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# Association of ABO Blood Group, Age, Body Mass Index and Symptomatic COVID-19 Infection with Signal Levels of Antibodies to COVID-19

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## ABSTRACT

***Objective:*** *To determine if ABO blood group, age, body mass index (BMI), or symptomatic COVID-19 infection are associated with COVID-19 antibody response in unvaccinated COVID-19 antibody positive pregnant women at time of delivery.*

***Methods****: At the time of delivery, 2,499 consecutive pregnant women were tested for ABO blood group and antibodies to both the spike protein and nucleocapsid protein of the COVID-19 virus. The DiaSorin assay was used for antibody to spike protein analysis and the Roche assay for antibody to nucleocapsid protein. Gamma regression models with a log link were used to compare antibody signals, with blood group, age, and BMI as the predictors.*

***Results:*** *260 (10.4%) of 2,499 women who had not been vaccinated for COVID-19, were positive for both spike and nucleocapsid protein antibodies to COVID-19. The mean signal for COVID-19 nucleocapsid antibody was significantly lower for blood group AB (p=0.028) compared with blood group O. A relationship between blood group and presence of symptomatic COVID-19 was detected (p = 0.028), with asymptomatic individuals having blood group B at a higher rate than the symptomatic individuals do.*

*No other significant pairwise differences between blood groups were detected. There was no significant difference in signal level of antibodies to COVID-19 spike protein between any of the blood groups. Mean signals for antibodies to spike and nucleocapsid proteins were significantly higher in older women (p=0.001 for spike protein antibody and p=0.002 for nucleocapsid antibody). Significantly higher signal levels of antibody to spike and nucleocapsid proteins were found in women with class 2/3 obesity (p=0.022 and p=0.003, respectively).*

***Conclusions:*** *Pregnant women of AB blood group had lower antibody signal to nucleocapsid protein compared to the O blood group, and women of older age and greater BMI had higher antibody signal to COVID-19 spike and nucleocapsid proteins. There was a significant association between women with blood group B and asymptomatic infections.*

**Keywords**
COVID-19, Antibody levels, Age, Obesity, Pregnancy.

## Introduction

Older age and obesity have been associated with COVID-19 disease severity [1-4] and a higher antibody titer to COVID-19 infection [5-7]. A recent report suggests that blood group O plasma has significantly lower levels of SARS-CoV-2 IgG nucleocapsid antibodies compared to blood group A plasma [8]. We collected plasma and clinical data on a prospective cohort of 2,499 pregnant women, consecutively admitted, who were tested for ABO blood group and antibodies to COVID-19 at the time of delivery between May 1, 2020, and April 30, 2021 at the University of Iowa Hospitals and Clinics (UIHC). Using the test results and clinical data, we sought to determine if ABO blood group, age, body mass index (BMI), or symptomatic COVID-19 infection are associated with COVID-19 antibody response in unvaccinated COVID-19 antibody positive pregnant women at time of delivery.

## Methods

This prospective cohort included all pregnant patients who delivered at UIHC between May 1, 2020, and April 30, 2021. The Institutional Review Board at the University of Iowa approved this study (IRB#: 202004278). Demographic and clinical data were obtained from the electronic medical record and double entered in a Research Electronic Data Capture (REDCap) database. The primary outcome of the original study was maternal and fetal outcomes in COVID-19 positive delivering women; this is a secondary analysis of data from the same cohort [9].

Excess plasma from routine blood samples for ABO blood typing was collected and frozen at -18°C within 3 days of admission and used to determine the seroprevalence of COVID-19 antibodies using the Elecsys Anti-SARS-CoV-2 assay (Roche Diagnostics) and the LIASON SARS-CoV-2 S1/S2 IgG assay (DiaSorin, Inc.). The DiaSorin assay detects IgG antibodies to spike protein whereas the Roche assay detects total antibodies (including IgM antibodies) to nucleocapsid protein. For the DiaSorin assay, antibody signal is expressed in AU/mL (arbitrary units/mL) and a result of 15 AU/mL indicates a positive result. For the Roche assay, antibody signal is expressed as a cut-off index (COI) and a result of 1.0 COI or higher indicates a positive result. Women were considered positive for antibodies to COVID-19 if both the DiaSorin and Roche assays yielded positive results, as defined above. None of the women who tested positive by both assays had received a COVID-19 vaccine. To assess specificity, 139 existing plasma samples collected from individuals prior to December 2019 (pre-COVID-19) were run on both the DiaSorin and Roche assays. 139 of 139 samples (100%) were antibody negative by Roche assay and 138 of 139 (99.3%) were antibody negative by DiaSorin assay [10].

Maternal BMI was calculated from recorded weight and height ($kg/m^2$) as collected at delivery admission. Mothers were classified by BMI into three categories: BMI 20-24.9 (normal), BMI 25-29.9 (overweight), and BMI ≥ 30 (obese). Obesity was further subdivided into BMI 30-34.9 (class 1), BMI 35-39.9 (class 2), and BMI ≥ 40 (class 3). Class 3 is also referred to as "severe" or "extreme" obesity. Women with a BMI < 20 or > 90 were excluded from analysis. Disease severity was defined as either asymptomatic or symptomatic for COVID-19 infection.

Gamma regression models with a log link were used to compare antibody signal values compared to cutoff value for each antibody, with blood group, age, and BMI as the predictors. Kruskal-Wallis rank sum tests were used to compare antibody levels between different age and BMI groups. Chi-Squared tests and Fisher's Exact tests were used where appropriate to compare differences in categorical variable distributions between symptomatic and asymptomatic mothers. Wilcoxon rank sum tests were used to compare the distributions of the assay values between these two groups due to the highly right-skewed nature of assay values. A p-value of 0.05 was considered statistically significant for all tests. Multiple comparisons adjustments were not employed due to the exploratory nature of this analysis. All analyses were conducted using R, version 4.1.1 [11].

## Results

260 (10.4%) of 2,499 women were positive for both antibodies to COVID-19 and had not been vaccinated. The ABO blood groups of the 260 women are shown in Tables 1 and 2. The mean signal for COVID-19 nucleocapsid antibody was found to be lower for blood group AB (p=0.028) compared with blood group O (Table 1). No other significant pairwise differences between blood groups were detected. There was no significant difference in signal level of antibodies to COVID-19 spike protein between any of the four blood groups (Table 2). Mean antibody signals to spike protein and nucleocapsid protein were significantly higher in older women (p=0.001 for spike protein antibody and p=0.002 for nucleocapsid antibody) (Tables 1-3). Significantly higher signal levels of antibody to spike and nucleocapsid protein were also found in women with class 2/3 obesity (p=0.022 and p=0.003, respectively) (Tables 1, 2 and 4).

Individuals with blood group B were more likely to have had asymptomatic infection compared to individuals of blood groups A, AB, or O (p = 0.028). There was no evidence that higher signals of antibody to spike and nucleocapsid protein were found in women with symptomatic COVID-19 infection compared to those with asymptomatic infection (p = 0.322 and p = 0.673, respectively) (Table 5). Symptomatic COVID-19 infection was not shown to be associated with age or class 2/3 obesity (p = 0.635 and p = 0.133, respectively).

## Discussion

Pregnant women with the AB blood group had lower COVID-19 antibody signals to nucleocapsid protein compared to those with the O blood group in this cohort of 2,499 consecutive delivering pregnant women during the first year of the COVID-19 pandemic, which included 260 women positive for both antibodies. Women of older age and women with higher BMI both had higher antibody

**Table 1:** Roche Nucleoside Antibody Assay Results by Blood Type, Age, and Obesity.

| Roche, N = 260 | Mean Ratio | 95% CI[1] | p-value | Antibody Signal Values[2] |
|---|---|---|---|---|
| Blood Type | | | | |
| O, *N = 122* (ref) | — | — | | 22 (7, 51) |
| A, *N = 97* | 0.99 | 0.725, 1.340 | 0.928 | 19 (7, 55) |
| B, *N = 33* | 1.019 | 0.654, 1.588 | 0.935 | 23 (12, 45) |
| AB, *N = 8* | 0.396 | 0.174, 0.901 | **0.028** | 8 (6, 21) |
| Age | 1.044 | 1.016, 1.073 | **0.002** | -- |
| Class 2/3 Obesity | 1.578 | 1.175, 2.118 | **0.003** | -- |
| [1]CI = Confidence Interval | | | | |
| [2]Unadjusted Antibody Signal (Median, IQR) provided for the blood groups | | | | |

**Table 2:** DiaSorin Spike Antibody Assay Results by Blood Group, Age, and Obesity.

| DiaSorin, N = 260 | Mean Ratio | 95% CI[1] | p-value | Antibody Signal Values[2] |
|---|---|---|---|---|
| Blood Type | | | | |
| O, *N = 122* (ref) | — | — | | 39 (24, 89) |
| A, *N = 97* | 1.020 | 0.776, 1.339 | 0.888 | 36 (22, 64) |
| B, *N = 33* | 1.130 | 0.762, 1.676 | 0.544 | 36 (25, 80) |
| AB, *N = 8* | 0.872 | 0.420, 1.811 | 0.713 | 52 (22, 82) |
| Age | 1.041 | 1.016, 1.067 | **0.001** | -- |
| Class 2/3 Obesity | 1.359 | 1.046, 1.766 | **0.022** | -- |
| [1]CI = Confidence Interval | | | | |
| [2]Unadjusted Antibody Signal Values (Median, IQR) provided for the blood groups | | | | |

**Table 3:** Mean COVID-19 antibody signal values by age group.

| Age | < 26, N = 125[1] | 26 - 31, N = 79[1] | 31+, N = 56[1] | p-value[2] |
|---|---|---|---|---|
| Roche Antibody Signal | 18 (6, 43) | 22 (7, 64) | 28 (10, 81) | 0.120 |
| DiaSorin Antibody Signal | 31 (21, 65) | 44 (28, 89) | 56 (32, 104) | **<0.001** |
| [1]Median (IQR) | | | | |
| [2]Kruskal-Wallis rank sum test; Note that this p-value is based on a general test of a relationship, not any specific pairwise comparison. | | | | |

**Table 4:** Mean COVID-19 antibody signal values by BMI Category.

| BMI | Healthy Weight, N = 16[1] | Overweight, N = 68[1] | Class 1 Obesity, N = 76[1] | Class 2/3 Obesity, N = 100[1] | p-value[2] |
|---|---|---|---|---|---|
| Roche Antibody Signal | 18 (7, 34) | 16 (7, 29) | 18 (6, 47) | 31 (12, 68) | **0.005** |
| DiaSorin Antibody Signal | 30 (19, 61) | 37 (24, 72) | 32 (22, 59) | 53 (31, 100) | **0.003** |
| [1]Median (IQR) | | | | | |
| [2]Kruskal-Wallis rank sum test; Note that this p-value is based on a general test of a relationship, not any specific pairwise comparison. | | | | | |

**Table 5:** Age, BMI Category, and Assay Values by Symptomatic Status.

| N = 260 | Symptomatic, N = 146[1] | Asymptomatic, N = 114[1] | p-value |
|---|---|---|---|
| **Age** | | | 0.635[2] |
| < 26 | 74 (51%) | 51 (45%) | |
| 26 - 31 | 42 (29%) | 37 (32%) | |
| 31+ | 30 (21%) | 26 (23%) | |
| **Class 2/3 Obesity** | 62 (42%) | 38 (33%) | 0.133[2] |
| **Blood Type** | | | **0.028**[3] |
| O | 70 (48%) | 52 (46%) | |
| A | 59 (40%) | 38 (33%) | |
| B | 11 (7.5%) | 22 (19%) | |
| AB | 6 (4.1%) | 2 (1.8%) | |
| **Roche** | 20 (7, 51) | 21 (8, 51) | 0.673[4] |
| **DiaSorin** | 36 (22, 85) | 43 (26, 77) | 0.322[4] |
| [1]n (%); Median (IQR); [2]Pearson's Chi-squared test; [3]Fisher's exact test; [4]Wilcoxon rank sum test. | | | |

signals to COVID-19 spike and nucleocapsid proteins.

A previous study of 232 COVID-19 convalescent plasma donations from 161 donors reported significantly lower levels of COVID-19 nucleocapsid antibodies in individuals with type O blood when compared to those with type a blood [8]. The association reported in the current study of significantly reduced antibodies to the COVID-19 nucleocapsid in pregnant women with group AB blood is a novel finding. This phenomenon may be limited to pregnant women or women of reproductive age.

The association between antibody levels to COVID-19 spike and nucleocapsid proteins and BMI is consistent with findings in previous studies [8]. Obesity is a known risk factor for severe disease in COVID-19 infection and previous research has shown that antibody titer level against COVID-19 is associated with disease severity, so this finding would be consistent with more severe disease in the obese population [7,12-14]. However, in the current study, no significant difference in severity of disease was demonstrated across BMI categories even in women with class 2/3 obesity. The finding of increased COVID-19 antibody signals in older individuals is also consistent with higher levels in other studies [5,6].

The association in the current study between symptomatic COVID-19 infection and individuals with group O, A, and AB blood is unique. A relationship between blood group and presence of symptomatic COVID-19 was detected ($p = 0.028$), with asymptomatic individuals having blood group B at a higher rate than the symptomatic individuals do. Previous studies have conflicted regarding blood group and risk of COVID-19 infection. Several studies found individuals with group A blood significantly more likely to be infected with COVID-19 compared to other blood groups [14], to have a higher rate of respiratory failure due to the virus [16,17], and to account for greatest proportion of deaths due to the virus [18]. Studies have also demonstrated individuals with group O blood have lower prevalence of infection [15,19]. This evidence conflicts with other reports that have found no difference between ABO blood group and risk of COVID-19 infection [20], that those with group AB and B blood are more likely to test positive for COVID-19 [21], and that those with group O and A blood were less likely to test positive for COVID-19 [22]. One study found that individuals with group O and B blood are more likely to become symptomatic from COVID-19 infection [21]. A study from Spain of COVID-19 positive pregnant women demonstrated that Rh+ mothers had increased odds of symptomatic COVID-19 infection. However, this Spanish study did not find associations between symptomatic infection and other blood groups [23].

Strengths of the current study include its prospective design and that all subjects were captured, limiting selection bias. Limitations of the current study include a small sample size, which may reduce the power of the study in identifying true significant differences between the factors analyzed. Future studies with a larger samples size are needed to examine differences in antibody responses between blood groups, BMI ranges, and age groups. Furthermore, the current study may not have detected all true COVID-19 infections due to exclusion from the study of women who only tested positive by one of the COVID-19 assays. Additionally, the differences in signals of patient antibody assays do not necessarily reflect a proportional difference in absolute antibody level. Study design also did not permit discrimination in timing of COVID-19 infection, so there may be variability in time from infection to testing. However, all testing occurred within 12 months and there is no reason to believe there was variability in time from infection to testing by age or BMI throughout the study period. Lastly, these findings are limited to a younger, female, pregnant population and thus cannot be generalized to the population at large.

In conclusion, pregnant women of AB blood group had lower antibody levels to nucleocapsid protein compared to the O blood group, and women of older age and greater BMI had higher antibody levels to COVID-19 spike and nucleocapsid proteins. Blood group B was significantly associated with asymptomatic infection.

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## References

1. Simonnet A, Chetboun M, Poissy J, et al. High Prevalence of Obesity in Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) Requiring Invasive Mechanical Ventilation. Obesity (Silver Spring). 2020; 28: 1195-1199.
2. Kalligeros M, Shehadeh F, Mylona EK, et al. Association of Obesity with Disease Severity Among Patients with Coronavirus Disease 2019. Obesity (Silver Spring). 2020; 28: 1200-1204.
3. Lighter J, Phillips M, Hochman S, et al. Obesity in Patients Younger Than 60 Years Is a Risk Factor for COVID-19 Hospital Admission. Clin Infect Dis. 2020; 71: 896-897.
4. Cunningham JW, Vaduganathan M, Claggett BL, et al. Clinical Outcomes in Young US Adults Hospitalized With COVID-19. JAMA Intern Med. 2020; 181: 379-381.
5. Klein SL, Pekosz A, Park HS, et al. Sex, age, and hospitalization drive antibody responses in a COVID-19 convalescent plasma donor population. J Clin Invest. 2020; 130: 6141-6150.
6. Yang HS, Costa V, Racine-Brzostek SE, et al. Association of Age With SARS-CoV-2 Antibody Response. JAMA Netw Open. 2021; 4: e214302.
7. Soffer S, Glicksberg BS, Zimlichman E, et al. The association

between obesity and peak antibody titer response in COVID-19 infection. Obesity (Silver Spring). 2021; 29: 1547-1553.

8. Hayes C, Rubenstein W, Gibb D, et al. Blood group O convalescent plasma donations have significantly lower levels of SARS-CoV-2 IgG antibodies compared to blood group A donations. Transfusion. 2021; 61: 2245-2249.
9. Steffen H, Swartz S, Jackson JB, et al. Severe acute respiratory syndrome coronavirus 2 infection in a rural Midwest all-delivery cohort. Am J Perinatology. 2021; 38: 614-621.
10. Merrill AE, Jackson JB, Ehlers A, et al. Head-to-Head Comparison of Two SARS-CoV-2 Serology Assays. J Appl Lab Med. 2020; 5: 1351-1357.
11. https://www.R-project.org/
12. Qu J, Wu C, Li X, et al. Profile of Immunoglobulin G and IgM Antibodies Against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Clin Infect Dis. 2020; 71: 2255-2258.
13. Long QX, Tang XJ, Shi QL, et al. Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. Nat Med. 2020; 26: 1200-1204.
14. Trinité B, Tarrés-Freixas F, Rodon J, et al. SARS-CoV-2 infection elicits a rapid neutralizing antibody response that correlates with disease severity. Sci Rep. 2021; 11: 2608.
15. Zietz M, Zucker J, Tatonetti NP. Testing the association between blood type and COVID-19 infection, intubation, and death. medRxiv. 2020; 11: 5761.
16. Ellinghaus D, Degenhardt F, Bujanda L, et al. Genome wide Association Study of Severe COVID-19 with Respiratory Failure. N Engl J Med. 2020; 383: 1522-1534.
17. Fan Q, Zhang W, Li B, et al. Association between ABO Blood Group System and COVID-19 Susceptibility in Wuhan. Front Cell Infect Microbiol. 2020; 10: 404.
18. 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.
19. Wu Y, Feng Z, Li P, et al. Relationship between ABO blood group distribution and clinical characteristics in patients with COVID-19. Clin Chim Acta. 2020; 509: 220-223.
20. Boudin L, Janvier F, Bylicki O, et al. ABO blood groups are not associated with risk of acquiring the SARS-CoV-2 infection in young adults. Haematologica. 2020; 105: 2841-2843.
21. Latz CA, DeCarlo C, Boitano L, et al. Blood type and outcomes in patients with COVID-19. Ann Hematol. 2020; 99: 2113-2118.
22. Kotila TR, Alonge TO, Fowotade A, et al. Association of the ABO blood group with SARS-CoV-2 infection in a community with low infection rate. Vox Sang. 2021; 116: 910-915.
23. Sainz Bueno JA, Cerrillos González L, Abascal-Saiz A, et al. Association of ABO and Rh blood groups with obstetric outcomes in SARS-CoV-2 infected pregnancies: A prospective study with a multivariate analysis. Eur J Obstet Gynecol Reprod Biol. 2021; 264: 41-48.