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

Similar to the SARS-CoV experience, a possible link between ABO blood groups with COVID-19 susceptibility and severity has been shown in multiple observational studies. Gérard et al 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. 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. Hoieland et al 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. Other studies found no association between ABO blood groups and COVID-19 severity/mortality. 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. 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 the 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 I² 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.

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.
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, presence of ACE1/C3 polymorphisms and variable levels of factor VIII/VWF levels.

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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Correction notice This article has been corrected since it first published. The provenance and peer review statement has been included.

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REFERENCES
Supplementary Figure 1. Flowchart showing the study selection process.

Articles identified through PubMed database searching (n=48)

Articles screened at title and abstract level (n=48)

Articles excluded (n=33)
- Irrelevant articles retrieved from PubMed database

Full text articles excluded (n=6)
- Studies performed only in critically ill patients (n=2)
- Data not reported in terms of clinical outcomes (n=2)
- Comments (n=2)

Full text articles assessed for eligibility (n=15)

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**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.

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