ABO blood groups and severe outcomes in COVID-19: A meta-analysis

Similar to the SARS-CoV experience,[1] a possible link between ABO blood groups with COVID-19 susceptibility and severity has been shown in multiple observational studies.[2–4] Gérard *et al*[5] have further noted that people with B and/or O blood groups were less represented among COVID-19 patients, thereby highlighting the possible beneficial role of anti-A antibodies in COVID-19 susceptibility. In fact, it was known that anti-A antibodies can block the adhesion of SARS-CoV S-protein to ACE2 expressing cell lines.[6] Given the genomic similarity between SARS-CoV-2 and SARS-CoV, it might be prudent to hypothesise a protective role of anti-A antibodies against COVID-19 severity as well. However, existing clinical evidence in this regard is controversial. Hoiland *et al*[7] had reported that critically ill COVID-19 patients with blood groups A and AB (lacking anti-A antibodies) were more likely to require mechanical ventilation and prolonged intensive care compared with patients with B/O (with anti-A antibodies). However, a genomewide association study of severe COVID-19 patients showed that those with blood group A had a higher risk of severe disease, while blood group O had a protective effect.[8] Other studies found no association between ABO blood groups and COVID-19 severity/mortality.[9–12] We aimed to summarise the available literature and provide a pooled analysis of the effect of A/AB (without anti-A antibodies) on clinical outcomes in COVID-19 patients compared with B/O (with anti-A antibodies) blood groups.

This meta-analysis was conducted and reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.[13]

We (SB and MB) independently performed a systematic search of the literature across the PubMed database from inception till 30 November 2020, using the following keywords interposed with appropriate Boolean operators: "COVID-19" OR "SARS-CoV-2" AND "ABO blood groups".

Observational studies of case–control or cohort design were selected. Studies reporting the absolute rate of occurrence of severe outcomes (number of patients requiring intubation or number of patients with dyspnoea where intubation data not reported) or intubation and/or deaths or deaths among confirmed COVID-19 patients with A/AB versus B/O blood groups were included in analysis. Studies conducted only in critically ill patients with COVID-19 were excluded. Reviews, commentaries, articles in non-English language, non-peer-reviewed articles/preprints and studies with incomplete data were also excluded. Any discrepancy was solved by a discussion with a third reviewer (RP). Study quality was assessed using the Newcastle-Ottawa scale.

Statistical analysis was performed using the RevMan V.5.4 software following data extraction. Being a dichotomous variable, the difference in the rate of occurrence of the reported clinical outcomes (events) in COVID-19 patients with A/AB versus B/O blood groups were calculated using the OR with 95% CIs after implementation of the Mantel-Haenszel (M-H) fixed-effects model. Heterogeneity was quantified as low, moderate and high with upper limits of 25%, 50% and 75% for I^2 respectively. Studies with moderate-to-high heterogeneity were reanalysed using the M-H random-effects model. A two-tailed $p<0.05$ was considered to be statistically significant.

After a scrupulous literature search and a meticulous study selection process, we included nine observational studies in our meta-analysis, pooling data retrieved from 233 006 patients with COVID-19[2–4 10 11 14–17] (online supplemental figure 1). Of note, we had excluded the studies by Hoiland *et al* and Leaf *et al* that were conducted only in critically ill COVID-19 patients.[7 18] Characteristics of all the studies along with quality assessment have been demonstrated in online supplemental table 1). The pooled analysis showed that there was no significant difference in severe clinical outcomes in patients with A/AB blood groups compared with those with B/O groups (OR 1.09; 95% CI 0.91 to 1.29, p=0.35, I^2=59%, random-effects model) (figure 1). Sensitivity analysis of studies that had reported only mortality as the severe outcome also showed no significant difference (OR 1.07; 95% CI 0.93 to 1.24, p=0.35, I^2=0%, fixed-effects model) (figure 2).

We found no significant differences in the unadjusted mortality and/or severity outcomes (defined by intubation or dyspnoea) related to COVID-19 in patients with blood groups A/AB (with no anti-A antibodies) as compared with B/O groups (with anti-A antibodies). However, in the meta-analysis performed among Spanish and Italian cohorts after adjusting for age and gender, odds for having severe COVID-19 disease (defined by respiratory failure) was higher in A/AB groups as compared with B/O groups (OR: 1.51, 95% CI 1.25 to 1.83). Nevertheless, no difference in ABO blood groups was observed among patients requiring any form of mechanical ventilation.[8]

The present study findings do have certain limitations. Most of the studies included in the meta-analysis had a retrospective design. Adjustment for age, gender and comorbidities were either not reported, or reported for each blood group separately. Hence, pooled analysis using adjusted ORs could not be done. Besides, the clinical outcomes reported across the included studies were variable, ranging from dyspnoea to intubation to

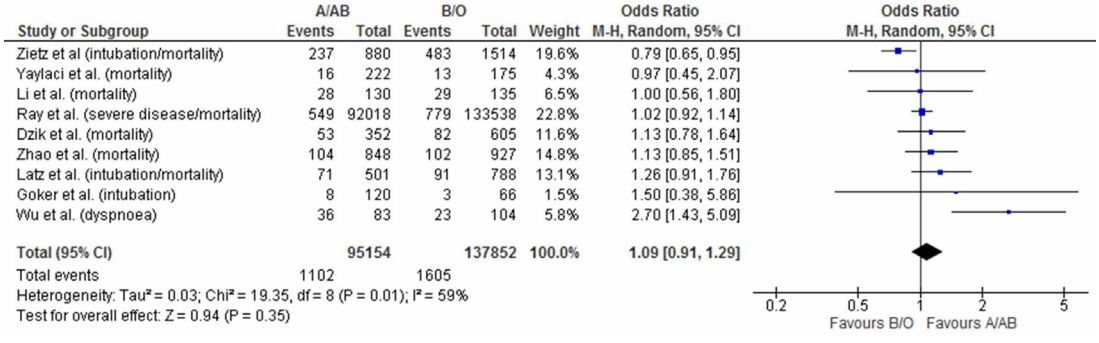

Figure 1 Forest plot showing the odds of severe outcomes in COVID-19 patients having blood groups A/AB (without anti-A antibodies) versus those having blood groups B/O (with anti-A antibodies). M-H, Mantel-Haenszel.

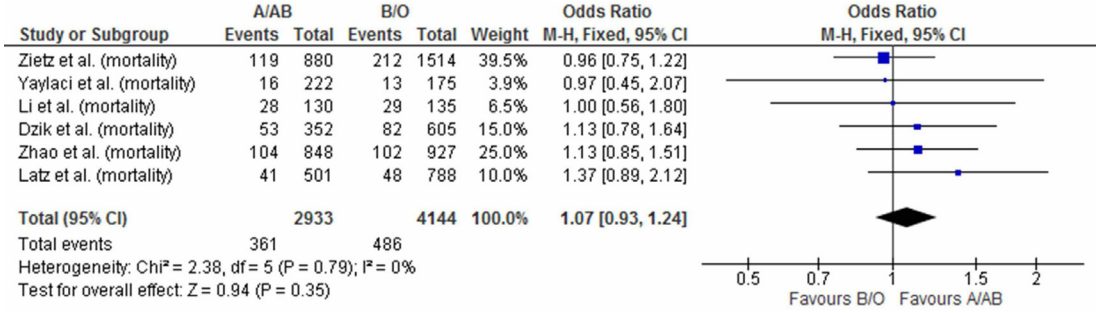

Figure 2 Forest plot showing the odds of mortality in COVID-19 patients having blood groups A/AB (without anti-A antibodies) versus those having blood groups B/O (with anti-A antibodies). M-H, Mantel-Haenszel.

death. However, we did perform a sensitivity analysis with mortality being the sole severe outcome. Finally, the relationship between COVID-19 severity and anti-A antibodies is indeed far from simple. Several other factors can act as potential confounders, including the immunoglobulin subtype of antibodies,[5] presence of ACE1/C3 polymorphisms[19] and variable levels of factor VIII/VWF levels.[20]

In conclusion, this preliminary, yet updated meta-analysis negates the possible significant association between the lack of anti-A antibodies (A/AB blood group), and poor clinical outcomes in patients with COVID-19. However, further studies on predefined endpoints in hospitalised patients (especially with critical COVID-19 disease), adjusting for possible covariates, are warranted to provide a reliable estimate of the risk.

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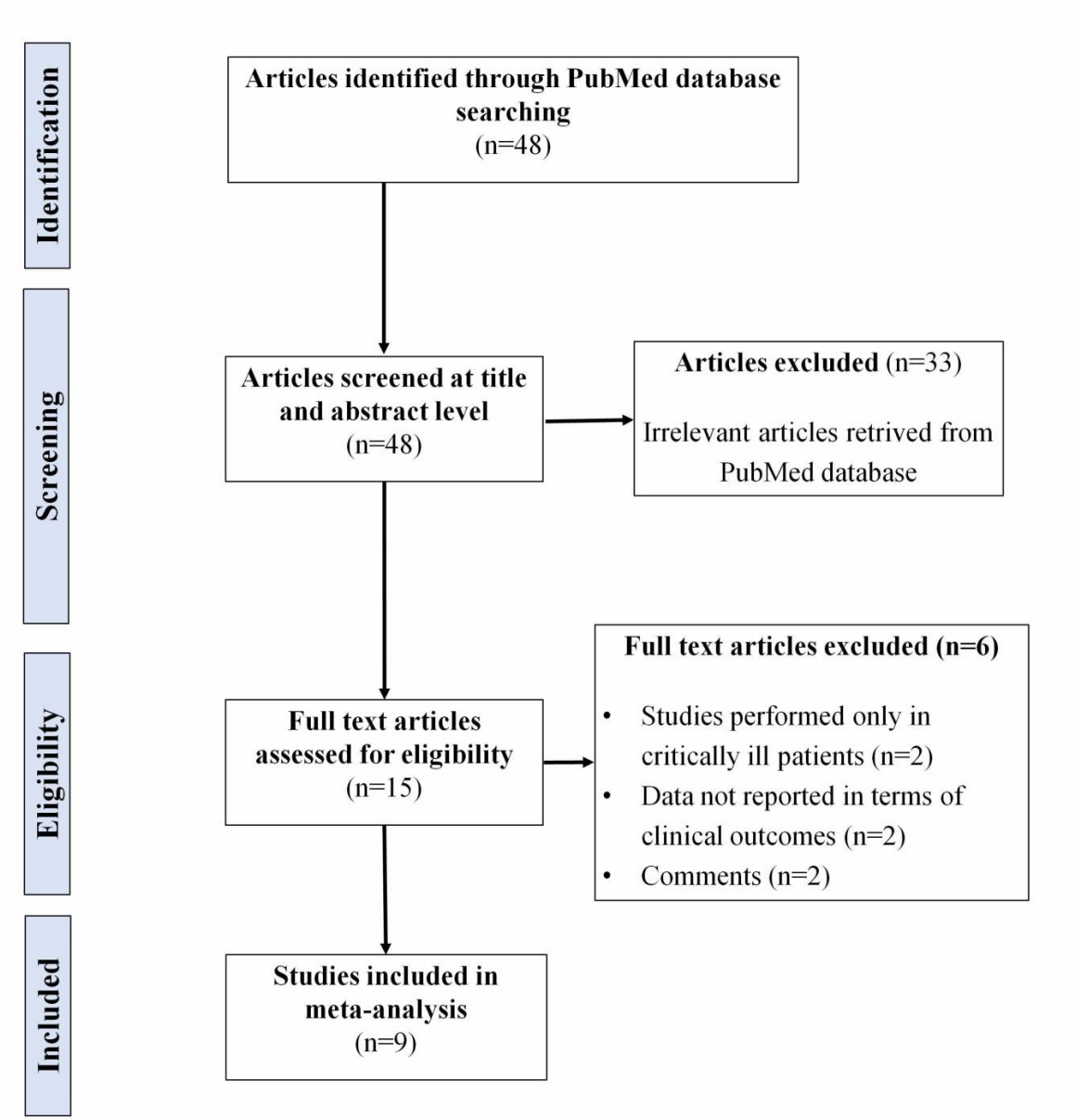
REFERENCES

1 Cheng Y, Cheng Y, Cheng G, *et al*. ABO blood group and susceptibility to severe acute respiratory syndrome. *JAMA* 2005;293:1450–1.
2 Li J, Wang X, Chen J, *et al*. Association between ABO blood groups and risk of SARS-CoV-2 pneumonia. *Br J Haematol* 2020;190:24–7.
3 Zhao J, Yang Y, Huang H, *et al*. Relationship between the ABO blood group and the COVID-19 susceptibility. *Clin Infect Dis* 2020.
4 Göker H, Aladağ Karakulak E, Demiroğlu H, *et al*. The effects of blood group types on the risk of COVID-19 infection and its clinical outcome. *Turk J Med Sci* 2020;50:679–83.
5 Gérard C, Maggipinto G, Minon Jean-Marc. COVID-19 and ABO blood group: another viewpoint. *Br J Haematol* 2020;190.
6 Guillon P, Clément M, Sébille V, *et al*. Inhibition of the interaction between the SARS-CoV spike protein and its cellular receptor by anti-histo-blood group antibodies. *Glycobiology* 2008;18:1085–93.
7 Hoiland RL, Fergusson NA, Mitra AR, *et al*. The association of ABO blood group with indices of disease severity and multiorgan dysfunction in COVID-19. *Blood Adv* 2020;4:4981–9.
8 Severe Covid-19 GWAS Group, Ellinghaus D, Degenhardt F, *et al*. Genomewide association study of severe Covid-19 with respiratory failure. *N Engl J Med* 2020;383:1522–34.
9 Li J, Wang X, Chen J, *et al*. Association between ABO blood groups and risk of SARS-CoV-2 pneumonia. *Br J Haematol* 2020;190:24–7.
10 Latz CA, DeCarlo C, Boitano L, *et al*. Blood type and outcomes in patients with COVID-19. *Ann Hematol* 2020;99:2113–8.
11 Dzik S, Eliason K, Morris EB, *et al*. COVID-19 and ABO blood groups. *Transfusion* 2020;60:1883–4.
12 Göker H, Aladağ Karakulak E, Demiroğlu H, *et al*. The effects of blood group types on the risk of COVID-19 infection and its clinical outcome. *Turk J Med Sci* 2020. doi:10.3906/sag-2005-395. [Epub ahead of print: 04 Jun 2020].
13 Liberati A, Altman DG, Tetzlaff J, *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009;339:b2700.
14 Ray JG, Schull MJ, Vermeulen MJ, *et al*. Association between ABO and Rh blood groups and SARS-CoV-2 infection or severe COVID-19 illness. *Ann Intern Med* 2020.
15 Wu Y, Feng Z, Li P, *et al*. Relationship between ABO blood group distribution and clinical characteristics in patients with COVID-19. *Clin Chim Acta* 2020;509:220–3.
16 Yaylacı S, Dheir H, İşsever K, *et al*. The effect of ABO and Rh blood group antigens on admission to intensive care unit and mortality in patients with COVID-19 infection. *Rev Assoc Med Bras* 2020;66 (Suppl 2):86–90.
17 Zietz M, Zucker J, Tatonetti NP. Associations between blood type and COVID-19 infection, intubation, and death. *Nat Commun* 2020;11:5761.
18 Leaf RK, Al-Samkari H, Brenner SK, *et al*. ABO phenotype and death in critically ill patients with COVID-19. *Br J Haematol* 2020;190:e204–8.
19 Delanghe JR, De Buyzere ML, Speeckaert MM. C3 and ACE1 polymorphisms are more important confounders in the spread and outcome of COVID-19 in comparison with ABO polymorphism. *Eur J Prev Cardiol* 2020;27:1331–2.
20 O'Donnell J, Laffan MA. The relationship between ABO histo-blood group, factor VIII and von Willebrand factor. *Transfus Med* 2001;11:343–51.

Supplementary Figure 1. Flowchart showing the study selection process.



Studies	Characteristics	Outcomes reported: n/N				Adjustment for covariates	N-O Scale*
		A	AB	B	O		
Li *et al.* (2)	N=265 Retrospective cohort study, China	Mortality				ND	8/9
		20/104	8/26	15/67	14/68		
Zhao *et al.* (3)	N=1775 Retrospective cohort study, China	Mortality				ND	8/9
		85/670	19/178	50/469	52/458		
Goker *et al.* (4)	N= 186 Retrospective cohort study, Turkey	Intubation				ND	7/9
		7/106	1/14	0/20	3/46		
Wu *et al.* (9)	N=187 Retrospective case control study, China	Dyspnea				ND	5/9
		29/69	7/14	10/63	13/41		
Latz *et al.* (10)	N=1289 Retrospective cohort study, USA	Intubation				Adjusted for sex, race, primary language, aspirin use, comorbidities	6/9
		38/440	6/61	15/201	49/587		
Dzik *et al.* (11)	N=957 Retrospective cohort study, USA	Mortality				ND	7/9
		45/311	8/41	17/140	65/465		
Ray *et al*. (16)	N=225556 Retrospective cohort study, Canada	Severe disease or mortality				Adjusted for age, sex, area-level income quintile, rurality, and local health integration network, history of cardiac ischemia or arrhythmia, cancer, CKD, CHF, DM	8/9
		474/ 81797	75/ 10221	242/ 33536	537/ 100002		
Yaylacı *et al*. (18)	N=397 Descriptive cross-sectional study, Turkey	Mortality				ND	6/9
		15/201	1/21	5/55	8/120		
Zietz *et al.* (19)		Intubation or Mortality				Adjusted for race and ethnicity	8/9
		215/ 786	32/94	124/ 392	359/ 1122		

Supplementary Table 1: Summarizing the characteristics of the studies included in the present meta-analysis.

*Newcastle-Ottawa quality assessment scale for cohort studies. Score >6 was taken as good quality and 5-6 as moderate quality. Clinical outcomes data in respective blood groups reported as n/N.

ND: not done, OR: odds ratio, CKD: Chronic kidney disease, CHF: Congestive heart failure, DM: Diabetes mellitus,

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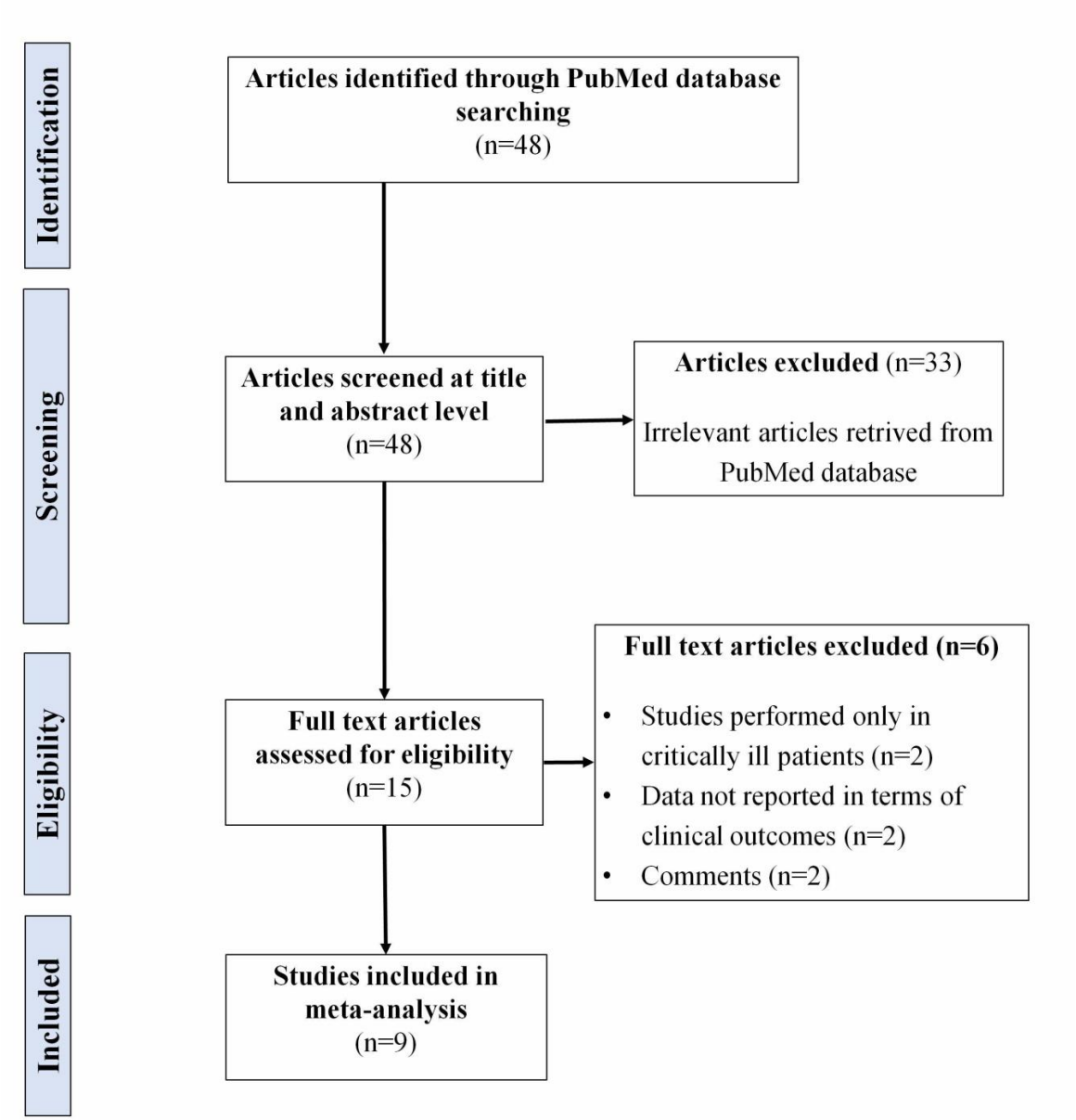

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