

ABO Blood Groups Are Not Associated With COVID-19 Disease Incidence and Severity When Correcting for Ethnicity Differences in Blood Type

Bryce E. Pasko, MD,^{1,2} Diana Abbott, PhD,³ Gregory T. Bocsi, DO,¹ and Nicole L. Draper, MD¹

From the ¹Department of Pathology, University of Colorado-Anschutz Medical Campus, Aurora, CO, USA; ²Department of Pathology and Laboratory Medicine, Children's Hospital Colorado, Aurora, CO, USA; and ³Center for Innovative Design & Analysis Department of Biostatistics & Informatics, Colorado School of Public Health, Aurora, CO, USA.

ABSTRACT

Objectives: To determine if blood type is a risk factor for coronavirus disease 2019 (COVID-19) disease incidence and severity after correcting for ethnicity differences between novel infections and known ABO blood type frequency differences.

Methods: We performed a retrospective analysis on all severe acute respiratory system coronavirus 2 (SARS-CoV-2) infections and disease severity across two major testing sites in Colorado. We evaluated all individuals with a SARS-CoV-2 nucleic acid test (NAT) and a known blood type between March 1, 2020, and June 1, 2020. We then created a prediction algorithm based on the corrected blood types by ethnicity using data from the Colorado Department of Health and established blood types by ethnicity. We applied this prediction algorithm to all patients in our sample.

Results: Of 8,676 patients, 485 (5.6%) had a positive SARS-CoV-2 NAT test and 8,191 (94.4%) had a negative test. All patients had ABO blood types that mirrored the expected blood type distribution within the state of Colorado ($P = .15$, χ^2 statistic = 5.31). No differences in expected blood groups were present between ethnicity-adjusted SARS-CoV-2-negative and SARS-CoV-2-positive patients ($\chi^2 = 3.416313$, $P = .332$).

Conclusions: Blood type is not associated with COVID-19 disease incidence or severity after correcting for ethnicity differences in expected blood type frequencies.

INTRODUCTION

The severe acute respiratory system coronavirus 2 (SARS-CoV-2) is responsible for the 2019 coronavirus disease (COVID-19) causing a worldwide pandemic, leading to staggering numbers of life lost and morbidity around the globe.¹ Thus, it is imperative to understand key risk factors associated with disease contraction and progression. Several risk factors have been associated with COVID-19 disease severity, such as age, diabetes, cardiovascular disease, and pulmonary disease. Other reported risk factors are less well understood but could play a major role in COVID-19 severity, such as blood type.²⁻⁹

Studies both before and after peer review have demonstrated that individuals with group A blood type are at a higher risk for contracting SARS-CoV-2 and for disease progression requiring hospital admission, intensive care unit (ICU) stays, and ultimately death, whereas

KEY POINTS

- Prior studies have made associations between ABO blood groups and coronavirus disease 2019 (COVID-19) disease and severity.
- Ethnicity is an important consideration when evaluating ABO blood group associations because the prevalence of blood groups is different across different ethnicities.
- When correcting for ethnicity and ABO blood groups, we found no association between COVID-19 disease or disease severity with blood type.

Am J Clin Pathol August 2022;158:249-253
[HTTPS://DOI.ORG/10.1093/AJCP/AQAC036](https://doi.org/10.1093/AJCP/AQAC036)

Received: January 13, 2022
 Accepted: February 24, 2022
 Advance publication: April 11, 2022

Corresponding author: Bryce E. Pasko, MD; bryce.pasko@childrenscolorado.org.

This article is available for CME credit. Go to academic.oup.com/ajcp/pages/journal_cme see the latest articles. The complete catalog of journal CME courses can be found at store.ascp.org.

people with group O blood type are relatively protected from SARS-CoV-2 infection and sequela.^{2-4,6} Multiple theories attempt to explain why individuals with differing ABO blood groups could have different disease courses and disease severity with COVID-19. It is important to highlight that none of these prior studies have examined the relationship of blood type when accounting for ethnicity and known differences in blood types based on ethnicity.

The most popular theory for an ABO association with COVID-19 relies on the angiotensin-converting enzyme 2 receptor, the proposed mechanism of cellular entry by SARS-CoV-2, being more prominent in individuals with group A blood type than those with group O blood type.⁶ This would imply that individuals with group A blood type would have a higher number of binding sites for SARS-CoV-2 attachment and cellular entry than group O individuals. However, conflicting data show no association with blood type and COVID-19 disease severity.⁵

Disease associations with blood type are not a new phenomenon and have been associated with increased risks of numerous diseases and infections with organisms based on cellular biochemistry and antigen-binding sites; for instance, blood groups A and B confer higher risk for contracting *Plasmodium falciparum*, or *Helicobacter pylori* infections have a strong association with blood group O.¹⁰ So, biologic plausibility exists. However, one major concern for our group when examining the data from prior studies is the lack of ethnicity correlation with expected blood types as a possible confounding variable. This was addressed briefly by Latz et al,⁵ who encouraged additional ethnicity specific analysis.

Ethnicity is a very important consideration when studying biologic markers of SARS-CoV-2 infection and disease severity for two reasons: (1) there are disproportionate numbers of Latinos and Blacks who are infected with SARS-CoV-2 compared with Whites,¹¹ and (2) expected blood type prevalence is different across different ethnic groups, which can bias the data used for analysis if the researchers are not controlling for ethnicity blood group variables. None of the other studies account for these differences in blood type across different ethnicities **TABLE 1**. Therefore, given the implications of the associations with ABO blood groups and COVID-19 disease incidence and severity, we sought to examine whether these associations would still be present after controlling for ethnicity differences in ABO blood type.

We set out to accomplish this by using the data from major COVID-19 testing centers in Colorado, the University of Colorado Hospital and Children's Hospital Colorado. We selected a time

period with high state reporting of demographics data and prior to the COVID-19 vaccinations and vaccine studies. We analyzed COVID-19 data, expected distributions of blood type by ethnicity, and ethnicity and SARS-CoV-2 infection data from the Colorado Department of Health.

MATERIALS AND METHODS

We performed a multi-institutional retrospective chart review for all patients with SARS-CoV-2 nasopharyngeal swab nucleic acid test (NP NAT) results using the Cepheid GeneXpert platform, Roche Cobas 6800, Centers for Disease Control and Prevention (CDC) 2019-nCoV Real-Time RT-PCR Diagnostic Panel, DiaSorin Simplexa COVID-19 Direct assay, Abbott RealTime SARS-CoV-2 assay on the M2000 RealTime analyzer, Cepheid Xpert Xpress, and ThermoFisher TaqPath COVID-19 Combo Kit between March 1, 2020, and June 1, 2020, who also had an ABO blood type result at the University of Colorado Hospital or the Children's Hospital Colorado. These were two of the major testing sites for COVID-19 in Colorado during the time of the study. A chart review was performed after July 1, 2020, for all patients with COVID-19 with a positive SARS-CoV-2 NP NAT to provide at least a 30-day follow-up after testing positive and capture delayed symptoms and disease severity.

While the authors recognize there is no perfect way to determine disease severity in a retrospective chart review, it was decided to use the most objective data available. Each disease severity score is known to be associated with increased medical interventions and monitoring. Using this reasoning, we stratified patients into four categories based on disease severity: category 1, never hospitalized; category 2, hospitalized but not in the ICU; category 3, hospitalized in the ICU on ventilator support; and category 4, hospitalized in the ICU on extracorporeal membrane oxygenation support. We further stratified each category into deceased or living. We collected comorbidity data associated with increased risk of disease severity, as determined by the CDC, including age, sex, chronic kidney disease (CKD), cancer, interstitial lung disease (ILD)/chronic obstructive pulmonary disease (COPD), heart failure, sickle cell disease, type 2 diabetes mellitus, obesity, hypertension, and a tobacco smoking history.⁹

Ethnicity-adjusted expected ABO percentages for the state of Colorado were calculated using two different sources of information: (1) Colorado Department of Public Health and Environment (CDPHE) population ethnicity data **TABLE 2**¹² and (2) well-established published ABO frequencies by ethnicity.¹⁰ Because we could not align a blood type distribution with individuals of the "other" category for ethnic groups, the expected blood group frequencies were determined using blood type distributions from only four ethnic groups: White, Hispanic, Black, and Asian.

For each blood type, ethnicity-adjusted expected frequency was calculated by multiplying the frequency of the blood type in a specific ethnic population by the relative frequency of that population among the four ethnic groups and then summing across all four ethnic groups. These frequencies were then used to determine the expected number of individuals in the state of Colorado with a certain

TABLE 1 Distribution of Expected Blood Type by Ethnicity

Blood Type	Ethnicity, %			
	White	Black	Asian	Hispanic
O	44	49	43	55
A	43	27	27	28
B	9	20	25	13
AB	4	4	5	4

^aData were modified from Reid et al.¹³

TABLE 2 Distribution of Ethnicity in Colorado^a

Ethnicity	Percent
White	67.8
Hispanic	21.7
Black	3.9
Asian	3.1
Other ^b	3.4

^aData published by the Colorado Department of Public Health and Environment, based on the 2018 Colorado population data.¹²

^bBecause we could not align a blood type distribution with individuals of “other” ethnic group, the expected blood group frequencies were determined using blood type distributions from only four ethnic groups: White, Hispanic, Black, and Asian.

blood type. To determine the expected number of individuals tested for SARS-CoV-2 who have blood type O, for example, we multiplied the ethnicity-adjusted frequency of the O blood type by the number of individuals tested for SARS-CoV-2. Calculations assumed that the individuals being tested for SARS-CoV-2 in the state of Colorado are a random sample of individuals from the state.

We used our ethnicity-adjusted expected frequencies of blood type to examine the following: (1) association between ethnicity and blood type in individuals tested for SARS-CoV-2 and (2) association between blood type and disease positivity adjusting for ethnicity.

Association Between Ethnicity and Blood Type in Individuals Tested for SARS-CoV-2

To assess the association between ethnicity and blood type among individuals tested for SARS-CoV-2 infections in Colorado, a χ^2 test statistic with 3 degrees of freedom was calculated—thus comparing the observed number of individuals of a given blood type with the ethnicity-adjusted expected number of individuals of a given blood type. A threshold significance of .05 was established a priori. For this test, a χ^2 test *P* value greater than .05 provides evidence that individuals being tested for SARS-CoV-2 do not have a blood type distribution that significantly differs from the blood type distribution in Colorado.

Association Between Blood Type and Disease Positivity Adjusting for Ethnicity

Using our ethnicity-adjusted expected frequencies of blood type, we calculated the expected number of disease-positive individuals for each ABO blood type if there was no association between blood type and disease outcome, positive or negative. Ethnicity-adjusted χ^2 analyses comparing the observed and expected numbers of disease-positive individuals with a given blood type were then performed to assess the association between blood type and disease while adjusting for ethnicity. Unadjusted χ^2 analyses that do not control for ethnicity were also calculated. Blood types were categorized to optimize any potential differences between blood groups as follows: O vs A vs B vs AB, O vs non-O, A vs non-A, and B vs non-B.

Association Between Blood Type and Disease Severity

To assess the association between blood type and disease severity, disease severity was defined in three ways: severity category score 1 vs severity category scores 2 to 4, severity score 1 or 2 vs

severity score 3 or 4, and alive vs dead. The χ^2 analyses were calculated to assess the association between blood type and disease severity. Next, using our ethnicity-adjusted expected blood type frequencies, we calculated the expected number of disease-severe individuals (using the three definitions above) for each ABO blood type if there was no association between blood type and disease severity. Ethnicity-adjusted χ^2 analyses comparing the observed and expected numbers of disease-severe individuals with a given blood type were then performed to assess the association between blood type and disease severity while adjusting for ethnicity.

Controlling for Comorbidities

To rule out effects from possible confounding due to known COVID-19 risk factors, a Mantel-Haenszel χ^2 test was run to assess whether there is evidence of confounding by a comorbidity in the association between blood type and disease severity. A significant *P* value for the Mantel-Haenszel test means that a Mantel-Haenszel confounding-adjusted χ^2 test should be used to assess the relationship between ABO blood group and outcome while controlling for the confounder. In the absence of a significant Mantel-Haenszel test, the unadjusted *P* value can be used to determine if there is a significant association between ABO blood group and disease severity or death status.

All procedures were in accordance with and reviewed by the Colorado Multiple Institutional Review Board to ensure ethical standards.

RESULTS

We identified 8,676 patients with a SARS-CoV-2 NP NAT and an ABO blood type result. Of those, 485 (5.6%) patients had a positive SARS-CoV-2 NP NAT test, and 8,191 (94.4%) had a negative SARS-CoV-2 NP NAT. These data included SARS-CoV-2–positive patients ranging in age from 4 months to 96 years, with 25 patients younger than 18 years and a mean age of 49 years.

Patients tested for SARS-CoV-2 had ABO blood types that mirrored the expected blood type distribution within Colorado (*P* = .15, χ^2 statistic = 5.31). No differences in expected blood groups were present between ethnicity-adjusted SARS-CoV-2–negative and SARS-CoV-2–positive patients (χ^2 = 3.416313, *P* = .332); however, when not adjusting for ethnicity, there was a significant difference between SARS-CoV-2–negative and SARS-CoV-2–positive patients (χ^2 = 12.2571, *P* = .007). There was no association between ethnicity-adjusted blood group A and disease-positive status (χ^2 = 0.860664, *P* = .354); however, when not adjusting for ethnicity, blood group A had a significantly lower incidence in SARS-CoV-2–positive patients than non-A blood groups (χ^2 = 9.8383 *P* = .002). There was no association between ethnicity-adjusted blood group O and disease-positive status (χ^2 = 2.383759, *P* = .123); however, when not adjusting for ethnicity, blood group O had a significantly higher incidence in SARS-CoV-2–positive patients than non-O blood groups (χ^2 = 8.7932 *P* = .003). There was no association between blood group B and non-B blood groups patients (ethnicity-adjusted χ^2 = 0.06779, *P* = .795; unadjusted χ^2 = 0.5517,

$P = .458$). There was no association between blood group AB and non-AB blood groups patients (ethnicity-adjusted $\chi^2 = 1.397557$, $P = .237$; unadjusted $\chi^2 = 1.1193$, $P = .290065$).

There was no association between blood type and disease severity: disease severity 1 vs 2 to 4 ($\chi^2 = 2.8039$, $P = .423$) across blood group A vs non-A blood type ($P = 0.299$), B vs non-B blood type ($P = .707$), and O vs non-O blood type ($P = .442$), as well as disease severity 1 and 2 vs 3 and 4 ($\chi^2 = 2.8039$, $P = .423$) across blood group A vs non-A blood type ($P = .054$), B vs non-B blood type ($P = .598$), and O vs non-O blood type ($P = 0.289$). While group A vs non-A was not significant, it approached significance, with group A having lower severity scores than non-A blood groups.

There was no association between blood type and death: death by blood type ($\chi^2 = 2.573$, $P = .839$). There was no association of blood type by death in the ethnicity-adjusted data ($\chi^2 = 28.1339209$, $P = .4622$). Adjusting for ethnicity across blood group A vs non-A, B vs non-B, O vs non-O, and AB vs non-AB blood types, there was no association ($P = .2041$, $.66806$, $.11003$, and $.81265$, respectively).

There was no evidence of confounding in the relationship between ABO blood group and disease severity due to comorbid conditions. All comorbidities were assessed using unadjusted P values, except for two, ILD/COPD and heart failure (HF). These two were compared using the adjusted P values (Mantel-Haenszel tests: ILD/COPD—unadjusted $P = .0431$, adjusted $P = .138$; HF—unadjusted $P = .0481$, adjusted $P = .087$) (see supplemental tables; all supplemental materials can be found at *American Journal of Clinical Pathology* online).

DISCUSSION

This study examined the association between ABO blood groups and COVID-19 disease incidence and severity at Colorado's major COVID-19 testing centers prior to COVID-19 vaccinations and vaccine-related clinical trials. The unique aspect of this study is that we controlled for known ABO blood group phenotypes across different ethnicities and used population data from the CDPHE to identify patient demographics with and without COVID-19 in the state.

Unlike earlier studies examining ABO blood group associations with COVID-19 disease incidence and severity, which showed blood group A as being significantly associated with COVID-19 disease incidence and severity and blood group O as being protective,¹⁻⁷ when we controlled for ethnicity, we found no association between blood group and disease incidence or severity. Interestingly, when examining our data unadjusted for ethnicity and known ethnicity-related ABO blood group phenotype demographics, we noted a significant increase in COVID-19 disease incidence for blood group O vs all other blood groups ($P = .003$) and a significant decrease in infections for blood group A vs all other blood groups ($P = .002$). Without correcting for ethnicity-adjusted ABO blood groups and ethnicity-adjusted infection rates, we would have made the false assumption that blood group O is associated with significantly increased incidence of SARS-CoV-2 infections, which is different from prior studies and an incorrect assumption.

The differences seen between our uncorrected data and those used in previous studies may appear unusual on the surface, but it is our opinion that this can be explained by examining the disproportionately increased percentage of Latinos infected with SARS-CoV-2 compared with White, non-Hispanic groups, relative to their population percentages. Colorado has a relatively large Latino population (21.7%) compared with the White, non-Hispanic population (67.8%). However, SARS-CoV-2 infection percentages constituted 28.1% for Latino vs 59.1% for White, non-Hispanic populations. These data demonstrate a 7.6% higher than expected infection rate in the Latino group and 8.7% fewer infections in the White, non-Hispanic group if infections were evenly distributed respectively to population. Now further compounding the differences in the infection rates by ABO blood types is that the Latino group has a much higher prevalence of group O blood types, 55%, than group A blood types, 28%, when compared with the White, non-Hispanic group, 44% and 43%, respectively. Thus, it is our opinion that when considering the differences in expected infection rates and blood types, it is much easier to see how the data can become easily skewed without controlling for ethnicity.

While these findings are interesting, they also highlight how research examining correlational elements can easily be identified as related or unrelated without all of the underlying information, such as the increased incidence of SARS-CoV-2 infections in ethnic minorities as compared with other populations and that ABO expected phenotypes are drastically different for different ethnicities.¹⁰ This type of error in correlation as causation is reminiscent of a classic case taught in many statistics classes that shows a strong correlation between ice cream sales and the homicide rates in New York City, trying to entice the students to blame ice cream sales for the increased homicide rates rather than control for factors such as the weather, number of people walking on the streets, alcohol sales, and many others. These types of examples, while often apparent at face value, attempt to highlight a critical point; correlation is not equivalent to causation.

While many medical centers are attempting to shed light on why some individuals have significantly worse outcomes with COVID-19 than others, it is our opinion that we should begin investing resources and time into alternative explanations for SARS-CoV-2 disease incidence and severity beyond blood group associations, such as other biological markers or examining population data of socioeconomic status that could increase the likelihood of infection and limit access to care.

In conclusion, we found no differences between COVID-19 incidence and severity by ABO blood groups when we controlled for ethnicity and expected differences in ABO blood groups by ethnicity.

REFERENCES

- Centers for Disease Control and Prevention. Covid-19. Secondary Covid-19. <https://www.cdc.gov/coronavirus/2019-ncov/index.html>. Accessed December 14, 2021.
- Zhao J, Yang Y, Huang H, et al. Relationship between the ABO blood group and the coronavirus disease 2019 (COVID-19) susceptibility. *Clin Infect Dis*. 2021;73:328-331.

3. 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: a population-based cohort study. *Ann Intern Med.* 2021;174:308-315.
4. 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.
5. Latz CA, DeCarlo C, Boitano L, et al. Blood type and outcomes in patients with COVID-19. *Ann Hematol.* 2020;99:2113-2118.
6. Dai X. ABO blood group predisposes to COVID-19 severity and cardiovascular diseases. *Eur J Prev Cardiol.* 2020;27:1436-1437.
7. Zietz M, Zucker J, Tatonetti NP. Associations between blood type and COVID-19 infection, intubation, and death. *Nat Commun.* 2020;11:5761.
8. Ellinghaus D, Degenhardt F, Bujanda L, et al; Severe Covid-19 GWAS Group. Genomewide association study of severe Covid-19 with respiratory failure. *N Engl J Med.* 2020;383:1522-1534.
9. Centers for Disease Control and Prevention. People with certain medical conditions. Secondary people with certain medical conditions. <https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html>. Accessed December 14, 2021.
10. Ewald DR, Sumner SC. Blood type biochemistry and human disease. *Wiley Interdiscip Rev Syst Biol Med.* 2016;8:517-535.
11. Mackey K, Ayers CK, Kondo KK, et al. Racial and ethnic disparities in COVID-19-related infections, hospitalizations, and deaths: a systematic review. *Ann Intern Med.* 2021;174:362-373.
12. Colorado Department of Public Health & Environment. State releases initial race and ethnicity data for COVID-19 cases. Secondary State releases initial race and ethnicity data for COVID-19 cases. <https://covid19.colorado.gov/press-release/state-releases-initial-race-and-ethnicity-data-for-covid-19-cases>. Accessed December 14, 2021.
13. Reid ME, Lomas-Francis C, Olsson ML. *The Blood Group Antigen Facts Book*. Waltham, MA: Academic Press; 2012.