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ORIGINAL RESEARCH

Infectious Disease

Association between ABO blood type and coronavirus disease 2019 severe outcomes across dominant variant strains

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Abstract

Objectives: Existing evidence suggests a link between ABO blood type and severe outcomes in coronavirus disease 2019 (COVID-19). We aimed to assess the relationship between blood type and severe outcomes across variant strains throughout the pandemic.

Methods: This was a multicenter retrospective observational cohort analysis from a large health system in southeastern Michigan using electronic medical records to evaluate emergency encounters, hospitalization, and severe outcomes in COVID-19 based on ABO blood type. Consecutive adult patients presenting to the emergency department with a primary diagnosis of COVID-19 (U07.1) from March 1, 2020 through December 31, 2022 were assessed. Patients who presented during three distinct time intervals that coincided with Alpha, Delta, and Omicron variant predominance were included in the analysis. Exclusions included no record of ABO blood type, positive PCR COVID-19 test within the preceding 28 days, and if transferred from out of the health system. Severe outcomes were inclusive of intensive care unit admission, mechanical ventilation, or death, which, as a composite, represented our primary outcome. Secondary outcomes were hospital admission and length of stay. A logistic regression model was employed to test the association between ABO blood type and severe outcome, adjusting for age, sex, race, vaccination status, Elixhauser comorbidity indices, and the dominant variant time period in which the encounter occurred.

Results: Of the 33,796 COVID-19 encounters, 9416 met inclusion criteria; 4071 (43.2%) were type O, 3417 (36.3%) were type A, 459 (4.9%) were type AB, and 1469 (15.6%) were type B blood. Note that 66.4% of the cohort was female ($p = 0.18$). The proportion of composite severe disease among the four blood types was similar and ranged between 8.6% and 8.9% ($p = 0.98$). Note that 53.0% of type A blood patients required hospital admission, compared to 51.9%, 50.4%, and 48.1% of type AB, B, and O blood, respectively ($p < 0.001$). Compared to patients with O blood type (43.2%), non-O blood type (58.8%; composite of A, AB, and B) exhibited no statistically

significant difference in the proportion of composite severe disease (8.8% vs. 8.7%; $p = 0.81$) Multivariable regression analyses exhibited no significant difference regarding the presence of severe outcomes among the four blood types or O versus non-O blood types during T1, T2, and T3.

Conclusions: ABO blood type was not associated with COVID-19 severe outcomes across the Delta, Alpha, and Omicron dominant COVID waves across a large health system in southeastern Michigan. Further research is needed to better understand if ABO blood type is a risk factor for severe disease among evolving COVID-19 variants and other viral upper respiratory infections.

KEYWORDS
ABO blood groups, Alpha, coronavirus, COVID-19, Delta, Omicron, SARS-CoV-2, severe outcomes

1 | INTRODUCTION

1.1 | Background

Coronavirus disease 2019 (COVID-19) has been at the forefront of public health concerns since December 2019 with Wuhan, China, as the epicenter of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus.[1] As of August 2023, there have been more than 750 million confirmed COVID-19 cases and 6.9 million COVID-19-associated deaths worldwide.[2] The United States, which officially ended its COVID-19 public health emergency in May 2023, reported COVID-19 as the third leading cause of death in 2020 and 2021 and the fourth leading cause of death in 2022.[3–6]

1.2 | Importance

Substantial evidence has accumulated characterizing predictors of severe illness in COVID-19 patients.[7–9] Severe illness is seen in patients with co-existing conditions such as older age, obesity, hypertension, diabetes, and chronic obstructive pulmonary disease.[7,9,10] Prior literature investigated the association between ABO blood type and susceptibility and outcome of non-COVID-19 conditions.[11–14] In the early COVID-19 pandemic, studies analyzed the role of ABO blood type and severe COVID-19 outcomes; while the data was mixed, initial studies suggested a protective factor with type O blood and higher risk for severe outcomes with type A blood.[15–18]

Wu et al. conducted a retrospective study of patients in early 2020 that compared the proportions of type A blood and type O blood in COVID-19 cases and non-COVID-19 controls and posited that the significant differences represent evidence of ABO-related COVID-19 susceptibility.[17] The evidence that ABO blood type may be associated with COVID-19 susceptibility led to a multitude of quasi-experimental studies occurring throughout the world at different phases of the COVID-19 pandemic. Muniz-Diaz et al. compared blood donors who had recovered from a mild COVID-19 infection to hospitalized COVID-19 patients who received a blood product transfusion and reported that ABO is associated with COVID-19 susceptibility as well as severity and mortality in a cohort in Spain.[16] A systematic review and meta-analysis of over 30,000 patients, with five of six studies included representing cohorts from China in 2020, was more cautious in their description of their findings, an association between ABO and susceptibility, and notably reported no correlation between ABO and severe outcome. [18] A systematic review and meta-analysis of over 6 million patients and 63 studies concluded that type O blood and type A blood have less risk and more risk for COVID-19 susceptibility, respectively. They further reported that while type A may be associated with risk for severe COVID-19 outcomes, type O did not influence outcomes.

In addition to ABO, there has been interest in whether Rhesus (Rh) factor may also have an impact on susceptibility or severity. Rh factor has been studied less widely than ABO, which may be related to the fact that Rh negative is ~15% of the United States and a lower percentage worldwide. Within the limited literature on Rh factor and COVID-19, studies have reported no association with COVID-19 susceptibility and severe outcomes.[19,20] While a Canadian cohort study did find that Rh negative and O negative patients are at reduced risk for COVID-19 infection and COVID-19 severe outcome (when they expanded their cohort to include COVID-19 negative patients), their analysis of only COVID-19 positive patients did not reveal any reduced risk (with Rh negative or O negative patients) for severe outcome.[21]

1.3 | Goals of this investigation

The SARS-CoV-2 virus has mutated creating numerous variant strains.[22,23] The prior literature on ABO blood type and assessing for association with COVID-19 severe outcome has yielded conflicting results. It is unclear whether the different conclusions may be attributed to patient-centered factors, clinical factors or may be reflective of the impact of ABO changing throughout different phases of the pandemic. Further, it is unknown whether ABO blood type is associated with severe outcomes across variant strains, where variant strains are

a surrogate for different phrases of the pandemic. This study serves to investigate the relationship between ABO blood types and COVID-19 severe outcomes across the Alpha, Delta, and Omicron strains.

2 | METHODS

2.1 | Study design

This retrospective multicenter observational cohort analysis utilized encounter-level data from electronic health records (EHR, Epic Systems) throughout three distinct time intervals within the COVID-19 pandemic.

2.2 | Setting

The study was conducted at Corewell Health East, an eight-hospital system that ranges from small community hospitals to a large tertiary academic center in Southeast Michigan.

2.3 | Selection of participants

Consecutive patients 18 years and older who had a principal diagnosis of COVID-19 (U07.1) in one of eight emergency departments (EDs) during three different strain-dominant time periods (time interval 1 (T1)—March 28, 2021–June 16, 2021: Alpha; T2—July 05, 21–December 20, 2021: Delta; T3 December 28, 2021–June 16, 2022: Omicron) were included. Time intervals were chosen based on 70% dominance of the desired strain specific to our study area.[24] Encounters were excluded if the patient had a positive PCR COVID-19 test in the preceding 28 days, as this was adjudicated as a persistent positive and not an acute infection. They were also excluded if no ABO blood type data were available or if they were transferred out of the health system (Figure 1). The study was approved by the Corewell Health Institutional Review Board. Written informed consent was not obtained due to the retrospective nature of this study.

2.4 | Measurements

All data were extracted from the EHR. These data included demographic, clinical, laboratory, and outcomes variables. Comorbidities were assessed using the Agency for Healthcare Research and Quality (AHRQ) Elixhauser comorbidity index.[25]

SARS-CoV-2 vaccination status of patients was verified via the institution's EHR data, which is integrated with the Michigan Care Improvement Registry (MCIR).[26] As a result, even patients vaccinated outside the Corewell Health System were accounted for. MCIR maintains comprehensive records of SARS-CoV-2 immunizations for individuals vaccinated within Michigan, detailing both the vaccine type and the date of administration.

2.5 | Outcomes

The primary outcome of this study was assessing the association between ABO blood type and the severe COVID-19 outcome (represented by intensive care unit level care, mechanical ventilation, or death) across the three time periods. This composite severe outcome for individuals with COVID-19 was first described by the Centers for Disease Control and Prevention[27] and weighs all three components equally. Secondary outcomes were hospital admission and length of stay. Outcomes data were gathered from three distinct time intervals that coincided with Alpha, Delta, and Omicron variant predominance.

2.6 | Data analyses

Analysis of variance (ANOVA) was used to compare continuous variables (such as age) between blood types, and chi-square or Fisher's exact test was used to compare categorical variables (such as sex and race) between blood types. A logistic regression model was used to test the association between ABO blood type and severe outcome, adjusting for age (continuous), sex (female vs. male), race (White or Caucasian, Black or African American, Other), vaccination status (unvaccinated, partially vaccinated, fully vaccinated), Elixhauser comorbidity indices (<0, 0, 1–4 and ≥ 5), and the dominant variant time period (Alpha, Delta or Omicron) when the encounter occurred. The ABO blood type and variants interaction was included in the model to test if the association differs by variants. The pairwise comparisons of blood types for each variant were obtained from the regression using R package emmeans, and forest plots were generated to present the odds ratios (ORs) and 95% confidence intervals. If the interaction is not significant, a type III test was used to assess the overall effect of blood type (an overall p-value was reported). For the comparison of type O versus non-O, in addition to the above regression analysis, inverse probability weighting (IPW) method was used to balance the above covariates. In the IPW, a logistic regression was used to generate a propensity score for each patient. In this regression, blood type (type O or non-O) was the dependent variable, and the above covariates were independent variables. The predicted probabilities from the regression model are the propensity scores. These scores were then used to conduct the weighted logistic regression to estimate the association between blood type and severe outcomes. Covariate balances were examined through the standardized mean difference (SMD) with SMD < 0.1 indicating good balances. The Hosmer–Lemeshow test was used to assess the goodness of fit for logistic regression models. Statistical analysis was performed on R (version 4.2.1). Statistical significance was defined as $p < 0.05$.

3 | RESULTS

Within the three distinct time intervals, there were 33,796 emergency encounters with a primary diagnosis of COVID-19. Within that cohort, there were a total of 9416 emergency encounters with documented

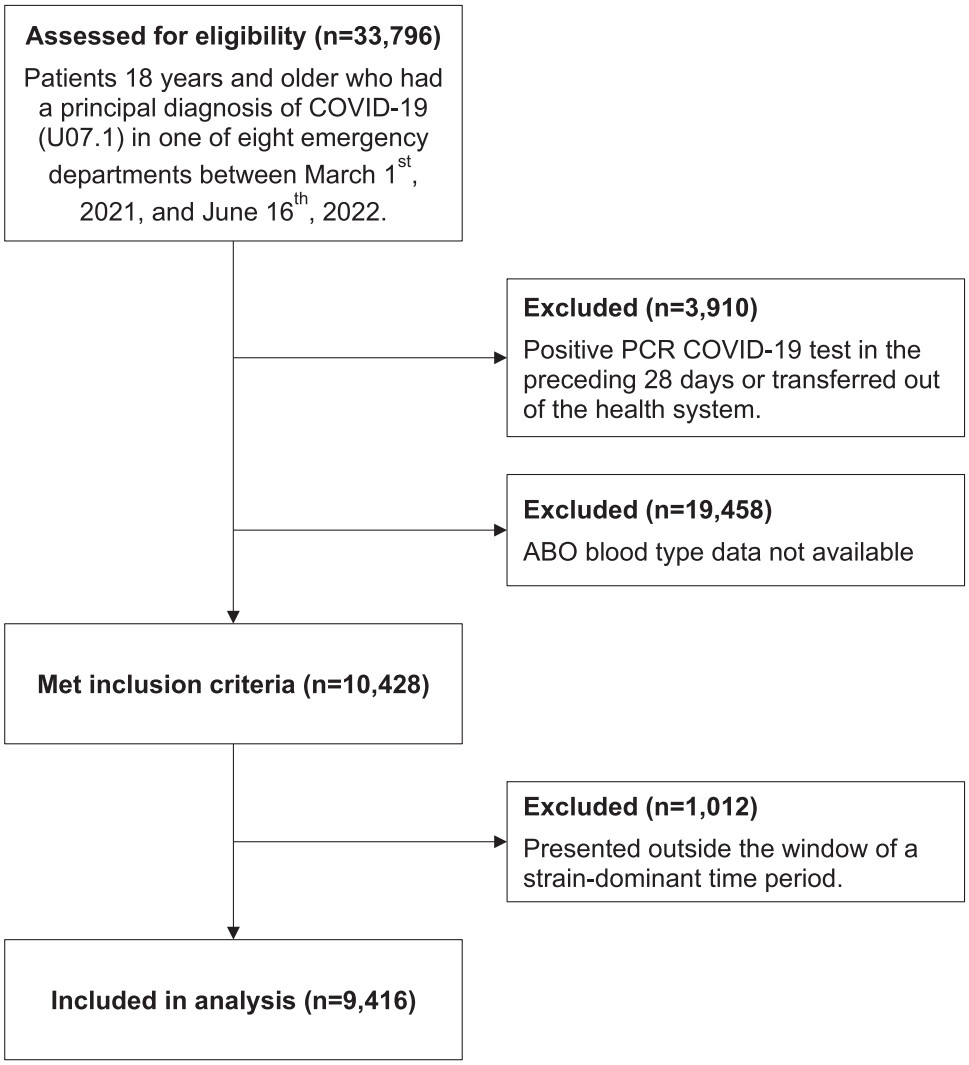

FIGURE 1 Flow figure of inclusion and exclusion criteria.

ABO blood type in the EHR system; among these, 4071 (43.2%) were type O, 3417 (36.3%) were type A, 459 (4.9%) were type AB, and 1469 (15.6%) were type B blood. Note that 66.4% of the cohort was female ($p = 0.18$). White or Caucasian race was present in 71.1%, 65.2%, 58.7%, and 50.9% of type A, AB, O, and B blood, respectively. African American race's highest prevalence was B blood type (40.4%) and least prevalent in type A blood (24.1%; $p < 0.001$). Among the four blood types, there was a significant difference in the utilization of oxygen therapy (type O 36.7%, type A 40.0%, type B 37.2%, and type AB 38.6%; $p = 0.03$). The proportion of composite severe disease among the four blood types was similar and ranged between 8.6% and 8.9% ($p = 0.98$). Note that 53.0% of type A blood patients required hospital admission, compared to 51.9%, 50.4%, and 48.1% of type AB, B, and O blood, respectively ($p < 0.001$; Table 1).

Patients with O blood type (43.2%) were compared to non-O blood type (58.8%; composite of A, AB, and B). Type non-O blood patients were older on average (56.4 vs. 54.6 years; $p < 0.001$), with 65.6% identifying as White or Caucasian compared to 58.7% of type O blood patients ($p < 0.001$). Non-O blood type required oxygen therapy 39.1% of the time, compared to 36.7% of O blood type ($p = 0.02$). There was no statistically significant difference in the proportion of composite severe disease between type O blood (8.8%) and type non-O blood (8.7%; $p = 0.81$). Hospital admission occurred in a higher proportion of non-O blood type (52.2%) compared to O blood type (48.1%; $p < 0.001$; Table 2).

Unadjusted and adjusted multivariable regression analyses were performed on the presence of severe outcomes among all possible combinations of the four blood types as well as O versus non-O blood types. There were no statistically significant findings among any of the groups (Figure 2). The null findings were adjusted for age, sex, race, Elixhauser comorbidity index, and vaccination status.

4 | LIMITATIONS

This study had some limitations. First, the variant data were not patient specific, but instead utilized population variant dominance

TABLE 1 Demographics, comorbidities, in-hospital therapies, and outcomes among emergency department patients with coronavirus disease 2019 (COVID-19) with available blood type.

Variables[a]	All	O blood type	A blood type	AB blood type	B blood type	*p* Value
N	9461	4071 (43.2%)	3417 (36.3%)	459 (4.9%)	1469 (15.6%)	
Demographics						
Age, years						<0.001
Mean	55.6 (20.0)	54.6 (19.9)	57.1 (20.0)	55.8 (19.9)	54.8 (20.0)	
Median	56.0 (39.0, 72.0)	55.0 (37.0, 71.0)	58.0 (40.0, 74.0)	57.0 (39.0, 72.0)	54.0 (37.0, 71.0)	
Sex						0.175
Female	6254 (66.4%)	2746 (67.5%)	2227 (65.2%)	312 (68.0%)	969 (66.0%)	
Male	3162 (33.6%)	1325 (32.5%)	1190 (34.8%)	147 (32.0%)	500 (34.0%)	
Race						<0.001
White or Caucasian	5863 (62.3%)	2388 (58.7%)	2429 (71.1%)	298 (65.2%)	748 (50.9%)	
Black or African American	2993 (31.8%)	1449 (35.6%)	824 (24.1%)	127 (27.8%)	593 (40.4%)	
Other	558 (5.9%)	234 (5.7%)	164 (4.8%)	32 (7.0%)	128 (8.7%)	
Body mass index, kg/m^2						0.695
Mean	31.2 (8.6)	31.1 (8.4)	31.1 (8.9)	31.3 (8.1)	31.4 (8.5)	
Median	29.8 (25.1, 35.8)	30.0 (25.2, 35.7)	29.4 (24.9, 35.8)	30.3 (25.3, 36.0)	30.0 (25.5, 35.9)	
Vaccination status						0.117
Unvaccinated	6275 (66.6%)	2739 (67.3%)	2229 (65.2%)	314 (68.4%)	993 (67.6%)	
Partially vaccinated	2543 (27.0%)	247 (6.1%)	213 (6.2%)	32 (7.0%)	106 (7.2%)	
Fully vaccinated	598 (6.4%)	1085 (26.7%)	975 (28.5%)	113 (24.6%)	370 (25.2%)	
Comorbidities						
Immunocompromised	1598 (17.0%)	682 (16.8%)	584 (17.1%)	83 (18.1%)	249 (17.0%)	0.902
Pre-existing end stage renal disease	484 (5.1%)	198 (4.9%)	168 (4.9%)	32 (7.0%)	86 (5.9%)	0.128
Elixhauser weighted score						
Mean	6.0 (9.9)	5.8 (9.8)	6.5 (10.0)	6.4 (10.8)	5.5 (9.7)	0.003
Median	3.0 (0.0, 11.0)	2.0 (0.0, 10.0)	3.0 (0.0, 11.0)	3.0 (0.0, 12.0)	1.0 (0.0, 9.0)	
Elixhauser, category						
<0	1299 (15.1%)	580 (15.6%)	432 (13.7%)	73 (17.7%)	214 (16.0%)	0.025
0	2634 (30.6%)	1171 (31.5%)	926 (29.4%)	112 (27.1%)	425 (31.8%)	
1–4	960 (11.1%)	408 (11.0%)	362 (11.5%)	45 (10.9%)	145 (10.9%)	
≥5	3721 (43.2%)	1556 (41.9%)	1431 (45.4%)	183 (44.3%)	551 (41.3%)	
Not available	802	356	266	46	134	
In-hospital therapies						
O_2 therapy	3586 (38.1%)	1496 (36.7%)	1366 (40.0%)	177 (38.6%)	547 (37.2%)	0.033
Nasal cannula/non-rebreather	2070 (22.0%)	851 (20.9%)	807 (23.6%)	95 (20.7%)	317 (21.6%)	0.034
High flow O_2	560 (5.9%)	225 (5.5%)	228 (6.7%)	23 (5.0%)	84 (5.7%)	0.147
Non-mechanical ventilation	457 (4.9%)	197 (4.8%)	153 (4.5%)	37 (8.1%)	70 (4.8%)	0.010
Vasopressor	504 (5.4%)	226 (5.6%)	178 (5.2%)	22 (4.8%)	78 (5.3%)	0.862
Primary outcomes						
Composite severe disease	825 (8.8%)	360 (8.8%)	294 (8.6%)	41 (8.9%)	130 (8.8%)	0.982
ICU-level care	687 (7.3%)	309 (7.6%)	235 (6.9%)	33 (7.2%)	110 (7.5%)	0.684
Mechanical ventilation	499 (5.3%)	223 (5.5%)	178 (5.2%)	22 (4.8%)	76 (5.2%)	0.898
Death	504 (5.4%)	221 (5.4%)	177 (5.2%)	29 (6.3%)	77 (5.2%)	0.770

(Continues)

TABLE 1 (Continued)

Variables[a]	All	O blood type	A blood type	AB blood type	B blood type	*p* Value
Secondary outcomes						
Hospital admission	4747 (50.4%)	1957 (48.1%)	1812 (53.0%)	238 (51.9%)	740 (50.4%)	<0.001
Length of stay, h						
Mean	211.2 (243.0)	213.3 (252.0)	208.5 (242.4)	206.7 (205.3)	213.4 (231.1)	0.916
Median	138.0 (78.0, 254.8)	139.0 (75.0, 262.0)	136.0 (79.0, 241.0)	143.0 (91.0, 248.3)	139.0 (80.5, 259.5)	

[a]For continuous variables, medians (interquartile ranges [IQRs]) and means (standard deviation [SD]) were presented. For categorical variables, frequencies (percentage) were presented.
Abbreviation: ICU, intensive care unit.

approximations. For Delta and Omicron, they were >90% dominant in all weeks. For alpha, the majority of weeks fell between 70% and 90% dominant.[24] Therefore, these data may not precisely demonstrate the impact of blood type on variants, particularly during transition periods between dominant variants. Second, only 27.9% of confirmed COVID-19 tests had blood type in the EHR system. We are therefore only looking at a small subset of COVID-19 patients and outcomes. It is possible that due to this, we selectively chose sicker patients at baseline since those with blood types tend to have more existing comorbidities. In a similar avenue, there is a higher proportion of females to males across all ABO blood types in a nearly two-to-one fashion. This can be explained by the fact that all pregnant females who receive prenatal care and/or deliver in a hospital receive blood type and screening to assess for ABO/RH incompatibility with the fetus. The mean age being in the mid-50s (rather than more closely aligned with child-bearing age) may be related to the fact we have had electronic medical record (and electronic records of ABO blood type) for ~15 years, and this may have mitigated the impact of recency bias. Third, our study did have an over-representation of type B blood. Only 10% of the overall US population is blood type B. However, Black patients are 13% of the US census data, yet 30% of our study cohort. Blood type B is higher in patients of Black race, and this is one explanation for our higher distribution of blood type B. Further, southeastern Michigan has a higher percentage of patients of Middle Eastern ethnicity, who also have higher rates of type B blood. When we analyzed for any association between severe outcome and ABO, we did adjust for race in our linear regression model. Fourth, the methodology of including all cases with a principal diagnosis of COVID-19 may have some limitations. While it is possible that some cases with a secondary diagnosis of COVID-19 may have been appropriate for inclusion, the number is likely small as after extensive auditing of the dataset, <1% of cases had a secondary diagnosis of COVID-19. Further, the authors have published four other studies using the same methodology with large scale (>40,000 encounters) datasets.[7,8,28,29] However, these limitations of ABO data hinder our ability to generalize the findings to the general population. Lastly, while 21.7% of the cohort received antiviral therapy and 12.0% received corticosteroids, the variables were not adjusted for in the analysis given the dynamic landscape of recommendations and availability of these therapies.

5 | DISCUSSION

This study assessed the correlation between ABO blood type and patient outcomes across the variant-dominant COVID-19 strains. The results did not demonstrate any difference in severe COVID-19 outcomes based on blood type throughout the pandemic. In comparison to some of the earlier studies, our findings present a nuanced perspective, especially considering the evolution of the virus and the emergence of new variants. While blood type as a risk factor for severe outcomes has been evaluated in COVID-19, there is a dearth of data that addresses this question based on variant strain. These data are clinically relevant as it more precisely characterizes blood type as a risk factor for COVID-19 and may have implications for management and treatment. This large data set across multiple sites within a diverse population illustrates that blood type is not associated with COVID-19 severe outcomes.

Blood type is a known risk factor in disease processes across a vast spectrum, including cardiovascular disease, malignancies, metabolic/endocrine disorders, and infectious etiologies.[30] With respect to infectious respiratory diseases, ABO blood groups have been shown to impact the contraction and the severity of disease. This broad association between blood type and various infectious respiratory diseases provides a foundation for understanding its potential role in COVID-19 and defining the highest risk populations. For instance, in a large observational study of over 1.6 million patients, Su et al. demonstrated that compared to blood group O, blood groups A, B, and AB had a higher risk of developing upper respiratory tract illness.[31] The protective effect of blood type O regarding severity of illness in respiratory infections is less clear, with some studies suggesting an increased risk for certain blood types,[32] while others find no significant difference in outcomes.[33] Further research is needed on COVID-19 and other respiratory illnesses to better comprehend the underlying immunological or physiological mechanisms that could also be at play in impacting infectivity and severity of illness.

Throughout the pandemic, there has been considerable interest in the association between blood type and COVID-19 susceptibility and severity, rooted in the historical understanding of the blood type's role in disease dynamics.[31–33] Preliminary evidence indicated potential protective effects of type O blood and increased adverse outcomes

TABLE 2 Demographics, comorbidities, in-hospital therapies, and outcomes among emergency department patients with coronavirus disease 2019 (COVID-19) with blood type O versus non-O.

Variables[a]	All	O blood type	Non-O blood type	*p* Value
N	9461	4071 (43.2%)	5345 (56.8%)	
Demographics				
Age, years				
Mean	55.6 (20.0)	54.6 (19.9)	56.4 (20.0)	<0.001
Median	56.0 (39.0, 72.0)	55.0 (37.0, 71.0)	57.0 (39.0, 73.0)	
Sex				
Female	6254 (66.4%)	2746 (67.5%)	3508 (65.6%)	0.064
Male	3162 (33.6%)	1325 (32.5%)	1837 (34.4%)	
Race				
White or Caucasian	5863 (62.3%)	2388 (58.7%)	3475 (65.0%)	<0.001
Black or African American	2993 (31.8%)	1449 (35.6%)	1544 (28.9%)	
Other	558 (5.9%)	234 (5.7%)	324 (6.1%)	
Body mass index, kg/m^2				
Mean	31.2 (8.6)	31.1 (8.4)	31.2 (8.7)	0.887
Median	29.8 (25.1, 35.8)	30.0 (25.2, 35.7)	29.6 (25.1, 35.8)	
Vaccination status				
Unvaccinated	6275 (66.6%)	2739 (67.3%)	3536 (66.2%)	0.431
Partially vaccinated	2543 (27.0%)	247 (6.1%)	351 (6.6%)	
Fully vaccinated	598 (6.4%)	1085 (26.7%)	1458 (27.3%)	
Comorbidities				
Immunocompromised	1598 (17.0%)	682 (16.8%)	916 (17.1%)	0.622
Pre-existing end stage renal disease	484 (5.1%)	198 (4.9%)	286 (5.4%)	0.289
Elixhauser weighted score				
Mean	6.0 (9.9)	5.8 (9.8)	6.2 (10.0)	0.032
Median	3.0 (0.0, 11.0)	2.0 (0.0, 10.0)	3.0 (0.0, 11.0)	
Elixhauser, category				
<0	1299 (15.1%)	580 (15.6%)	719 (14.7%)	0.117
0	2634 (30.6%)	1171 (31.5%)	1463 (29.9%)	
1–4	960 (11.1%)	408 (11.0%)	552 (11.3%)	
≥5	3721 (43.2%)	1556 (41.9%)	2165 (44.2%)	
Not available	802	356	446	
In-hospital therapies				
O_2 therapy	3586 (38.1%)	1496 (36.7%)	2090 (39.1%)	0.020
Nasal cannula/nonrebreather	2070 (22.0%)	851 (20.9%)	1219 (22.8%)	0.027
High flow O_2	560 (5.9%)	225 (5.5%)	335 (6.3%)	0.132
Non-mechanical ventilation	457 (4.9%)	197 (4.8%)	260 (4.9%)	0.955
Vasopressor	504 (5.4%)	226 (5.6%)	278 (5.2%)	0.454
Primary outcomes				
Composite severe disease	825 (8.8%)	360 (8.8%)	465 (8.7%)	0.807
ICU-level care	687 (7.3%)	309 (7.6%)	378 (7.1%)	0.338
Mechanical ventilation	499 (5.3%)	223 (5.5%)	276 (5.2%)	0.500
Death	504 (5.4%)	221 (5.4%)	283 (5.3%)	0.775

(Continues)

TABLE 2 (Continued)

Variables[a]	All	O blood type	Non-O blood type	*p* Value
Secondary outcomes				
Hospital admission	4747 (50.4%)	1957 (48.1%)	2790 (52.2%)	<0.001
Length of stay, h				
Mean	211.2 (243.0)	213.3 (252.0)	209.7 (236.4)	
Median	138.0 (78.0, 254.8)	139.0 (75.0, 262.0)	138.0 (80.0, 245.0)	0.607

[a]For continuous variables, medians (interquartile ranges [IQRs]) and means (standard deviation [SD]) were presented. For categorical variables, frequencies (percentage) were presented.
Abbreviation: ICU, intensive care unit.

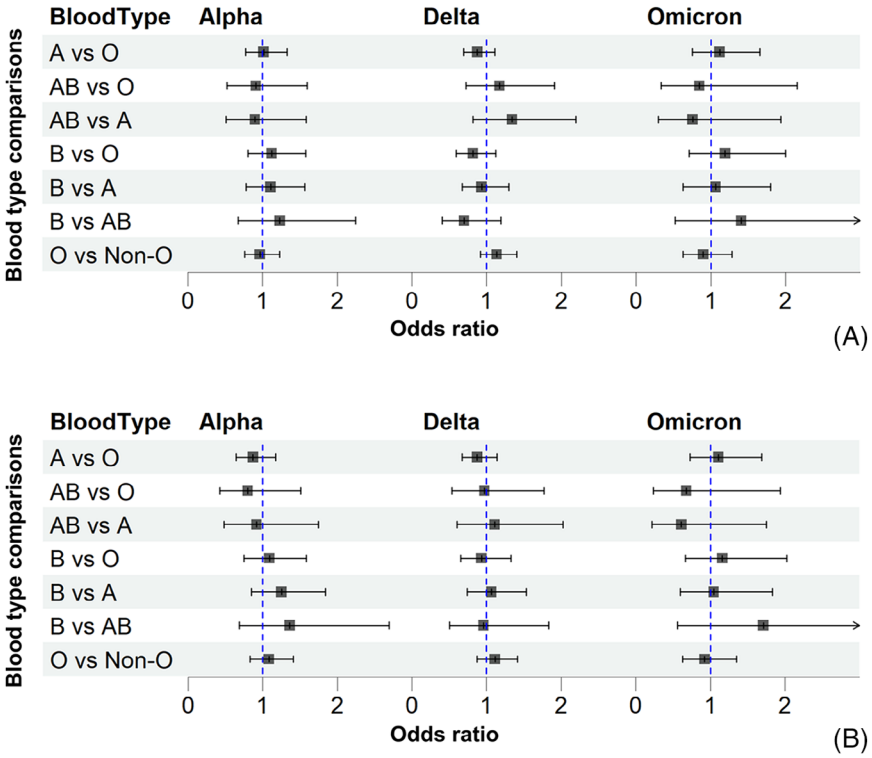

FIGURE 2 Unadjusted and adjusted logistic regression model of the interaction between blood type and time period in terms of composite severe outcome. Odds ratio (dark square) and a 95% confidence interval truncated at 0 and 3 (the arrow indicating the truncation) for time period of Alpha, Delta and Omicron, which were obtained from a logistic regression model with an interaction term between blood type and time period (Alpha, Delta or Omicron), with (A) unadjusted and (B) adjusted for age, sex, race, Elixhauser comorbidity index, and vaccination status. OR of 1 means no difference in the rate of severe outcome between the two blood types; OR > 1 means the first blood type has a higher odd of severe outcome compared to the reference blood type.

in individuals with type A blood.[7–9] Such initial findings led to a surge in investigations worldwide. An early study from China revealed a distinct distribution of COVID-19 cases by blood type, with type A and B showing higher incidences, despite type O being more prevalent in the general population.[17] This led to questions about the inherent protective mechanisms in certain blood types. Subsequent research, both from China and globally, reinforced the protective association of type O blood.[15,18] Moreover, when assessing the influence of blood type on severe illness outcomes, consistent findings underscored the role of blood type in both susceptibility and the severity of COVID-19.[21,34]

Other data have illustrated a lack of or different association between blood type and COVID-19 infection. This divergence in findings underscores the complexity of the relationship and the potential influence of other confounding factors. In one systematic review and meta-analysis, results indicate that the COVID-19 infection rate was higher in persons with blood group A > O > B > AB.[35] In another study conducted in Spain, there was no significant association between ABO blood type and the development of infection.[36] Such variations in findings across studies emphasize the need for comprehensive and well-controlled investigations to tease apart the true nature of the association. Similarly, this study did not demonstrate any difference in blood type and COVID-19 severe outcomes. Our research adds to this body of evidence, suggesting that while blood type may play a role in some contexts, it is not a consistent predictor of severe outcomes. This study took an additional and novel step and investigated if the association between blood type and severe infection changed over time as the virus mutated. Once again, the results demonstrated no association between blood type and dominant variant strain. This novel approach underscores the importance of considering the evolving nature of the virus when evaluating potential risk factors. Given the conflicting evidence, further research is needed to better understand the association between COVID-19 variants and blood type.

AUTHOR CONTRIBUTIONS

Nicholas Mielke, Rebecca Gorz, Amit Bahl, and David A Berger designed the study, had full access to the data, and take responsibility for the integrity and accuracy of the data analysis. Lili Zhao and Nicholas Mielke contributed to data and statistical analysis. All authors contributed to the writing and editing of the manuscript. All authors contributed to data acquisition, analysis, and interpretation, and reviewed and approved the final version of the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

CONFLICT OF INTEREST STATEMENT

Dr. Amit Bahl, MD, has received grant funding from Moderna. All other authors declare no relevant conflicts of interest relevant to this work.

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