Review

ABO blood group and COVID-19: an updated systematic literature review and meta-analysis

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Background - Following the first reports in the literature, the association between the ABO blood group and SARS-CoV-2 infection has been investigated by a number of studies, although with varying results. The main object of this systematic review was to assess the relationship between the ABO blood group and the occurrence and severity of COVID-19.

Materials and methods - A systematic literature search using appropriate MeSH terms was performed through Medline and PubMed. The outcomes considered were the prevalence of the blood group O *vs* non-O types in SARS-CoV-2 infected and non-infected subjects, and the severity of SARS-CoV-2 infection according to ABO group. The methodological quality of the studies included in the analysis was assessed with the Newcastle-Ottawa Scale, and the overall quality of the available evidence using the GRADE system. Benchmarks used to evaluate the effect size were odd ratios (ORs) for case control studies and risk ratios (RRs) for cohort studies.

Results - Twenty-one studies were included in the analysis. Overall, individuals with group O had a lower infection rate compared to individuals of non-O group (OR: 0.81; 95% CI: 0.75, 0.86). However, the difference in the effect size was significantly lower in cohort studies compared to case control studies. No evidence was found indicating an effect of the O type on the disease severity in the infected patients.

Discussion - We have found low/very low evidence that group O individuals are less susceptible to SARS-CoV-2 infection compared to those in the non-O group. No evidence was found indicating an effect of the O type on disease severity in SARS-CoV-2 infection.

Keywords: *ABO blood group, COVID-19, disease, systematic review.*

INTRODUCTION

The ABO blood group is the most important among human blood group systems and consists of complex carbohydrate moieties at the extracellular surface of red blood cell (RBC) membrane[1,2]. While the A and B alleles of the ABO locus encode A and B glycosyltransferase activities, which convert precursor H antigen into either A or B determinants by adding an extra saccharide unit, group O individuals lack such transferase

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enzymes and express basic, unchanged H-antigen[3]. Along with their expression on RBCs, ABO antigens (namely A, B, AB and O) are also highly expressed on the surface of a variety of human cells and tissues[4]. Although the physiological role of ABO antigens and their related anti-A and anti-B natural isoagglutinins is still largely unknown, they play a prominent role in blood transfusion and cell, tissue, and organ transplantation[4]. In addition, several studies over the last 50 years have documented a close link between ABO blood groups and a wide array of diseases, including cancers and cardiovascular disorders[5]. The latter association is particularly relevant, considering the profound influence of ABO antigens on haemostasis, particularly in modulating von Willebrand factor (VWF) and factor VIII (FVIII) circulating levels[6-10]. In addition, the ABO blood group-related susceptibility to various types of viral infections, including HIV, hepatitis B, dengue and influenza viruses, has been consistently reported by several investigators over the last 20 years[11-14]. This has recently gained renewed interest thanks to the observation on the association between ABO blood type and the pandemic Coronavirus Disease 2019 (COVID-19)[15]. In particular, it has been hypothesised that individuals belonging to O blood type are less susceptible to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection than those belonging to non-O blood groups, or that they have a milder disease[16]. The hypothesis for this phenomenon lies in the presence in O blood group subjects of IgG anti-A isoagglutinins which would prevent the binding of SARS-CoV-2 to its receptor thereby stopping the virus entering the targeted human cells[17]. In this review, we will show and critically discuss the results of a systematic literature review and meta-analysis on the correlation between ABO blood groups and SARS-CoV-2 infection and severity, along with its possible implications for future health policies.

MATERIALS AND METHODS

Search methods

For this systematic review, we analysed the medical literature for published articles on the association between ABO blood type and SARS-CoV-2 infection. The Medline and PubMed electronic databases were searched for English language articles published from 1st January 2020 to 30th December 2020. Only those articles that had been subjected to peer review were included in the final analysis. The Medical Subject Heading and key words used were: "novel coronavirus disease", "COVID-19", "SARS-CoV-2", "acute respiratory distress syndrome", "ABO blood groups", and "ABO blood type". We also screened the reference lists of the most relevant review articles for additional studies that had not been captured in our initial literature search. Studies were selected independently by two reviewers (M.F. and M.C.), with disagreements resolved through discussion and on the basis of the opinion of a third reviewer (C.M.).

Criteria for study selection

Inclusion criteria were: 1) studies that reported ABO blood group prevalence among SARS-CoV-2 infected subjects and in non-infected subjects; 2) studies that reported severity of SARS-CoV-2 according to ABO group. Both cohort studies and case control studies were included; case reports were excluded.

Outcomes

The outcomes were: i) prevalence of the blood group O *vs* non-O types in SARS-CoV-2 infected subjects and in non-infected subjects; and ii) the severity of SARS-CoV-2 infection according to ABO group. The severity of SARS-CoV-2 infection we have considered were the endpoints used to define the severity reported in the selected studies.

Quality assessment

We evaluated both the quality of reporting and the methodological quality of the studies included in the analysis. For this purpose, we used the Newcastle-Ottawa Scale (NOS) checklist. The NOS is a 9-point scale that assigns points on the basis of the process of selection of the cohorts or of the case and of the controls (0-4 points), of the comparability of the cohorts or of the case and of the controls (0-2 points), and of the identification of the exposure and of the outcomes of study participants (0-3 points). The NOS was developed to assess the quality of non-randomised studies for the purpose of incorporating quality assessments in the interpretation of meta-analytic results. This scale is recommended by the Cochrane non-randomised studies methods[18,19]. This quality assessment was performed independently in duplicate (M.C., M.F.) and any disagreement was resolved by consensus. Using the NOS, a study can be awarded a maximum of 4 stars for selection, a maximum of 2 stars

for comparability, and a maximum of 3 stars for outcome. Since some of the studies reporting prevalence of ABO group among SARS-CoV-2 infected and non-infected subjects also reported severity of SARS-CoV-2 infection, and as such, in this context, can be regarded as cohort studies, the quality assessment was performed separately for the two pre-specified outcomes. We considered a study which scored ≥7 a high-quality study, and the remaining as non-high quality studies. The publication bias was investigated by the funnel plot and the Egger test for funnel plot asymmetry in meta-analysis.

Summary of findings

We used the principles of the GRADE system to assess the quality of the body of evidence associated with specific outcomes, and constructed "Summary of findings" tables (**Tables I** and **II**). These tables present key information concerning the certainty of the evidence, the magnitude of the effects in the groups of subjects examined, and the sum of available data for the main outcomes. The "Summary of findings" tables also include an overall grading of the evidence related to each of the main outcomes using the GRADE approach, which defines the certainty of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest. The certainty of a body of evidence involves consideration of within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates, and risk of publication bias. Outcomes in terms of occurrence of infection and severity of infection are presented in **Table II**.

Statistical analysis

The role of the O-type blood group in SARS-CoV-2 infection was evaluated comparing the prevalence of O type in infected patients (cases) and in non-infected subjects (controls). The meta-analysis was performed using the inverse variance (IV) method for study weighting, pooling odd ratios (ORs) and/or risk ratios (RRs) at study level. A random-effects approach was followed, with DerSimonian-Laird estimator for tau. The *I*-squared index for inconsistence was calculated to address the heterogeneity between studies.

The effect size calculation for case-control studies is based on the prevalence of the exposure in the diseased and in the not diseased, and should be calculated with an OR ratio[20]. In any case, often the OR is a good approximation of RR, especially if the incidence in both exposed and not exposed is low (<10%) and the true RR remains close to 1. For cohort studies, we evaluated the mean relative risk (RR) for the infection as this represents a more understandable quantification of effect size and preventable fraction in the exposed population (PFE).

Subgroup analyses

Subgroup analysis was carried out according to the study design (case control or cohort). Differences in effect size between case control and cohort studies were evaluated with a test for subgroup difference. $p<0.1$ was considered to be a statistically significant subgroup effect[21]. Stata 16.1 and package "meta" with R version 4.0.3 software were used to perform calculations.

RESULTS

Overall, we identified 746 references through electronic and manual searches (**Figure 1**). Seven hundred and eight studies were excluded as duplicates or as not relevant to this review according to the title and/or abstract. After reading the full text of the remaining 38 potentially eligible studies, 17 were excluded (reviews, commentaries, non-peer reviewed publication, insufficient data). Only those studies fulfilling the selection criteria were included in the final analysis. Thus, for this systematic review, we considered 21 studies fulfilling our pre-specified criteria[22-42]. **Table I** summarises the main characteristics and results of these studies. Some studies included different cohorts of patients and, where 2×2 data were available, we calculated separate ORs for each cohort. Ellinghaus *et al.* provided data from Italian and Spanish hospitals[22]. Leaf *et al.*[31] stratified the analysis according to race/ethnicity (White non-Hispanic, Black non-Hispanic, Asian non-Hispanic, and Hispanic). Zhao *et al.*[36] collected patients and controls at the Jinyintan Hospital in Wuhan, and at Shenzhen Hospital, Guangdong Province, in the People's Republic of China. In a Spanish study, Muñiz-Diaz *et al.*[41] included a cohort of blood donors recruited for convalescent plasma donation after recovering from a mild SARS-CoV-2 infection, and a cohort of patients with severe SARS-CoV-2 infection who were transfused during hospitalisation (donors and transfused).

Bias assessment

The NOS checklists for individual studies are presented in the *Online Supplementary Content* (**Tables SI-SIII**). In cohort

Table I - *Main characteristics and results of the studies on the association between ABO blood groups and COVID-19*

Author, year	Country	Study design	Sample[1] (n)	Mean age (years)	Gender (M/F)	ABO blood group prevalence (O *vs* non-O)	Main results
Abdollahi, 2020[23]	Iran	Case-control	Cases: 397 Controls: 500	Cases: 58.8 Controls: 48.5	Cases: 252/145 Controls: 231/269	Cases: 28 *vs* 72%[1] Controls: 38 *vs* 62%	Group O subjects have a reduced vulnerability to COVID-19. No association between ABO blood types and COVID-19 severity was observed.
Boudin, 2020[24]	France	Cross-sectional cohort, retrospective	Cases: 1,279 Controls: 409	Cases: 28[2] Controls: 27[2]	Cases: 1,112/167 Controls: 354/55	Cases: 43.2 *vs* 56.8% Controls: 46.2 *vs* 53.8%	In a large population confined to an aircraft carrier, ABO blood groups were not associated with increase/decrease in risk of SARS-CoV-2.
Dzik, 2020[25]	USA	Case-control	Cases: 957 Controls: 5,840	Cases: NR Controls: NR	Cases: NR Controls: NR	Cases: 48.6 *vs* 51.4% Controls: 46.6 *vs* 53.4%	No association between ABO distribution and SARS-CoV-2 infection or mortality was observed.
Ellinghaus, 2020[22]	Italy, Spain	Case-control	Cases: 1,610 Controls: 2,205	Cases: NR Controls: NR	Cases: 1,126/484 Controls: NR	Cases: 37.5 *vs* 62.5% Controls: 47.8 *vs* 52.2%	A protective effect in blood group O as compared with other blood groups was observed.
Fan, 2020[26]	China	Case-control	Cases: 105 Controls: 103	Cases: 56.8 Controls: 54.0	Cases: 55/50 Controls: 56/47	Cases: 21.9 *vs* 78.1% Controls: 29.1 *vs* 70.9%	Females with blood type A were more susceptible to COVID-19.
Franchini, 2020[27]	Italy	Case-control	Cases: 447 Controls: 16,911	Cases: 47.7 Controls: 47.1	Cases: 385/62 Controls:10,321/6,590	Cases: 36.2 *vs* 63.8% Controls: 43.6 *vs* 56.4%	The prevalence of O blood type in convalescent plasma donors recovered from COVID-19 was significantly lower than that observed in healthy blood donors.
Gallian, 2020[28]	France	Cross-sectional cohort, prospective	Cases: 27 Controls: 971	Cases: NR Controls: NR	Cases: NR Controls: NR	Cases: 22.2 *vs* 78.2% Controls: 46.1 *vs* 53.9%	A lower prevalence of anti-SARS-CoV-2 neutralising antibodies was found in French group O blood donors.
Göker 2020[29]	Turkey	Case-control	Cases: 186 Controls: 1,881	Cases: 42 Controls: NR	Cases: 100/86 Controls: NR	Cases: 24.8 *vs* 75.2% Controls: 37.2 *vs* 62.8%	The frequency of O blood group was significantly lower in COVID-19 patients compared to controls. Blood group types did not affect clinical outcomes.
Latz 2020[30]	USA	Cross-sectional cohort, retrospective	Cases: 1,289 Controls: 6,359	Cases: NR Controls: NR	Cases: 427/862 Controls: NR	Cases: 45.5 *vs* 54.5% Controls: 48.3 *vs* 51.7%	ABO blood type was not associated with disease severity. O blood group subjects were less likely to test positive for COVID-19 than AB and B groups.
Leaf, 2020[31]	USA	Case-control	Cases: 2,033 Controls: 3.1 m	Cases: 62[2] Controls: NR	Cases: 1,297/736 Controls: NR	Cases: 46.7 *vs* 53.3% Controls: NR	O blood type was a protective risk factor for severe COVID-19 in white race individuals. No association was found with the risk of death.
Li, 2020[32]	China	Case-control	Cases: 2,153 Controls: 3,694	Cases: NR Controls: NR	Cases: NR Controls: NR	Cases: 25.7 *vs* 74.3% Controls: 33.8 *vs* 66.2%	People with blood group O had a significantly lower risk of SARS-CoV-2 infection.
Wu, 2020[33]	China	Case-control	Cases: 187 Controls: 1,991	Cases: NR Controls: NR	Cases: NR Controls: NR	Cases: 21.9 *vs* 78.1% Controls: 30.2 *vs* 69.8%	Individuals with group O had a lower risk of COVID-19 than non-O blood group subjects.
Yaylaci, 2020[34]	Turkey	Cross-sectional cohort, prospective	Cases: 397 Controls: NR	Cases: 47.2 Controls: NR	Cases: 176/221 Controls: NR	Cases: 27.5 *vs* 72.5% Controls: NR	No relationship was found between blood groups and mortality or ICU admission.
Zhang, 2020[35]	China	Cross-sectional cohort, retrospective	Cases: 134 Controls: 3,694	Cases: 60.8 Controls: NR	Cases: 87/47 Controls: NR	Cases: 19.2 *vs* 71.8% Controls: 33.8 *vs* 66.2%	A lower infection rate was observed among group O subjects. There was no significant difference in ABO blood type distribution between survivors and non-survivors.
Zhao, 2020[36]	China	Case-control	Cases: 1,775 Controls: 3,694	Cases: NR Controls: NR	Cases: NR Controls: NR	Cases: 25.8 *vs* 74.2% Controls: 32.2 *vs* 67.8%	Individuals with group O had a higher risk and those with group A a lower risk for SARS-CoV-2 infection.

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Table I - *Main characteristics and results of the studies on the association between ABO blood groups and COVID-19 (continued from previous page)*

Author, year	Country	Study design	Sample[1] (n)	Mean age (years)	Gender (M/F)	ABO blood group prevalence (O vs non-O)	Main results
Ray, 2020[38]	Canada	Population-based cohort, retrospective	Cases: 225,556 Controls: NR	Cases: NR Controls: NR	Cases: 65,566/159,820 Controls: NR	Cases: NR Controls: NR	The O and Rh- blood groups may be associated with a slightly lower risk for SARS-CoV-2 infection and severe COVID-19 illness.
Ziezt, 2020[39]	USA	Cross-sectional cohort, retrospective	Cases: 2,394 Controls: 10,657	Cases: NR Controls: NR	Cases: NR Controls: NR	Cases: NR Controls: NR	A slightly increased infection prevalence among non-O types was found. Risk of intubation was decreased among A and increased among AB and B types, compared with type O.
Muniz-Diaz, 2020[41]	Spain	Case-control	Cases: 854 Controls:75,870	Cases: 45[2] Controls: 45[2]	Cases: 338/516 Controls:39,014/36,856	Cases: 41.5 *vs* 48.5% Controls: 47.3 *vs* 42.7%	ABO blood group is associated with susceptibility to acquire SARS-CoV-2 infection and with COVID-19 severity and mortality.
May, 2020[40]	USA	Cohort, retrospective	Cases: 165 Controls: NR	Cases: 57 Controls: NR	Cases: 61%/39% Controls: NR	Cases: 43 *vs* 57% Controls: NR	ABO blood group did not influence outcomes of patients with COVID-19.
Levi, 2020[37]	Brail	Cross-sectional cohort, retrospective	Cases: 2,037 Controls:1,813,237	Cases: NR Controls: NR	Cases: NR Controls: NR	Cases: 44.8 *vs* 55.2% Controls: 46.5 *vs* 53.5%	ABO blood group types did not significantly impact the risk for SARS-CoV-2 infection.
Barnkob, 2020[42]	Denmark	Cohort, retrospective	Cases: 7,422 Controls:466,232	Cases: 52[2] Controls: 50[2]	Cases: 32.9% men Controls: 32% men	Cases: 38.4 *vs* 61.6% Controls: 41.7 *vs* 58.3%	ABO blood group is a risk factor for SARS-CoV-2 infection but not for hospitalisation or death from COVID-19

studies, the quality was judged high for both the outcomes analysed since all studies achieved from 7 to 9 stars. For the outcome prevalence of COVID-19 in case control studies, the NOS score was <7 in 8 of the 11 case control studies (*Online Supplementary* **Table SII**).

Publication bias was evaluated for the outcome prevalence of infection. On the whole, the asymmetric aspect of the funnel plot seems to be at least partly due to the different distributions of the study effect sizes according to the study designs (*Online Supplementary* **Figures S1** and **S2**). When the two designs were examined jointly, the Egger test was significant (p=0.025); however, when the two designs were examined separately the significance was lost.

Quantitative analysis

Outcome: prevalence of O type vs non-O blood types in SARS-CoV-2 infected patients

The outcome prevalence of ABO groups in COVID-19 infected or non-infected individuals was reported in 17 studies, including 7 cohort studies[24,28,30,37-39,42] and 10 case control studies[22,23,25-27,29,32,33,36,41]. **Figure 2** reports the forest plot of the prevalence of the blood group O *vs* non-O types in cases (infected SARS-CoV-2 patients) and control (non-infected) subjects. The role of the O-type blood group in SARS-CoV-2 infection was evaluated in 17 studies, accounting for 19 2×2 tables. Overall mean OR was 0.81 (95% confidence interval [CI]: 0.75, 0.86). The effect was significantly different from the null hypothesis of absence of effect by O type on the probability of SARS-CoV-2 infection (z=6.19, p<0.0001). The effect was protective, suggesting a lower risk in subjects of O type. The quality of the evidence was graded as very low for inconsistency due to heterogeneity, and for risk of biases in case control studies (confounding, selection, ascertainment) (**Table II**). The mean OR of case control studies was 0.73 (95% CI: 0.64, 0.83), whereas the mean OR of cohort studies was 0.89 (95% CI: 0.85, 0.94). Thus, the null hypothesis of OR=1 was rejected in both cases, but the difference in the effect size was significantly lower in cohort studies compared to case control studies (test for subgroup difference: Q=8.31, degree of freedom: 1, p=0.0039).

Mean RR, evaluated in cohort studies, was 0.92 (95% CI: 0.87, 0.97), with z-score=3.21, p=0.001, and substantial heterogeneity (*I*-squared=72.7%). PFE was 8.1% (95% CI: 3.2%, 12.7%). The quality of the evidence in cohort studies was graded as low due to inconsistency,

Table II - *Summary of findings table. Relationship between ABO blood group and occurrence and severity of COVID-19*

Patient or population: COVID-19 infected subjects and uninfected controls. **Settings**: Inpatients and Outpatients. **Comparison**: ABO prevalence among COVID-19 infected and non-infected individuals; ABO prevalence in patients with severe or non-severe COVID-19 infections.						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**N. of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	***Corresponding risk***				
	Non-O group	***O group***				
Overall comparison	382,537/892,496 (42.8%)	34.6% (32.1/36.8%)	OR, 0.81 (0.75/0.86)	922,145 (16; 18 cohorts)	⊕⊖⊖⊖ **very low**[1]	There was evidence that individuals with blood group 0 had a decreased risk of SARS-COV-2 infection
Case-control studies	81,183/184,966 (43.8%)	31.9% (28.0/36.3%)	OR, 0.73 (0.64/0.83)	193,112 (10; 12 cohorts)	⊕⊖⊖⊖ **very low**[1]	There was evidence that individuals with blood group 0 had a decreased risk of SARS-COV-2 infection
Cohort studies	301,354/707,530 (42.5%)	37.8% (36.1/39.9%)	OR, 0.89 (0.85/0.94)	729,033 (7)	⊕⊕⊖⊖ **low**[2]	There was evidence that individuals with blood group 0 had a decreased risk of SARS-COV-2 infection. However, compared to case-control studies, the magnitude of the effect size in cohort studies was significantly lower
Severity of infections (endpoint severe infection/ICU admission)	1,083/5,541 (19.5%)	19.5% (17.7/21.2%)	RR, 1.00 (0.91/1.09)	9,147 (7)	⊕⊕⊖⊖ **low**[3]	Overall, individuals with blood group 0 had the same risk of severe SARS-CoV-2 infection compared to individuals with non-0 blood group

*The assumed risk is the mean control group risk across studies. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). [1]Downgraded for inconsistency due to heterogeneity, and twice for risk of bias in case-control studies (confounding, selection, ascertainment); [2]downgraded twice for inconsistency, and because not all the studies performed matching or adjustment of plausible prognostic variables; [3]downgraded for imprecision (95% CI includes line of no effect), and because not all the studies adjusted for prognostic factors

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality:** We are very uncertain about the estimate. CI: confidence interval; RR: risk ratio.

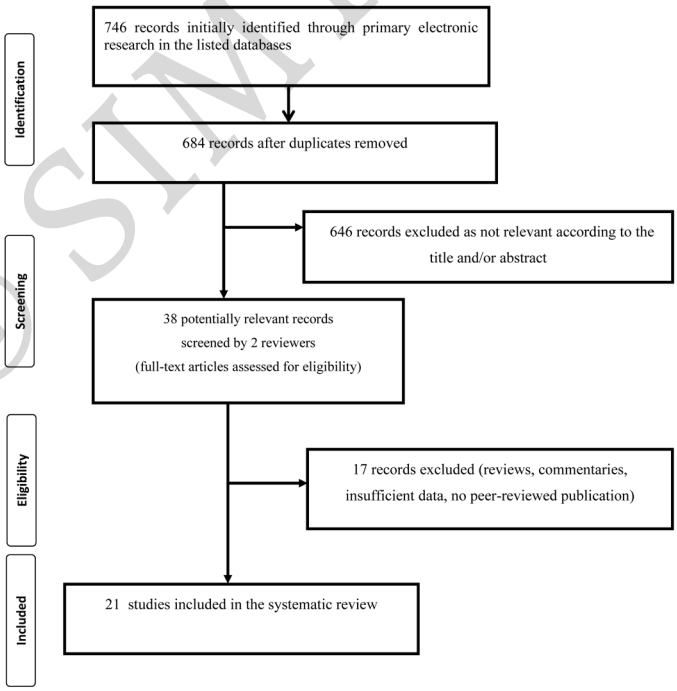

Figure 1 - Flow chart of the selection of studies

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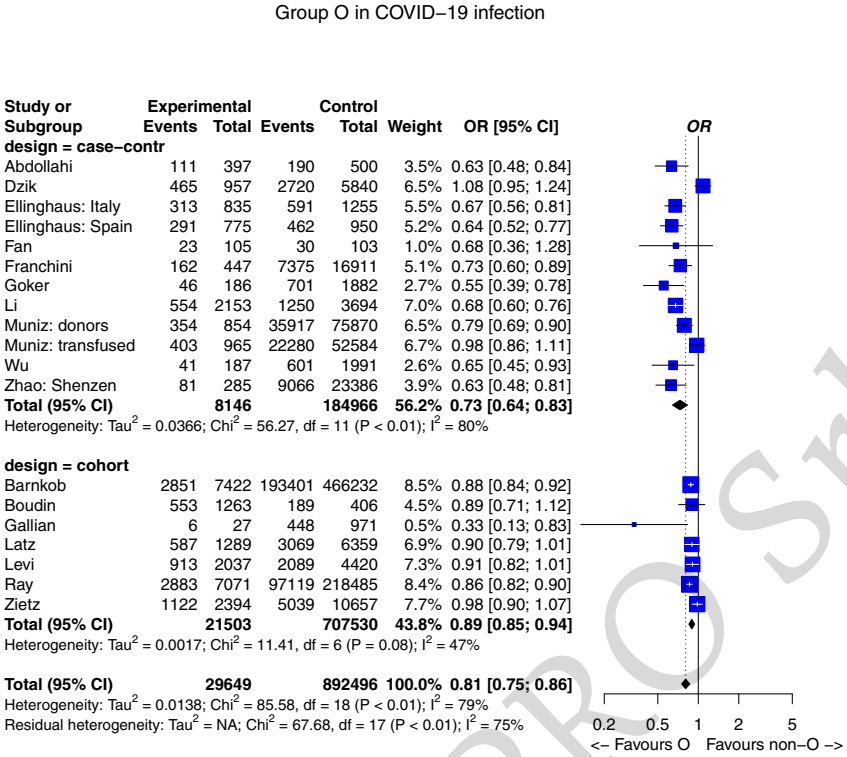

Figure 2 - Forest plot of the prevalence of the blood group 0 *vs* non-0 types in cases (infected SARS-CoV-2 patients) and control (uninfected) subjects

and because not all the studies performed matching or adjustment of plausible prognostic variables.

Outcome: severity of SARS-CoV-2 infection

The differential exposure to O blood group in cases (severe infection) and controls (non-severe infection) was expressed as RR, and the RRs were then pooled using a random-effect model. The outcome severity of SARS-CoV-2 infection was reported in 14 studies[23,25,27,29,30-32,34-36,38-40,42]. The severity of the disease was not uniformly defined in the cohorts of infected patients, and 8 endpoints of severity were assessed, each *vs* the opposite condition. The endpoints included in the selected studies were: i) severe *vs* non-severe clinical disease (7 studies)[23,27,29,30,34,38,40]; ii) death (11 studies)[25,29-32,34-36,39,40]; iii) hospitalisation *vs* non-hospitalisation (1 study)[42]; iv) need for intubation (4 studies)[29-31,39]; v) requirement of proning in the treatment of respiratory insufficiency (1 study)[30]; vi) acute kidney injury at admission (1 study)[31]; vii) shock (1 study)[31]; viii) thrombosis (1 study)[40].

Endpoints indicating clinical severity and related O type distribution are summarised in **Figure 3**; none were significantly associated to the O type blood group. In other words, no evidence was found indicating an effect of the O type on the disease severity in the infected patients. The RR was 1.0 (95% CI: 0.92-1.09) for the endpoint severe infection, and 0.95 (95% CI: 0.89-1.02) for death. The quality of the evidence was graded as low due to imprecision (95% CI includes line of no effect), and because not all the studies adjusted for prognostic factors

DISCUSSION

Due to the severity of the disease, mostly unpredictable, the identification of risk factors associated with SARS-CoV-2 infection and outcomes has become a research priority. Thus, following the first reports in literature on the association between ABO blood group and COVID-19, this has been the focus of attention in a number of investigative studies and, in particular, whether ABO blood type was associated not only with COVID-19 onset but also with its severity and disease-related mortality[43]. This growing interest is not surprising considering that the study of the

interaction between ABO blood system and infections has a long history and extensive literature[12]. Individuals with blood group O were reported to be more susceptible to Norovirus, and also had a significantly higher prevalence of *Helicobacter pylori*, but were less susceptible to SARS and hepatitis B virus[11,44-47]. In another study, blood group A was associated with an increased risk of acute respiratory distress syndrome (ARDS) in trauma and sepsis patients[48]. A study by Lebiush *et al.* on influenza A (H1N1) observed a higher seroconversion rate in blood groups A and B[49]. Elnady *et al.* found that individuals with blood type A were more susceptible to rotavirus gastroenteritis than those with blood type B[50]. Among patients infected with dengue virus, Murugananthan *et al.* found that individuals with AB blood type had a 2.5 times higher risk of developing dengue haemorrhagic fever than those with other blood types[51]. Finally, there is strong evidence that ABO phenotype modulates severity of *Plasmodium falciparum*-associated malaria, with group A associated with severe disease and blood group O with milder disease[52].

Regarding the issue of this systematic review, the first reports on the evidence of a relationship between

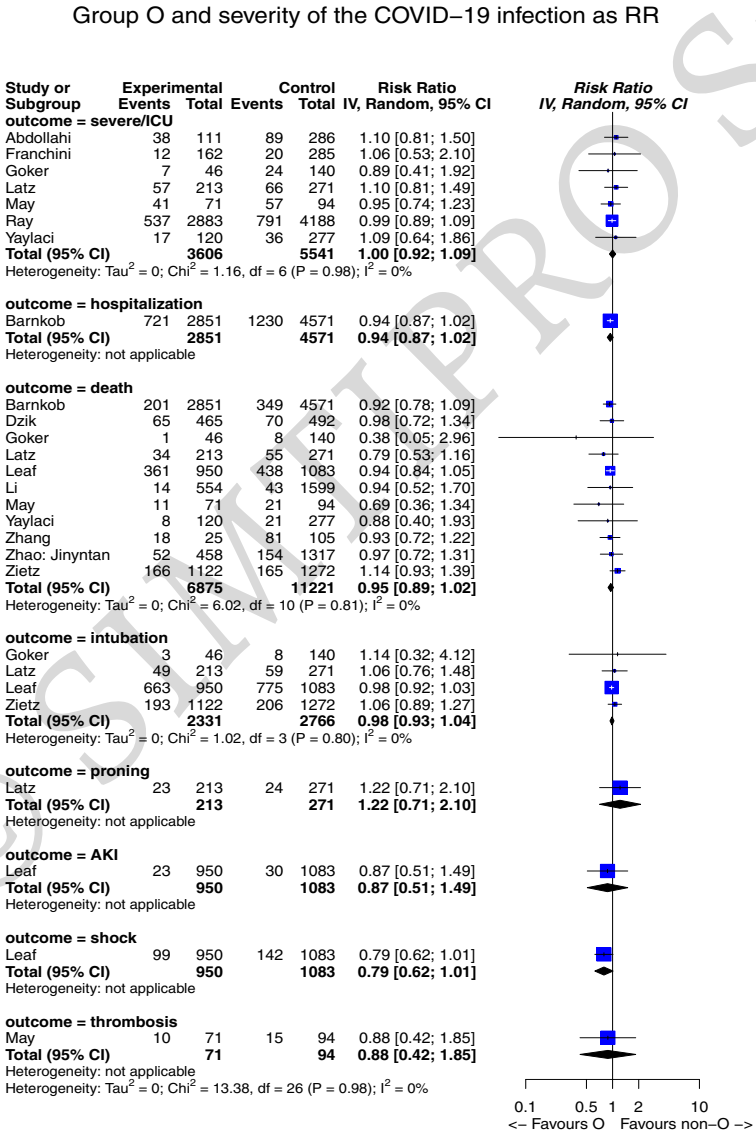

Figure 3 - Forest plot of the severity of SARS-CoV-2 infection according to blood group (O *vs* non-O blood group)

SARS-CoV-2 infection and ABO blood groups were published early in China and so far 21 articles have been published worldwide, covering a large number of cases. The pathogenic mechanism underlying this association is quite complex and encompasses several molecular pathways. Further experimental studies are needed to better characterise the role of anti-SARS-CoV-2 neutralising anti-A IgG antibodies in COVID-19 onset, and the importance of plasma VWF/ FVIII levels and endothelial cell activation in COVID-19-induced coagulopathy and pulmonary microvascular occlusion[17,53]. Whatever the underlying mechanism, this correlation is quite intriguing as it allows us to make some considerations that could have potentially important implications. First, the ABO-driven COVID-19 susceptibility could account for the inter-ethnic epidemiological difference in SARS-CoV-2 infection. Indeed, Africa is the continent with the lowest number of cases and deaths (1,044,513 confirmed cases with 21,722 deaths at 30th August 2020; data available at: https://covid19.who.int/). Curiously, among the different ethnicities, Africans have the highest percentage of O blood type (up to 60%). Another interesting observation regards the distribution of COVID-19 across different ages and genders. In fact, it is equally well known that men and the elderly are more affected by SARS-CoV-2 infection than women and young people. Previous studies had demonstrated that women with O blood type have higher anti-A IgG antibody levels than males, and that the titer of anti-A and anti-B isoagglutinins declines with age[54,55]. Although these findings do not constitute the definitive proof of the causal association between ABO blood type and gender-, age- and ethnic-related differences in the epidemiological distribution of COVID-19, these considerations are quite curious and deserve further investigation.

The results of this systematic review, which are in agreement with those published in another recent meta-analysis[15], indicate the lower susceptibility of O blood type individuals to being infected by SARS-CoV-2 than non-O subjects. The investigational hypothesis of a protective effect exerted by the O type on the risk of the SARS-CoV-2 infection was confirmed by both study designs, case control and cohort. However, the effect size was lower in cohort studies compared to case control studies. This is not surprising since, compared to cohort design, case control studies are more susceptible to bias due to confounding co-variates with different distributions in cases (infected patients) and the control population. Sample size for case control studies is based on prevalence of exposure, not on incidence of outcome. Because the prevalence of the exposure is usually larger than the incidence of outcome, in most practical situations a case control study is more powerful than a cohort study for the same problem. On the other hand, case control studies are very likely to suffer from bias. Controls should be drawn from the same general population that gave rise to the cases. However, in practice, the comparability of cases and controls is difficult to achieve, making this aspect the Achilles heel of case control design. In the present systematic review, no evidence was found indicating an effect of the O blood type on the disease severity in the infected patients. Larger, well-designed epidemiological trials are, however, needed to clarify the relationship between the ABO blood group system and the risk of developing COVID-19 or a more severe disease.

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