COVID-19 and ABO blood groups

Coronavirus disease 2019 (COVID-19) exhibits a very wide spectrum of severity. This strongly suggests that host factors influence outcomes. While acquired comorbidities—such as age, obesity, history of smoking—are very likely related to clinical severity, it is also likely that genetic factors will prove to be relevant to the host thromboinflammatory response. Recently, investigators from China reported that ABO type was strongly statistically associated not only with acquiring severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection but also with survival following infection. Zhao et al[1] compared ABO distributions on 1775 patients with SARS-CoV-2 infection in China with 3694 ABO types from a background healthy population. Of note, their reference population was not a cohort of uninfected patients admitted to the same hospital but rather was a background reference population of "normal individuals" from Wuhan. (The details of that cohort were not reported.) They found that blood group O was less common among infected individuals (25.8%) compared with healthy population-based controls (33.8%) and that group A was more common among infected individuals (37.7%) compared with healthy population-based controls (32.2%;, $p < 0.001$). They also reported that, among 206 patients with COVID-19 who died, blood group O was significantly less common (25.2%) compared with their reference population (33.8%; $p = 0.014$). Their data are shown in the Table 1. They did not compare the ABO distributions among those hospitalized with COVID-19 versus those hospitalized with non–COVID-19–associated conditions, nor among infected survivors versus infected fatal cases. This latter comparison would be the most informative way to understand if a particular ABO group was associated with mortality within a cohort of infected individuals. Reanalyzing their data in this way, we find no association between ABO type and death among individuals hospitalized with COVID-19 (chi-squared = 1.35; $p = 0.717$). Similar findings from Wuhan were published by Li et al.[2]

Although there are only four basic ABO phenotypes, they derive from 235 known ABO gene variants, which vary among different ethnic population groups.[3] To explore whether ABO phenotype might be associated with fatal outcome in a cohort of patients from the United States, we examined ABO types among patients infected with SARS-CoV-2 at Massachusetts General Hospital (MGH; n = 745) and Brigham and Women's Hospital (BWH; n = 212) in Boston. We analyzed ABO results from unique patients who were documented to have SARS-CoV-2 infection by nasal swab polymerase chain reaction, who were hospitalized and discharged between February 12 and May 13, 2020, and for whom an ABO typing was on record. Approximately 65% of SARS-CoV-2 hospitalized patients had ABO testing performed. The ABO results are shown in the Table 1. Death occurred in hospital among 135 patients (14%). When comparing survivors versus nonsurvivors among SARS-CoV-2–infected patients, we observed no association between ABO distribution and fatal outcome ($p = 0.69$).

Growing evidence suggests that SARS-CoV-2 infection that is serious enough to require hospitalization may disproportionately affect racial and ethnic minorities in the United States.[4] Since ABO blood group varies by ethnicity, this might influence the observed ABO distribution when comparing infected versus uninfected cohorts. We explored this hypothesis by comparing the distribution of ABO blood type among MGH and BWH patients with documented SARS-CoV-2 infection compared with 5840 randomly selected patients who were hospitalized at MGH and BWH during March and April 2019 in the pre-COVID era. The proportion of cases and

TABLE 1. ABO distributions among patients with COVID-19 in Wuhan (China) and MGH-BWH (Boston)

	Total	A, n (%)	B, n (%)	AB, n (%)	O, n (%)
Wuhan patients (all)	1775	670 (37.7)	469 (26.5)	178 (10)	458 (25.8)
Wuhan (fatal)	206	85 (41.3)	50 (24.3)	19 (9.2)	52 (25.2)
Wuhan healthy population	3694	1188 (32.2)	920 (24.9)	336 (9.1)	1250 (33.8)
MGH and BWH patients with COVID-19 (all)	957	311 (32.5%)	140 (14.6%)	41 (4.3)	465 (48.6)
MGH and BWH patients with COVID-19 (fatal)	135	45 (33.3)	17 (12.6%)	8 (5.9)	65 (48.2)
MGH and BWH non–COVID-19 patients	5840	2128 (36.4)	761 (13.0%)	231 (4.0)	2720 (46.6)

Among MGH-BWH patients with COVID-19, a comparison of ABO distribution (2×4 chi-square) among survivors versus nonsurvivors is chi-squared = 1.47, $p = 0.6882$.
Among MGH-BWH patients, a comparison of ABO distribution among COVID-19–infected versus MGH pre–COVID-19 era patients is chi-squared = 6.08, $p = 0.1079$.
BWH = Brigham and Women's Hospital; COVID-19 = coronavirus disease 2019; MGH = Massachusetts General Hospital.

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controls contributed by the two hospitals was the same. As shown in the Table 1, we found a nonsignificant slightly higher proportion of blood group O individuals among our cohort with SARS-CoV-2 infection (p = 0.1079). One possible explanation for the slightly higher proportion of group O in patients with COVID-19 may be that, in Boston, the pandemic has disproportionately affected those of Latin or Hispanic descent, among whom group O is more frequent.[5]

The ABO blood group polymorphism has been shown to be associated with survival outcome in *Plasmodium falciparum* infection, where the association has a strong mechanistic explanation.[6] Our data do not support an association between ABO blood group polymorphism and fatality from COVID-19; and do not support the recommendation by Li et al. that group A individuals "should strengthen protection to reduce the risk of infection."[2] Importantly, our results highlight that reference populations used to compare ABO distributions must be selected with care. For example, a recent genome-wide association study reported higher group A and lower group O genotypes in a study of 1610 patients with COVID-19 from Italy and Spain.[7] However, the study used normal blood donors for the overwhelming majority of their comparison controls. This is a flawed comparison population because blood donors are well known to be selected in favor of people in group O based on their active recruitment as preferred blood donors. The importance of a proper comparison group was, in fact, demonstrated in that study when they failed to show any ABO association when comparing patients using supplemental oxygen versus patients requiring mechanical ventilation. Analyses of additional data sets from around the world and studies with carefully selected comparison controls that include the contribution of emerging cofactors, both genetic and acquired, will continue to improve our understanding of the relationship, if any, between COVID-19 and ABO blood group.

CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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REFERENCES

1. Zhao J, Yang Y, Huang H, et al. Relationship between the ABO blood group and the COVID-19 susceptibility. medRxiv (preprint) 2020. https://doi.org/10.1101/2020.03.11.20031096.
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;190:24-27. https://doi.org/10.1111/bjh.16797. Online ahead of print.
3. Möller M, Jöud M, Storry JR, et al. Erythrogene: a database for in-depth analysis of the extensive variation in 36 blood group systems in the 1000 Genomes Project. Blood Adv 2016;1:240-9.
4. United States Center for Disease Prevention and Control (CDC). COVID-19 in Racial and Ethnic Minority Groups. [cited 2020 Jun 25]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/racial-ethnic-minorities.html.
5. Garratty G, Glynn SA, McEntire R. ABO and Rh(D) phenotype frequencies of different racial/ethnic groups in the United States. Transfusion 2004;44:703-6.
6. Cserti-Gazdewich CM, Dhabangi A, Musoke C, et al. Cytoadherence in paediatric malaria: ABO blood group, CD36, and ICAM-1 expression and severe *Plasmodium falciparum* infection. Br J Haematol 2012;159:223-36.
7. Ellinghaus D, Degenhardt F, Bujanda L, et al. Genomewide association study of severe covid-19 with respiratory failure. N Engl J Med 2020;NEJMoa2020283. https://doi.org/10.1056/NEJMoa2020283.