Does ABO Blood Groups Affect Outcomes in Hospitalized COVID-19 Patients?

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Abstract

Background: Blood group type A has been associated with increased susceptibility for coronavirus disease 2019 (COVID-19) infection when compared to group O. The aim of our study was to examine outcomes in hospitalized COVID-19 patients among blood groups A and O.

Methods: This is an observational study. Kruskal-Wallis and Chi-square tests were used to compare continuous and categorical variables. Multivariable logistic regression models were used to examine association of blood groups with rates of mortality and severity of disease. All adult patients (> 18 years) admitted with COVID-19 infection between March 1, 2020 and March 10, 2021 at a large community hospital in Northeast Georgia were included. We compared mortality, severity of disease (use of mechanical ventilation, vasopressor, and acute renal failure), rates of venous thromboembolism and inflammatory markers between the blood groups. We used multivariable logistic regression model to adjust for demographical and clinical characteristics, use of COVID-19 medications and severity.

Results: A total of 3,563 of 5,204 admitted patients had information on blood groups. Of these, 1,301 (36.5%) were group A, 377 (10.6 %) were group B, 133 (3.7%) were group AB and 1,752 (49.2%) were group O. On adjusted analysis, there were no significant differences in rates of intensive care unit (ICU) admissions, mechanical ventilation, vasopressors, acute renal failure, venous thromboembolism and readmission rate between the blood groups A and O. In-hospital mortality was also not statistically different among the blood groups A and O (17.5% vs. 20.1%; P = 0.07). On adjusted analysis, in-hospital mortality was not lower in blood groups O (odds ratio (OR): 1.06; 95% confidence interval (CI): 0.80 - 1.40, P = 0.70).

Conclusions: Once hospitalized with COVID-19 infection, blood groups A and O are not associated with increased severity or in-hospital mortality.

Keywords: COVID-19; ABO blood group; In-hospital mortality

Introduction

Blood group O has been reported to be at lower risk of certain disease like diabetes mellitus, atherosclerosis, cardiac disease and certain infections due to certain underlying molecular traits [1-6]. In the beginning of this pandemic, Zhao et al reported lower risk of blood group O as compared to non-O population [7]. This was followed by GWAS study identifying a 3p21.31 gene cluster as a genetic susceptibility locus in patients with coronavirus disease 2019 (COVID-19) with respiratory failure [8]. They reported association of signal at locus 9q34.2 with ABO blood group locus and higher risk in blood group A and a protective effect in blood group O when compared to other blood groups. Pare et al had earlier showed similar observation that 9q34.2 locus was associated with plasma soluble intercellular adhesion molecule 1 (sICAM-1) concentration, a molecule involved in leucocytes recruitment in inflammatory disease, which has been associated with other disease processes like acute myocardial infarction, diabetes and stroke [4]. Whether these associations

Key Points

- Question: Does blood group types affect outcomes in hospitalized COVID-19 patients?
- Findings: In this observational study of 3,563 patients, there were no significant differences in rates of mechanical ventilation, use of vasopressors, acute kidney injury requiring hemodialysis, in-hospital mortality or rates of readmission between the blood group types.
- Meaning: Once hospitalized, blood group subtypes are not associated with increased risk for severity of disease or in-hospital mortality in COVID-19 infection.

result in clinically worse outcomes with different blood groups has been debated. Multiple observational studies reported increased risk and worse outcome in blood group A as compared to blood group O; however, many other observational studies did not find any significant differences [9-15].

We studied hospitalized COVID-19 patients and examined relationship between the blood groups and in-hospital mortality and severity of this disease.

Materials and Methods

Study design and data source

We performed a retrospective analysis of adult COVID-19 patients (age ≥ 18 years) admitted to a large community hospital in a rural setting in Northeast Georgia between March 1, 2020 and March 10, 2020. COVID-19 patients were identified from our Epic® electronic medical record (EMR) using International Classification of Disease, 10th Revision, Clinical Modification (ICD-10-CM) and/or Current Procedural Terminology (CPT) codes for COVID-19 infection and/or positive COVID-19 polymerase chain reaction (PCR) testing. We obtained clinical and demographical details from Epic® Caboodle data warehouse and Cerner Acute Physiology and Chronic Health Enquiry Score (APACHE®) Outcomes. Systems integration was provided by IPC Global by leveraging their in-process data factory innovation running on an Amazon Web Services (AWS®) VPC. We excluded COVID-19 patients who required readmission to the hospital after initial discharge. The study was reviewed and found exempt by the Northeast Georgia Health System Institutional Review Board (IRB); and this study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration.

Outcomes

Our primary outcome of interest was in-hospital mortality. We also determined the association of blood groups with severity of COVID-19 infection. We defined COVID-19 infections as severe if patients required invasive mechanical ventilation (IMV), vasopressor support (shock) or had acute kidney injury (AKI) requiring hemodialysis. We also used 4C score as an additional severity score. We compared inflammatory markers (ferritin, C-reactive protein (CRP), lactate dehydrogenase (LDH), fibrinogen, and D-dimer) along with rates of venous thromboembolism (VTE), and readmissions within the blood groups.

Statistics

We described categorical data using frequency count and percentages. We reported medians and inter quartile ranges for continuous variables as they were not normally distributed. We compared categorical variables using Chi-square tests and continuous variables with Kruskal-Wallis tests. For all analyses we deemed statistical significance a P value < 0.05.

We developed multivariable logistic regression models to examine differences in blood groups for rates of mortality or severity of COVID-19 infection. This was adjusted for the confounders of age, gender, comorbidities, use of COVID-19 medications (steroids, remdesivir, hydroxychloroquine and tocilizumab), organ failures (IMV, AKI and shock), 4C score [16] and complications such as acute VTE, blood transfusions and hospital-acquired infections. We checked variables used in the final model for multicollinearity using tolerance and variance inflation factor (Supplementary Material 1, www.thejh. org). These models were bootstrapped using 2,000 bootstrap replicates and case resampling with replacement from the original dataset. All analyses were done in STATA/MP ver. 16.0.

Results

Of 5,204 patients admitted with COVID-19 infection, blood group data were available for 3,563 patients. Of these, 1,301 (36.5%) were group A, 377 (10.6 %) were group B, 133 (3.7%) were group AB and 1,752 (49.2%) were group O.

The demographical and clinical characteristics of patient according to ABO blood groups are shown in Tables 1 and 2. The groups were well matched in terms of age and gender but were different in their racial distribution. Amongst comorbidities present on admissions, end-stage renal disease (ESRD) was observed to be higher in blood group O while VTE was found to be higher in blood group A.

Most COVID-19 medication except steroids and remdesivir were distributed unequally among the blood group type. However, when comparing only blood groups A and O, the use of steroids was not statistically different. Severity of COVID-19 as per 4C score was similar in all groups.

The rates of intensive care unit (ICU) admission were similar among the blood groups. However, blood group O had significantly higher rates of IMV (those admitted to ICU) (60.1% vs. 48.9%, P = 0.001), and vasopressor use (56% vs. 48.2%, P = 0.016) when compared to blood group A. Once on IMV, use of paralytic or inhaled vasodilators and the duration of IMV were not different between the blood groups. Rates of tracheostomy were not significantly different in various blood groups A and O, but were observed to be significantly higher in group AB.

Rates of acute stroke or intracerebral hemorrhage (ICH), AKI (with and without hemodialysis) and health care-associated infections (HAIs) were not significantly different between the blood groups (Table 3). However, rates of VTE were significantly higher in blood group AB. There was no difference in VTE between blood groups A and O (5.7% vs. 6.6%, P = 0.32). Rates of blood transfusions were significantly higher in blood group O.

In-hospital mortality was significantly higher in blood group B (A: 17.5%, B: 20.4%, AB: 11.3% and O: 20.1%; P = 0.03). Length of stay in survivors and length of stay in those who died was not significantly different between the blood groups (Table 3).

Initial levels of inflammatory markers were not significantly different within the blood groups (Table 4). However,

Table 1. Demographical and Clinical Characteristics of COVID-19 Patients According to ABO Groups

	A	B	AB	O	P
Total	1,301	377	133	1,752	
Age, median (IQR)	67 (54 - 77)	67 (52 - 78)	68 (53 - 77)	66 (52 - 76)	0.20
Male (%)	53.8	52.8	54.9	50.3	0.23
Race (%)					< 0.001
White	81.8	58.4	68.4	67.4	
Blacks	5	18.6	15.0	8.3	
Hispanics	10.8	13.5	9.0	20.5	
Asians/Pacific Islander	1.1	5.8	2.2	1.3	
Not answered	1.4	3.7	5.3	2.5	
Rh positive	89.5	89.4	88.7	91.2	0.33
BMI	30.3	30.6	29.7	30.2	0.58
Comorbidities (%)					
Hypertension	74.6	76.4	69.9	72.1	0.17
Congestive heart failure	33.2	39.5	33.8	35.1	0.15
Diabetes mellitus	48.7	49.1	45.1	45.0	0.17
COPD	38.5	38.9	32.3	37.7	0.54
ESRD	3.6	3.2	5.3	6.3	0.003
Cirrhosis	13.1	13.0	15.8	12.8	0.81
Cancer	14.6	12.2	12.0	13.8	0.58
VTE	8.1	7.7	11.3	5.2	0.002
Medications					
Anticoagulation	14.1	13.5	15.0	12.9	0.73
Aspirin	17.9	16.7	18.1	16.8	0.86
ACEI	30.6	28.1	30.8	29.0	0.7
Statins	33.6	30.2	26.5	30.6	0.16
COVID-19 medications (%)					
Hydroxychloroquine	3.3	4.5	5.3	4.3	0.42
Tocilizumab	6.6	9.3	6.0	7.8	0.28
Steroids	71.2	74.8	80.4	68.8	0.006
Convalescent plasma	37.9	35.5	43.6	35	0.11
Remdesivir	60.9	61.5	63.2	55.1	0.003
Anticoagulation					0.08
Standard	54.8	53.1	53.4	54.3	
High	33.6	33.4	39.9	31.6	
4C score	11 (7 - 14)	11 (7 - 14)	11 (7 - 13)	11 (7 - 14)	0.47

COVID-19: coronavirus disease 2019; IQR: interquartile range; BMI: body mass index; COPD: chronic obstructive pulmonary disease; ESRD: end-stage renal disease; VTE: venous thromboembolism; ACEI: angiotensin-converting enzyme inhibitor.

blood groups AB and O had significantly higher levels of ferritin during the admission.

Regression models

On adjusted analysis, in-hospital mortality was not signifi-cantly different among the blood groups A, B and O (Table 5). The odds were lower in blood group AB (odds ratio (OR) 0.32; 95% confidence interval (CI): 0.11 - 0.96, P = 0.04); however, the sample size of this group was the lowest. We did not observe any significant difference in rates of ICU admissions, IMV, AKI, VTE, vasopressor use and readmissions between the blood groups. Rh-positive status was also not associated

Table 2. Clinical Features of ICU Admissions in COVID-19 Patients According to ABO Groups

	A	B	AB	O	P
ICU transfers, n	394	122	39	589	0.23
Use of mechanical ventilation, n (%)	193 (48.9)	74 (60.8)	22 (56.4)	354 (60.1)	0.005
Length of mechanical ventilation (in days), median (IQR)	7 (2 - 16)	9.5 (2 - 20)	10 (2 - 22)	6 (2 - 16)	0.59
Paralytic use (%)	35.2	31.1	22.7	35.9	0.56
Inhaled vasodilator (%)	13.5	9.5	0	12.4	0.27
Tracheostomy (%)	14.5	20.3	36.4	14.4	0.03
Use of vasopressors (%)					
Required norepinephrine	48.2	59.8	48.7	55.9	0.045
Required vasopressin	24.6	34.4	17.9	30.4	0.04
Required epinephrine	9.9	15.6	7.7	14.9	0.07
Any vasopressor	48.2	60.7	48.7	56.0	0.03

ICU: intensive care unit; COVID-19: coronavirus disease 2019; IQR: interquartile range.

with increased severity of COVID-19 (Supplementary Material 2, www.thejh.org).

Discussion

Published experience suggests that people with blood group A are genetically more susceptible to COVID-19 and maybe hospitalized more frequently [8]. Whether this phenomenon translates to worse outcomes in these individuals is currently debated. We did not observe increased likelihood of death and developing severe disease in COVID-19 according to blood groups in about 3,500 patients. The levels of inflammatory markers, rates of IMV, AKI, VTE and degree of shock also did not differ significantly between blood groups. The rates of readmissions also did not vary significantly within the groups.

Table 3. Outcomes of Hospitalized COVID-19 Patients According to ABO Groups

	A	B	AB	O	P
Outcomes					
In-hospital mortality (%)	17.5	20.4	11.3	20.1	0.03
28-day mortality (%)	16.4	18.6	9.6	18.8	0.04
LOS in survivors (in days), median (IQR)	5 (3 - 11)	6 (4 - 12)	6 (3 - 15)	6 (3 - 11)	0.09
Time to death (in days), median (IQR)	14 (7 - 24)	14 (8.5 - 27.5)	24 (8 - 39)	14 (7 - 22)	0.52
Disposition (%)					0.20
Home	62.0	62.4	54.7	63.4	
Home with health	20.9	20.0	22.2	19.5	
Rehab/SNF/LTAC/acute care	15	15.6	17.1	13.7	
Others	2.1	2.0	6	3.5	
Readmission	16.4	17.3	17.8	16.3	0.95
Complications (%)					
Acute stroke	2.3	4.0	5.3	2.7	0.11
Acute ICH	1.1	2.7	1.5	1.2	0.14
Acute kidney injury	18.2	19.9	18.8	21.9	0.09
Acute kidney injury requiring hemodialysis	3.1	2.6	1.5	4.5	0.19
Acute VTE	5.7	6.9	12.0	6.6	0.04
Blood transfusion	11.7	13.5	15.0	15.8	0.01
HAI	4.3	5.0	4.5	6.1	0.17

COVID-19: coronavirus disease 2019; IQR: interquartile range; LOS: length of stay; ICH: intracerebral hemorrhage; SNF: skilled nursing facility; LTAC: long-term acute care; HAI: health care-associated infection.

Table 4. Inflammatory Markers in COVID-19 Patients According to ABO Groups

Inflammatory markers[a]	A	B	AB	O	P
Initial ferritin	436 (194 - 868)	456 (223 - 954)	544 (253 - 945)	457 (209 - 987)	0.13
Initial CRP	8 (3 - 13)	8 (4 - 14)	8 (5 - 14)	8 (4 - 14)	0.36
Initial LDH	318 (240 - 425)	334 (261 - 471)	352 (251 - 432)	324 (244 - 441)	0.15
Initial D-dimer	0.9 (0.5 - 1.7)	0.9 (0.5 - 1.8)	0.8 (0.5 - 1.5)	1 (0.6 - 1.9)	0.09
Initial fibrinogen	545 (431 - 682)	559 (453 - 657)	542 (414 - 704)	543 (423 - 695)	0.93
Highest ferritin	551 (1,081 - 1,060)	574 (273 - 1,182)	696 (304 - 1,210)	614 (267 - 1,260)	0.04
Highest CRP	9 (4 - 15)	10 (5 - 16)	10 (6 - 16)	10 (5 - 16)	0.39
Highest LDH	346 (256 - 471)	375 (277 - 521)	370 (268 - 458)	350 (263 - 504)	0.09
Highest D-dimer	1.2 (0.7 - 4)	1.3 (0.7 - 4)	1.2 (0.6 - 4)	1.4 (0.8 - 4)	0.06
Highest fibrinogen	574 (459 - 721)	599 (453 - 725)	572 (440 - 738)	574 (453 - 725)	0.93

[a]Median (IQR), total samples. COVID-19: coronavirus disease 2019; CRP: C-reactive protein; LDH: lactate dehydrogenase.

Persons with blood group O have some basic differences when compared to other blood groups. They have been reported to have 25-30% lower levels of circulating factors VII and von Willebrand factors [2, 17]. There is reported association of variation at the ABO locus with sICAM-1, soluble P-selectin, and soluble E-selectin levels. These molecules are involved in leucocytes recruitment in inflammatory disease and have been associated with risk of atherosclerosis, diabetes and heart diseases [18]. Other associations of lower angiotensin-converting enzyme (ACE) activity in blood group O have been identified [1, 19]. Another genomic study reported increased interleukin-6 (IL-6) levels in blood group O [20]. Ellinghaus et al identified a 3p21.31 gene cluster as a genetic susceptibility locus in patients with COVID-19 with respiratory failure [8]. They reported association of signal at locus 9q34.2 with ABO blood group locus, and higher risk in blood group A, and a protective effect in blood group O, when compared to other blood groups. This has led to slurry of papers on this topic where authors have attempted to study clinical outcomes in COVID-19 as per blood groups.

Leaf et al performed the largest study investigating the predisposition of blood group A with outcomes in critically ill patients [9]. Whiles rates of admission were higher in people with blood group A, the investigators were unable to discern mortality differences. Conversely, Zhao et al observed both higher admission and death rates people in blood group A when compared with group O [7]. A drawback of these studies is the extrapolation of data for their population from surveys and blood donor data. Since surveys and blood donor data predated their studies, they may have resulted in erroneous assumptions for blood group distribution in the local population. Boudin et al did not find differences in symptoms and rates of COVID-19 infection between blood groups, but they did not report outcome differences [21]. Latz et al did not find significant differences in peak inflammatory markers, clinical severity and in-hospital mortality between the blood groups [10]. May et al also did not observe any association of severity and mortality among the blood groups [11]. In a cross-sectional study, Solmaz et al reported higher rate of hospitalization in blood group A in a community in Turkey; however, they did not find increased rate of ICU hospitalization or death among the various blood groups [14].

Muniz-Diaz et al found higher proportion of blood donors with group O in patients who presented for convalescent plas-

Table 5. Comparison Between Blood Groups With Regards to Rates of ICU Transfers, AKI, Acute VTE, Mechanical Ventilation, Use of Vasopressors, In-Hospital Mortality and Readmissions in COVID-19

	B	AB	O
ICU transfer	0.74 (0.49 - 1.09), 0.13	0.62 (0.33 - 1.17), 0.14	1.01 (0.79 - 1.28), 0.92
Acute kidney injury	0.83 (0.56 - 1.24), 0.37	0.66 (0.35 - 1.25), 0.20	1.01 (0.78 - 1.29), 0.93
Acute VTE	1.07 (0.63 - 1.78), 0.8	2.25 (1.18 - 4.29), 0.014	1.05 (0.75 - 1.46), 0.76
Mechanical ventilation	1.06 (0.59 - 1.90), 0.84	1.16 (0.48 - 2.79), 0.72	1.35 (0.92 - 1.99), 0.12
Pressor use	1.28 (0.72 - 2.29), 0.39	0.58 (0.21 - 1.64), 0.31	0.82 (0.57 - 1.19), 0.31
In hospital mortality	1.03 (0.66 - 1.59), 0.88	0.34 (0.12 - 0.96), 0.04	1.05 (0.79 - 1.39), 0.07
Readmission	1.12 (0.78 - 1.58), 0.54	1.39 (0.81 - 2.39), 0.22	1.04 (0.83 - 1.31), 0.71

A is the comparison group. The regression adjusts for age, gender, race, comorbidities, clinical characteristics, inflammatory markers, 4C score and COVID-19 medications including anticoagulation status. The model was bootstrapped 2,000 times with replacement. The values shown are odds ratio (95% confidence interval), P value. ICU: intensive care unit; AKI: acute kidney injury; VTE: venous thromboembolism; COVID-19: coronavirus disease 2019.

ma donations [22]. They also found higher mortality in blood group A as compared to O in patients receiving convalescent plasma. This was suggested to be a sign that blood group O was more likely to be affected. However, Gallian et al found lower seropositive rates in blood group O in 998 samples, and suggested that patients with blood group O are less likely to be infected [23]. Given limitations of testing neutralizing antibodies, extrapolation from these studies may not reflect true relationship between incidence and disease outcomes. In another large population-based cohort study, Ray et al reported lower risk for COVID-19 in blood group O when compared to others (A, B and AB together); however, they did not find any difference in risk when they compared only blood groups A and O [24]. Similarly, they reported lower risk of COVID-19 in blood group O when compared to all other (A, B and AB together), but did not find any differences in severity between blood groups A and O. Blood group B appeared to be at highest risk for COVID-19 and its severity.

Although a genome wide association study found that people with blood group A were predisposed to respiratory failure, in our study, patients with blood group A has similar rates and duration of IMV as compared to other blood groups [8]. Similarly, use of prone-positioning, paralytics and inhaled vasodilators were not different between blood groups. The length of mechanical ventilation and use of tracheostomy were also not different. In 1,732 ICU patients admitted for non-COVID-19 causes, ABO blood groups did not correlate with ICU mortality and ICU length of stay [25].

One possible explanation for finding no relationship between severity and mortality with ABO groups may be presence of other genetic associations with severe COVID-19, which are not related to the locus of the blood group types. In a study to examine the genome-wide association, GenOMICC study found many new associations with severity of COVID-19 [26]. They reported multiple other associations such as chromosome 12q24.13 (encodes antiviral restriction enzyme activators), chromosome 19p13.2 (encodes tyrosine kinase 2), chromosome 19p13.3 (encodes dipeptidyl peptidase 9) and chromosome 21q22.1 (encodes interferon receptor IFNAR2). Gavriilaki et al reported ADAMTS13 variants which were associated with ICU hospitalizations [27]. These findings may also explain variability of association between blood group types in different studies from different regions in the world. Both race and ethnicity have been reported to attenuate the associations between ABO/Rh and COVID-19 infection rate [28].

Marcos et al studied 226 patients and found lower incidence of COVID-19 and thrombosis in blood group O when compared to general population [29]. We did not observe lower rates of venous thrombosis or embolism in blood group O. We did not find any study comparing ABO blood groups with acute renal failure.

Rh-positive status has been reported to be risk factor for both COVID-19 infection and its severity in a large Canadian population [24]. We did not find any difference between Rh-positive and negative persons in severity of illness and mortality once they are admitted to hospitals. Niles et al reported diminished effect of Rh positivity after adjusting for race and ethnicity [28]. Our differences may be explained by difference in population characteristics. We did not find any genomic studies associating with Rh-positive status. Further research is needed in this area.

Our study has some important limitations such as primarily single center, retrospective nature. Our sample size is larger than many other studies. We applied bootstrapping estimated to our data to add the robustness of our models. This removes many uncertainties related to smaller sample size. However, we cannot still discount unmeasured confounders which may have biased our results. We also could not comment on rates of admissions with COVID-19 per blood groups because we did not have local distributions of ABO group in our community.

Conclusions

Despite these limitations, our study provides additional data to this topic. We conclude that blood groups are not associated with increased risk for severity of disease or in-hospital mortality, once COVID-19 patients are admitted to hospital. Larger prospective observational studies may help confirm our findings.

Supplementary Material

Suppl 1. Evaluating for multicollinearity using collin function in STATA.
Suppl 2. Comparison between Rh groups with regards to rates of ICU transfers, AKI, acute VTE, mechanical ventilation, use of vasopressors, in-hospital mortality and readmissions in COVID-19 (Rh negative is the comparison group).

Acknowledgments

None to declare.

Financial Disclosure

None to declare.

Conflict of Interest

The authors declare no conflict of interest.

Informed Consent

The IRB had reviewed this retrospective study and have waived the requirement of an informed consent. It was based on the following criteria: no patient identifying data is being published, no patient interaction was involved and no patient intervention was done during the course of this retrospective study.

Author Contributions

Gagan Kumar MD: study design, data analysis, and manuscript writing; Mark Meersman CPA: data validation; Drew Dalton BS: data validation; Dhaval Patel MD: study design and manuscript writing; Rahul Nanchal MD: study design, data analysis, and manuscript writing; Ankit Sakhuja: study design, data analysis, and manuscript writing; Martin Hererra: manuscript writing; Achuta Kumar Guddati MD: study design, data analysis, and manuscript writing.

Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author.

Abbreviations

OR: odds ratio; CI: confidence interval; AWS: Amazon Web Services; EMR: electronic medical record; APACHE score: Acute Physiology and Chronic Health Enquiry score; ICD-10-CM: International Classification of Disease, 10th Revision, Clinical Modification; CPT: Current Procedural Terminology; ICU: intensive care unit; AKI: acute kidney injury; CRP: C-reactive protein; LDH: lactate dehydrogenase; VTE: venous thromboembolism; IMV: invasive mechanical ventilation; SNF: skilled nursing facility; LTAC: long-term acute care

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