed Asim Ali Shah et al,2022	Pakistan	Cross-Sectional	248	52.77±15.58	Male= 186, Female =62	SARS-CoV-2 confirmed by RT-PCR	Positive = 220, Negative = 28	17.70%	39.50%	30.60%	12.10%	The study found a link between ABO blood groups and Rh factor, Blood group B positive was found to be more sussceptible to Covid-19 infection. Rh positive groups were linked with
Fazal U. Rehman et al, 2021	Pakistan	Cross-Sectional	369	52.8 ± 17.7	Male= 212, Female =157	SARS-CoV-2 confirmed by RT-PCR	NA	21.90%	39.80%	30.00%	8.10%	They found no any association of Blood groups with Covid-19, however co morbities like diabetes and hypertension were directly associated
Muhammad Nisar Khan et al 2022	Pakistan	Cross-Sectional	4047	27.27±7.13	Male= 4000, Female =47	Kit method for auto anti bodies against COVID-19	NA	27.03%	32.34%	30.12%	10.5%	The study found out that susceptibility of SARS-COV-2 varies with blood types and Blood type O is associated with low risk of infection.
Yuqin Wu et al, 2020	China	Retrospective case-control study	2178 (Cases = 187, Controls = 1991)	NA	COVID-19 +ve male = 97, COVID-19 +ve female = 90	COVID-19 +ve patients and controls	NA	Cases = 36.90%, Controls = 27.47%	Cases = 33.69%, Controls = 32.35%	Cases = 21.92%, Controls = 30.19%	Cases = 7.49%, Controls = 9.99%	Patients with blood group A had an increased risk for infection with SARS-CoV-2, whereas blood group O was associated with a decreased risk, indicating that certain ABO blood groups were correlated with
Dr. Fawad Rahim et al, 2021	Pakistan	Cross sectional	3870 (Cases = 1935, Comparison group = 1935)	COVID-19 +ve = 39.73±15.26, Comparison group = 32.36 ± 8.65	COVID-19 +ve male = 1328, COVID-19 +ve female = 607, Comparison group male = 1310, Comparison group female = 625	SARS-CoV-2 confirmed cases and blood donors was used as a comparison group.	COVID-19 group Rh+ = 1806, Comparison group Rh+ = 1837	COVID-19 group = 27%, Comparison group = 28.8%	COVID-19 group = 35.9%, Comparison group = 31.9%	COVID-19 group = 25.3%, Comparison group = 25.1%	COVID-19 group = 11.8%, Comparison group = 14.2%	This study found a significant association with blood groups B and AB, but not with blood groups O and A. They further mentioned there was less risk of susceptibility with rh positive blood types

Study Year	Country	Study Design	Sample Size	Age (years)	Gender	Patients	Rhesus	ABO blood group prevalence				Main findings
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Mohammad Rabiul Halim et al, 2021	Bangladesh	Cross Sectional	771	Above 18	Male = 627, Female = 147	SARS-CoV-2 confirmed by RT-PCR	Positive = 724, Negative = 47	37.35%	17.38%	18.81%	26.46%	In this study the association of COVID-19 severity with ABO blood groups was evaluated. Blood type A was found more prevalent to develop severity. Blood group o has less impact oon the complications of COVID-19. Mortality was reported in 11.7% cases.
Ahmet Nalbant et al, 2021	China	Cross-Sectional	313	COVID-19 +ve cases = 57.74±16, COVID-19 -ve cases = 66.41±15	Male = 168, Female = 145	SARS-CoV-2 confirmed by RT-PCR	Positive = 279, Negative = 34	46.90%	14.40%	31.60%	7.03%	Incidence of COVID-19 is more in blood group O and in younger population. Mortality was found to be 6.7% and mostly found in the patients having blood group B.
Elaina Pasangha et al, 2021	India	Cross Sectional	370	Mean age = 48.02	Male = 186, Female = 184	SARS-CoV-2 confirmed by RT-PCR	NA	22.20%	39.20%	34.60%	4%	The study concluded that blood group B was more prevalent but AB blood type was found to be more associated with severity of COVID-19. Mild cases = 40.5%, Moderate cases = 7.1%, Severe cases = 7.1%, Critical = 45.4%
Priya Bhardwaj et al, 2022	India	Cross-Sectional	1146, COVID-19 +ve = 605, COVID-19 -ve = 541	18 and above	COVID-19 +ve male = 355, COVID-19 +ve female = 250	Enrolled infected and non-infected people by online and offline survey.	NA	19.60%	41.90%	29.90%	8.60%	Blood group B had higher susceptibility to COVID-19. Blood group A was found to be associated with lower risk of severe infection.
Maryam Nasiri et al, 2021	Iran	Cross Sectional	329	64.7 ±18.5	Male = 167 , Female = 162	SARS-CoV-2 confirmed by RT-PCR and chest CT scans	Positive = 297, Negative = 32	39.20%	20.10%	34.30%	6.40%	Blood type was not found to be associated with Covid-19 death rate or associated

Study Year	Country	Study Design	Sample Size	Age (years)	Gender	Patients	Rhesus	ABO blood group prevalence				Main findings
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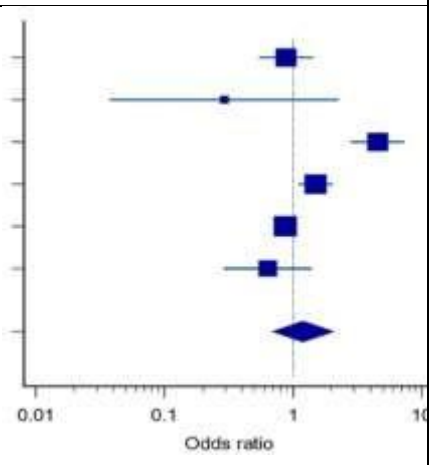
Afshan Noor et al, May 2021	Pakistan	Cross sectional analytical study	2653 (COVID-19 +ve = 326, Normal population = 2327)	COVID-19 +ve = 41.18 ± 12.56	COVID-19 +ve male = 310, COVID-19 +ve female = 16	SARS-CoV-2 confirmed by RT-PCR	COVID-19 +ve Rh positive = 303, COVID-19 +ve Rh negative = 23	COVID-19 +ve = 37.4%, Normal population = 22.7%	COVID-19 +ve = 32.8%, Normal population = 40.6%	COVID-19 +ve = 21.8%, Normal population = 26.6%	COVID-19 +ve = 8%, Normal population = 10.1%	Blood group A had a significant association where as people with blood group O had a least association for COVID-19 infection and severity. The findings of the
Nagla A. El-Shitany et al, 2021	Saudi Arabia	Retrospective Cross-Sectional study	1433 (COVID-19 recovered pts = 726, Healthy people = 707)	All age groups	COVID-19 recovered male = 110, COVID-19 recovered female = 616, Healthy male = 117, Healthy female = 590	COVID-19 recovered patients and healthy people	COVID-19 recovered pts Rh+ = 591, COVID-19 recovered pts Rh- = 135, Healthy people Rh+ = 594, Healthy people Rh- = 113	COVID-19 recovered pts = 35%, Healthy people = 29%	COVID-19 recovered pts = 25%, Healthy people = 23%	COVID-19 recovered pts = 28%, Healthy people = 36%	COVID-19 recovered pts = 12%, Healthy people = 12%	The people of blood group O may be the least likely to be infected with COVID-19, however, they may be the more in need of treatment in the hospital.
Nora Y Hakami et al, 2022	Saudi Arabia	Cross-Sectional	204 (COVID-19 group = 104, Control group = 100)	NA	NA	COVID-19 diagnosed patients and healthy individuals	COVID-19 group Rh+ = 93, COVID-19 group Rh- = 11, Control group Rh+ = 93, Control group Rh- = 7	COVID-19 group = 23.1%, Control group = 30%	COVID-19 group = 14.4%, Control group = 12%	COVID-19 group = 57.7%, Control group = 48%	COVID-19 group = 4.8%, Control group = 10%	This study showed no significant association between ABO and rhesus factor. This study did not show any significant association of blood groups with severity and of COVID-19 disease and COVID-19-associated mortality.
Uzma Ishaq et al, 2021	stan	Retrospective study	1067	Blood group A = 47.37 ± 20.21, Blood group B = 47.71 ± 18.45, Blood group O = 47.54 ± 18.84, Blood group AB = 48.87 ± 21.31	Male = 712, Female = 355	SARS-CoV-2 confirmed by RT-PCR	NA	18.93%	27.64%	48.82%	4.59%	This study did not show any significant association of blood groups with severity and of COVID-19 disease and COVID-19-associated mortality.

Table – 1: Basic characteristics and main findings of the included studies (contd…)

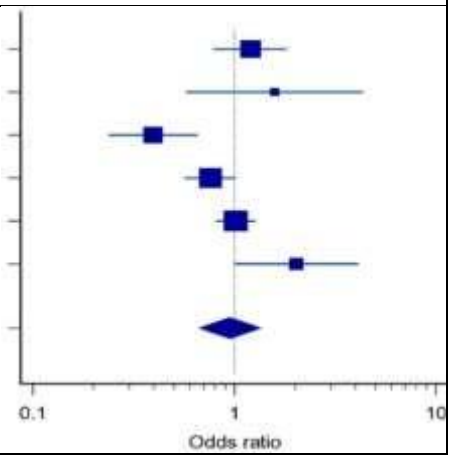
Study Year	Country	Study Design	Sample Size	Age (years)	Gender	Patients	Rhesus	ABO blood group prevalence				Main findings
								Blood group "A"	Blood group "B"	Blood group "O"	Blood group "AB"	
Ryan L. Hoiland et al, 2020	Canada	Case series with nested prospective substudy	125 (Available data for blood groups = 95)	Blood group O / B = 66 (58-73), Blood group A / AB = 71 (65-78),	Blood group O / B male = 34, Blood group O / B female = 23, Blood group A / AB male = 27, Blood group A / AB female = 11	All ICU patients with SARS-CoV-2 confirmed by RT-PCR	NA	37%	17%	43%	3%	This study found out that critically ill COVID-19 patients with blood group A or AB are at increased risk for requiring mechanical ventilation, CRRT, and prolonged ICU admission compared with patients with blood group O or B.
Gagan Kumar et al, 2021	USA	Observational study	3563	Blood group A = 67 (54 - 77), Blood group B = 67 (52 - 78), Blood group O = 66 (52 - 76), Blood group AB = 68 (53 - 77)	Blood group A: Male = 53.8%, Female = 46.2%, Blood group B: Male = 52.8%, Female = 47.2%, Blood group O: Male = 50.3%,	SARS-CoV-2 confirmed by RT-PCR	Blood group A Rh+ = 89.5%, Blood group B Rh+ = 89.4%, Blood group O Rh+ = 91.2%, Blood group AB Rh+ = 88.7%	36.50%	10.60%	49.20%	3.70%	This study demonstrated that blood types A and O are not associated with severity.
Mina Khasayesi et al, 2021	Iran	Cross-Sectional Analytical study	3646 (COVID-19 group = 171, General population = 3475)	COVID-19 group: 54.9±1.2	Male = 94, Female = 77	Patients of SARS-CoV-2 confirmed by RT-PCR and Iranian general population	COVID-19 group Rh+ = 167, COVID-19 group Rh- = 4, General population Rh+ = 3152, General population Rh- = 323	COVID-19 group = 26.3%, General population = 32.1%	COVID-19 group = 28.1%, General population = 23.7%	COVID-19 group = 38.6%, General population = 36.5%	COVID-19 group = 7%, General population = 7.7%	In this study a positive correlation was found between blood type B and COVID-19 severity. Also, mechanical ventilation was significantly more in Rh-negative patients.

Study	Critical		Non-critical		Weights (%)	Odds Ratio [95% CI]
	Events	Total	Events	Total		
Elaina Pasangha, 2021	41	194	41	176	18.68	0.882 [0.54; 1.442]
Syed Asim Ali Shah, 2022	1	16	43	232	5.45	0.293 [0.0377; 2.279]
Afshan Noor, 2020	75	128	47	198	18.8	4.546 [2.812; 7.351]
Uzma Ishaq, 2021	83	357	119	711	20.46	1.507 [1.1; 2.064]
Gagan Kumar, 2021	394	1144	907	2419	21.58	0.876 [0.756; 1.015]
Mina Khasayesi, 2021	10	49	35	122	15.04	0.637 [0.287; 1.415]
Total	**604**	**1888**	**1192**	**3858**	**100**	**1.2 [0.691; 2.084]**



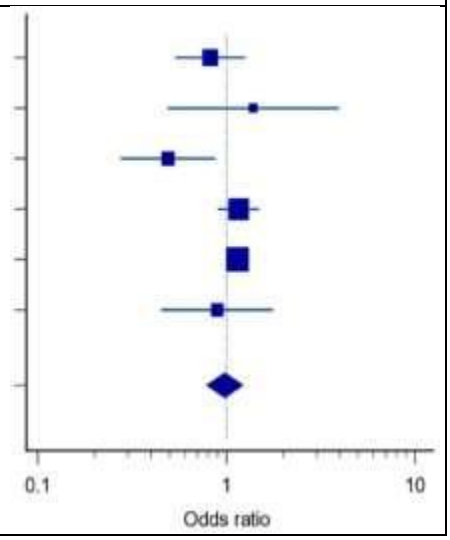
Heterogeneity: Q = 50.1135, df = 5 (P < 0.0001), I^2 = 90.02%
Test for overall effect Z = 0.646 (P = 0.518)
The above forest plot represents the prevalence of blood group A in critical and non-critical cases of COVID-19. The overall odds ratio was found to be 1.2 with 95% confidence interval [0.691, 2.084]. The overall effect was statistically insignificant (z = 0.646, p = 0.518) which represents that blood group A has no association with the severity of COVID-19. The quality of evidence was seemed to be very low for inconsistency due to heterogeneity (I^2 = 90.02%).

Study	Critical		Non-critical		Weights (%)	Odds Ratio [95% CI]
	Events	Total	Events	Total		
Elaina Pasangha, 2021	80	194	65	176	18.59	1.198 [0.788; 1.822]
Syed Asim Ali Shah, 2022	8	16	90	232	8.22	1.578 [0.572; 4.353]
Afshan Noor, 2020	27	128	80	198	16.5	0.394 [0.237; 0.657]
Uzma Ishaq, 2021	86	357	210	711	21.45	0.757 [0.566; 1.013]
Gagan Kumar, 2021	122	1144	255	2419	22.72	1.013 [0.806; 1.273]
Mina Khasayesi, 2021	19	49	29	122	12.52	2.031 [0.999; 4.131]
Total	**342**	**1888**	**729**	**3858**	**100**	**0.951 [0.667; 1.356]**



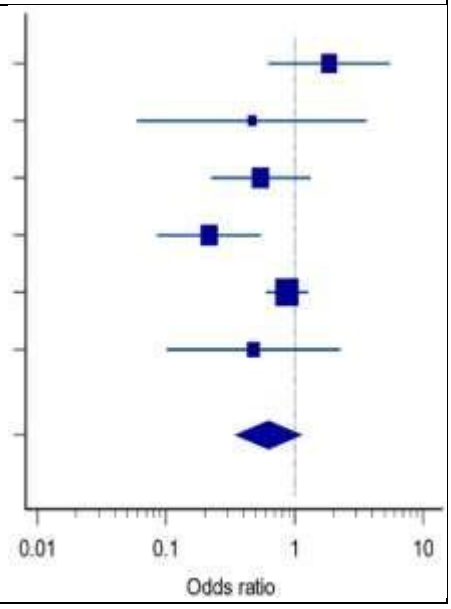
Heterogeneity: Q = 20.3818, df = 5 (P < 0.0011), I^2 = 75.47%
Test for overall effect Z = -0.279 (P = 0.780)
The forest plot above illustrates the occurrence of blood group B in both critical and non-critical cases of COVID-19. The total odds ratio was determined as 0.951, with 95% confidence interval of [0.667, 1.356]. The aggregate impact was deemed statistically insignificant (z = -0.279, p = 0.78), indicating the absence of a correlation between blood group B and the severity of COVID-19. The level of evidence was observed to be notably low, primarily attributed to considerable heterogeneity (I^2 =75.47%).

Study	Critical		Non-critical		Weights (%)	Odds Ratio [95% CI]
	Events	Total	Events	Total		
Elaina Pasangha, 2021	63	194	65	176	16.18	0.821 [0.535; 1.261]
Syed Asim Ali Shah, 2022	6	16	70	232	4.1	1.389 [0.486; 3.969]
Afshan Noor, 2020	19	128	52	198	10.84	0.489 [0.274; 0.875]
Uzma Ishaq, 2021	183	357	338	711	26.22	1.161 [0.9; 1.497]
Gagan Kumar, 2021	589	1144	1163	2419	34.22	1.146 [0.996; 1.319]
Mina Khasayesi, 2021	18	49	48	122	8.45	0.895 [0.451; 1.776]
Total	**878**	**1888**	**1736**	**3858**	**100**	**0.981 [0.784; 1.228]**



Heterogeneity: Q = 10.1977, df = 5 (P = 0.0698), I^2 = 50.97%
Test for overall effect Z = -0.170 (P = 0.865)
The above forest plot displays the prevalence of blood group O in critical and non-critical COVID-19 cases. The overall odds ratio was found to be 0.981 having 95% confidence interval of [0.784, 1.228]. The overall effect yielded a statistically insignificant outcome (z = -0.170, p = 0.865), signifying the lack of an association between blood group O and COVID-19 severity. The quality of evidence was good, reflecting considerable less heterogeneity among studies as compared to the above two forest plots. (I^2 = 50.97%).

Study	Critical		Non-critical		Weights (%)	Odds Ratio [95% CI]
	Events	Total	Events	Total		
Elaina Pasangha, 2021	10	194	5	176	15.8	1.859 [0.623; 5.548]
Syed Asim Ali Shah, 2022	1	16	29	232	6.69	0.467 [0.0594; 3.666]
Afshan Noor, 2020	7	128	19	198	19.13	0.545 [0.222; 1.336]
Uzma Ishaq, 2021	5	357	44	711	18.45	0.215 [0.0846; 0.548]
Gagan Kumar, 2021	39	1144	94	2419	29.71	0.873 [0.597; 1.277]
Mina Khasayesi, 2021	2	49	10	122	10.22	0.477 [0.101; 2.259]
Total	**64**	**1888**	**201**	**3858**	**100**	**0.626 [0.345; 1.135]**



Heterogeneity: Q = 11.3031, df = 5 (P = 0.0457), I^2 = 55.76%
Test for overall effect Z = -1.543 (P = 0.123)
Depicted in the forest plot above is the prevalence of blood group AB in both critical and non-critical cases of COVID-19. The overall odds ratio was calculated as 0.626, accompanied by a 95% confidence interval of [0.345, 1.135]. The overall effect was found to be statistically insignificant (z = -1.543, p = 0.123), suggesting the absence of association between blood group AB and the severity of

COVID-19. The quality of evidence appeared to be of a low standard, mainly due to the substantial heterogeneity observed (I^2 = 55.76%).

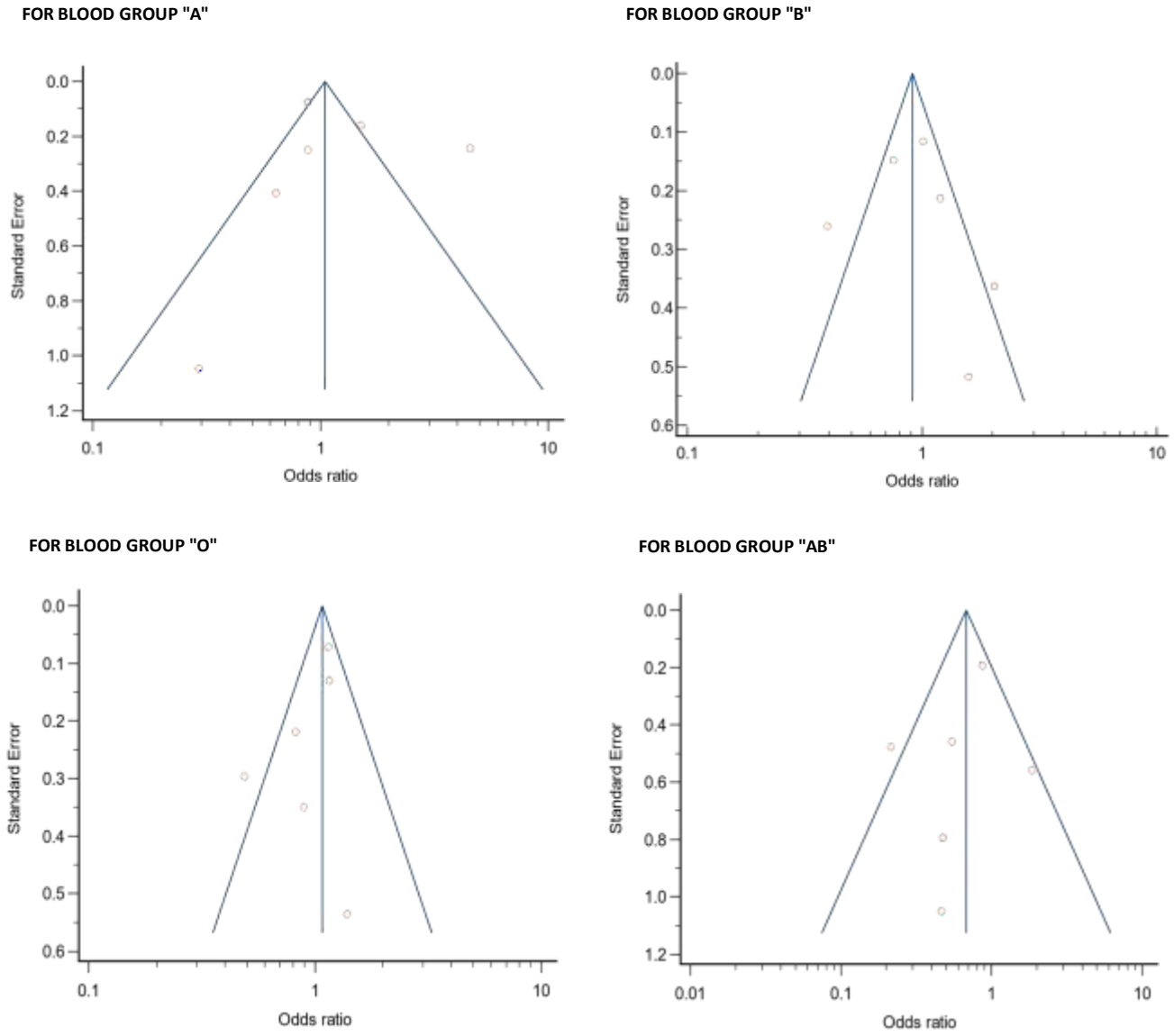


Figure – 2: Funnel plots for blood groups A, B, O and AB

Figure – 2 represents the funnel plots constructed for the prevalence of blood group types in critical and non-critical COVID-19 cases to evaluate the publication bias. For blood groups A, B, O and AB the Egger's test was found to be insignificant with p-value = 0.6174, p-value = 0.7546, p-value = 0.2257 and p-value = 0.484 respectively, which indicates that there is not enough statistical support to reject the null hypothesis i.e. there is no publication bias.

9. Discussion

The studies conducted in diverse populations aimed to investigate the potential associations between ABO blood groups and the severity or susceptibility of COVID-19. The South Indian study (20) found that blood group B was the most prevalent among COVID-19-positive patients, with the AB blood group demonstrating significant associations with adverse outcomes such as acute respiratory distress syndrome (ARDS), sepsis, and septic shock. Conversely, the O blood group showed lower rates of lymphopenia and leucocytosis, but without significant clinical associations. Pakistani studies revealed varying findings. Observational cross-sectional survey, identified a significant link between

ABO blood groups, Rh factor, and COVID-19 severity. In this study, individuals with blood group B and Rh-positive antigen were found to be more susceptible to COVID-19.(21) Another Pakistani study, conducted at a tertiary care center, reported a significant association between blood group A and COVID-19 infection and mortality, while blood group O had the least prevalence in COVID-19 cases.(22). (23) Fazal U rehman in Pakistan found no significant difference in COVID-19-related mortality among different blood groups, and acute phase reactants were not positively associated with any specific blood type.

The Northeast Georgia, USA study, covering a substantial number of subjects, concluded that once hospitalized with COVID-19 infection, blood groups A and O were not associated with increased severity or mortality. (24) The Iranian study, exploring the relationship between blood types and the severity of COVID-19 infection, found that blood group B was associated with the development of severe COVID-19. However, no statistically significant difference in mortality based on blood group or Rh factor was observed.(25)

When comparing these studies, discrepancies emerge regarding the associations between ABO blood groups and COVID-19 outcomes. The South Indian and Iranian studies suggest specific blood groups may be linked to adverse outcomes, while the Pakistani studies show associations with susceptibility but present inconsistent findings regarding specific blood types. The study from Northeast Georgia in the USA did not find significant associations between blood groups and severity or mortality once patients were hospitalized. These variations highlight the need for larger, well-designed studies across diverse populations to establish a more conclusive understanding of the relationship between ABO blood groups and COVID-19 outcomes.

10.Conclusion:-

In this evidence based meta-analysis, the results showed there was no any significant association between the blood groups and severity outcomes of Covid-19. We found that Covid- 19 infection severity and its outcomes vary from population to population. Data varies from one demographic area to other as well. Certain factor like male gender, age and co morbidities play a more important role in disease progression and its end outcome. ABO blood groups play no any significant role in identifying that any particular blood group give rise to severe outcome of Covid-19. Further studies are still required to understand complex mechanisms to understand how ABO blood groups might affect severity of infection. A larger data subset and extensive reporting of blood groups along with their subtypes should be reported to have more extensive studies in this area.

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