

Exploring the distribution and prognostic effect of the ABO blood types of COVID-19 patients during delta and omicron waves: A case control study

Hakan Göker¹

ORCID: 0000-0002-1039-7756

Olgu Erkin Çınar¹

ORCID: 0000-0003-1226-5797

Rashad Ismayilov²

ORCID: 0000-0002-7093-2722

Ela Özdemir²

ORCID: 0000-0003-2735-918X

Ümit Yavuz Malkan¹

ORCID: 0000-0001-5444-4895

Elifcan Aladağ Karakulak¹

ORCID: 0000-0002-1206-9908

Yahya Büyükaşık¹

ORCID: 0000-0002-2700-295X

Nilgün Sayınalp¹

ORCID: 0000-0002-5748-4056

İbrahim C. Haznedaroğlu¹

ORCID: 0000-0001-8028-9462

Osman Özcebe¹

ORCID: 0000-0002-0359-5148

Gülçin Telli Dizman³

ORCID: 0000-0001-8195-3345

Meliha Çağla Sönmezer³

ORCID: 0000-0001-6529-5282

Ahmet Çağkan İnkaya³

ORCID: 0000-0001-7943-8715

Haluk Demiroğlu¹

ORCID: 0000-0002-6790-8748

¹ Department of Hematology, Hacettepe University Faculty of Medicine, Ankara, Türkiye.

² Department of Internal Medicine, Hacettepe University Faculty of Medicine, Ankara, Türkiye.

³ Department of Infectious Diseases and Clinical Microbiology, Hacettepe University Faculty of Medicine, Ankara, Türkiye.

Corresponding Author: Hakan Göker
E-mail: hgoker1@yahoo.com

ABSTRACT

Objective: We aimed to delineate the effects of the ABO groups and the main clinical outcomes with the current SARS-CoV-2 variants, i.e., delta and omicron.

Materials and Methods: In this retrospective case-control study, the total 360 adult COVID-19 patients who were followed in the pandemic waves of delta and omicron variants and had ABO blood group analysis were included and divided into two groups according to the waves of variant. Demographic characteristics, comorbidities, length of hospitalization and intensive care needs, survival and ABO groups of cases were recorded. These groups were then compared with the ABO group distribution of population-reflecting 1881 healthy individuals and 186 historical alpha variant cases.

Results: The demographic characteristics of the case groups and control group were similar. ABO distributions of the delta and omicron wave groups compared to the control group did not show a statistically significant difference. While advanced age ($p < 0.001$) and presence of comorbidity ($p = 0.006$) showed statistically significant differences in terms of overall survival, ABO blood group was not found to be a risk factor for mortality ($p = 0.114$ in delta, and 0.526 in omicron), hospitalization time ($p = 0.148$ in delta, $p = 0.224$ in omicron), and intensive care unit admission ($p = 0.096$ in delta, $p = 0.229$ in omicron).

Conclusion: The risk of infection among ABO blood groups, which has been shown in previous studies for the alpha variant against group A and in favor of group O, does not appear to be valid for delta and omicron period patients. Therefore, the anti-infective measures, especially vaccination, should not differ for individuals according to ABO blood group.

Keywords: COVID-19, blood groups, delta variant, omicron variant.

INTRODUCTION

Many million people have died from coronavirus disease-19 (COVID-19), out of approximately 430 million cases, and thousands of deaths continue worldwide [1]. The COVID-19 causes a wide spectrum disease ranging from asymptomatic contagious to fatal respiratory failure, and it cannot be predicted with high accuracy which patient will have a poorer prognosis. Factors and biomarkers that may predict the course of the disease are still an area of research, although a long period has passed since the onset of the pandemic. In this context, many factors including demographics such as gender and ethnicity, comorbidities, routine tests such as blood glucose and vitamin D, inflammatory biomarkers such as IL-6 and TNF-alpha, have been evaluated in studies [2-6]. Since the discovery of blood groups at the beginning of the 20th century, interest in the role of blood groups in infectious diseases has continued [7]. Today, it is possible to find publications on the relationship of all kinds of pathogens, including bacteria, fungi, parasites, and viruses, with dozens of different blood group systems [8]. Among viruses, the relationship of influenza with blood groups has been investigated for decades [9]. The relationship between coronaviruses, including SARS-CoV subtypes and blood groups, has been demonstrated in various studies [10, 11].

Along with the pandemic caused by SARS-CoV-2, the relationship with the ABO blood groups was investigated. In a previous study, we found that the risk of infection may be increased in group A and the risk may be less in group O [12]. However, many different variants have caused consecutive pandemic waves to date, and the present study is designed to investigate whether the previously determined relationship with blood groups is also valid in new variants including delta and omicron. This study aims to delineate the effects of the ABO groups and the main clinical outcomes with the current SARS-CoV-2 variants, i.e., delta and omicron.

PATIENTS AND METHODS

Inclusion, Exclusion Criteria, and Patient Groups

Adult patients (>18 years old) who applied to Hacettepe University Hospitals between 1 May

2021 - 1 February 2022 were diagnosed with COVID-19, and whose SARS-CoV-2 variant was assumed as delta or omicron were included in this retrospective cohort. Cases without ABO group analysis were excluded. As a result, the medical records of 4,600 patients were examined and, 360 cases were analyzed as the study group. Then, the cases in the study group were divided into two groups; delta wave and omicron wave patients. The basic demographic data of the patients, the follow-up setting (outpatient or inpatient), duration of stay, and intensive care unit admission, and whether the infection resulted in death were recorded.

In order to compare the patients' distribution among blood groups with the population at risk, 1881 healthy individuals, who applied to the Hacettepe University Blood Bank between 1 March 2020 and 1 May 2020, were included as the control group. The blood group distributions, age, and sex of these patients were recorded. Finally, the blood group distributions of the patients were compared with our study in the early alpha variant period of the pandemic [12] as a historical control group and the differences from the previous 186 COVID-19 patients were analyzed. Ethics committee approval for this study was obtained from the Hacettepe University Non-interventional Clinical Researches Ethics Board. Approval was also obtained from the General Directorate of Health Services of the Ministry of Health of the Republic of Turkey.

Variant Assumption of SARS-CoV-2 Positive Clinical Samples

The COVID-19 infection was diagnosed with SARS-CoV-2 polymerase chain reaction (PCR) positivity with a maximum of thirty cycle threshold (CT) value made from nasopharyngeal swabs as the universal standard.

Since variant analysis could not be performed from all samples in our center, the pandemic wave after May 2021, which WHO declared "variant of concern (VOC)", was taken as a basis for the delta variant period [13]. In this context, patients diagnosed between 1 May 2021 and 1 November 2021 were recorded as delta variant wave patients. Similarly, all cases after 1 December 2021 were recorded as omicron wave patients.

Statistical Analyses

Analyses were made using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). The descriptive statistics were presented as frequency (percent), mean \pm standard deviation (SD), or median (min-max). The χ^2 test was used to compare the proportions in different categorical groups. Continuous variables were investigated with visual and analytical methods to determine the normal distribution and analyzed with the Mann-Whitney U test or the Student's t-test. Odds ratios and their significance were determined by univariate logistic regression analysis. The Kaplan-Meier survival estimates were calculated. The log-rank test was used to identify the independent effects on survival. Risk factors for mortality were specified by Cox regression analysis. A 5% type-I error level was used to infer statistical significance.

RESULTS

In the total 360 delta (n=185) and omicron (n=175) wave COVID-19 patients, the mean age was 44.8 ± 17 years. The number of female and male patients was similar (52.2% vs. 47.8% respectively, $p=0.399$). Fifty (13.9%) patients were 65 years of age or older. The mean age of the alpha group (historical control) was 44.5 ± 16.8 years, the delta group was 46.7 ± 17.3 years, and the omicron group was 42.8 ± 16.9 years ($p=0.097$). The frequency of female sex in the alpha, delta, and omicron groups was 46.2%, 51.4%, and 53.1%, respectively ($p=0.392$).

The O blood group percentage was 24.7% in the alpha, 34.1% in the delta, 37.7% in the omicron groups, and 37.2% in the healthy controls ($p=0.007$). Post-hoc analyses revealed a statistically significant difference between the alpha group

and controls ($p=0.001$) for O blood type. While there was no statistically significant difference between the delta and omicron groups with the controls, they showed significant differences from the alpha group ($p=0.049$ and 0.001 , respectively). The frequency of A blood type was 57% in the alpha group, 43.7% in the delta group, 40% in the omicron group, and 38% in the controls ($p<0.001$). As the statistical difference was due to the alpha group (v. the controls, $p<0.001$), there was no statistically significant difference between the delta, omicron groups, and the controls. Therewithal, the statistical difference between alpha with delta and omicron was also significant ($p=0.011$ and 0.003 , respectively). According to B and AB blood types, the groups showed similar distributions (Table 1).

The median follow-up period of the patients was 26 days (1 - 245). While there was no statistically significant difference in overall survival (OS) by gender ($p=0.868$), the OS of the ≥ 65 years was lower than those below (3.8 vs. 7.8 months, $p<0.001$, Figure 1). When alpha, delta and omicron variants were compared, no statistically significant difference in OS was observed (2.6, 7.4, and 2.9 months, respectively, $p=0.164$). The presence of comorbidity was a significant predictor of mortality (HR: 146, 95% CI: 4.3-4955, $p=0.006$, Figure 2). Moreover, there was a negative correlation between the number of comorbidities and OS (Figure 3). There was no statistically significant relationship between ABO blood groups with mortality in delta and omicron patients ($p=0.114$ and 0.526 , resp.). Similarly, no significant difference was detected between the ABO blood groups in terms of hospitalization time ($p=0.148$ in delta, $p=0.224$ in omicron) and intensive care unit admission ($p=0.096$ in delta, $p=0.229$ in omicron) in patients infected with new variants.

Table 1. The demographics and the blood types according to the groups

Characteristics	Alpha, n (%)	Delta, n (%)	Omicron, n (%)	Controls, n (%)	p value
Age, mean \pm SD, y	44.5 \pm 16.8	46.7 \pm 17.3	42.8 \pm 16.9	-	0.097
Female sex	86 (46.2%)	95 (51.4%)	93 (53.1%)	-	0.392
Blood types					
O	46 (24.7%) ^a	63 (34.1%) ^b	66 (37.7%) ^b	701 (37.2%) ^b	0.007*
A	106 (57%) ^a	81 (43.7%) ^b	70 (40%) ^b	716 (38%) ^b	<0.001*
B	20 (10.8%)	29 (15.7%)	18 (10.3%)	277 (14.7%)	0.190
AB	14 (7.5%)	12 (6.5%)	21 (12%)	188 (10%)	0.219

*Post-hoc analysis showed a statistical significance between the a's and b's in the respective rows.

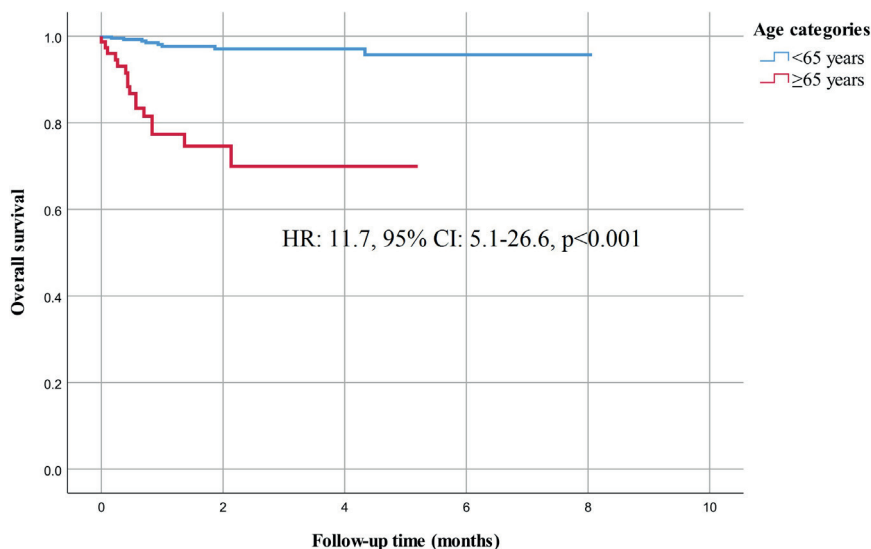


Figure 1. The age categories and overall survival

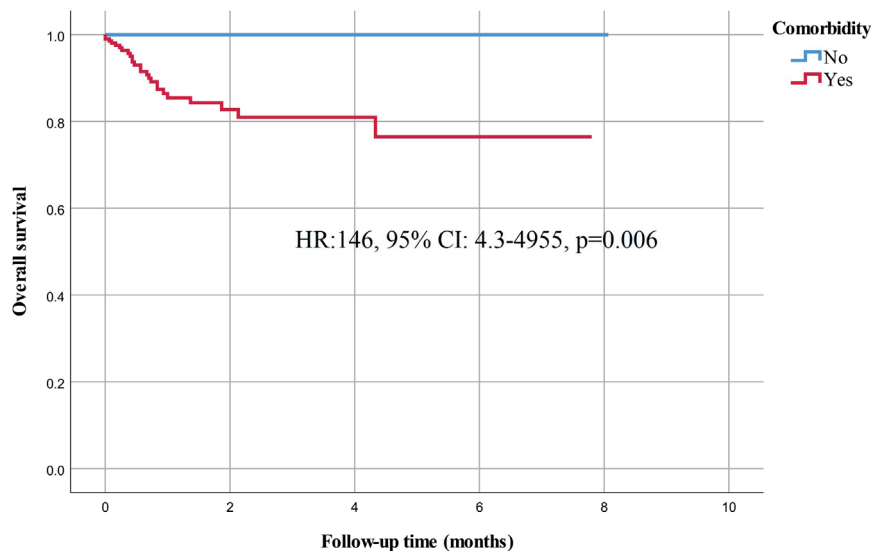


Figure 2. The comorbidity and overall survival

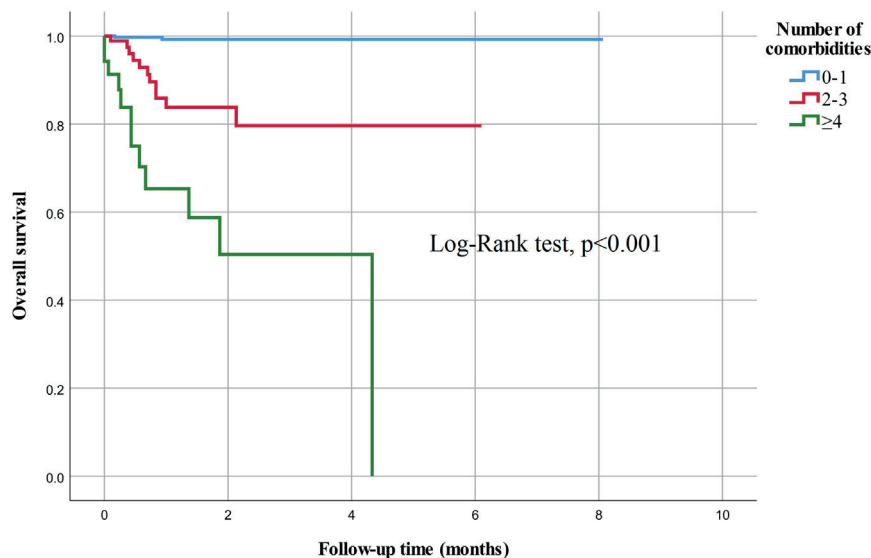


Figure 3. Number of comorbidities and overall survival

DISCUSSION

Like other common viruses, the relationship between coronaviruses and blood groups has been studied for a long time. SARS-CoV-2 enters the cell by providing viral adhesion with its spike protein (S), which has more than 20 potential N-glycosylation sites [11]. The fact that the S protein contains structures similar to ABO antigens may lead to a change in the risk of infection in individuals with antibodies to these antigens. However, it has been hypothesized that secretory status and anti-ABO antibody titers also affect the risk of infection. Studies show that even the country's development level can be effective in the antibody titers in the population [14]. In the 2003 major SARS outbreak in Hong-Kong, analysis of 45 health staff with similar blood group distributions to population showed that blood type was associated with the risk of infection [10]. Group O participants were less likely to become infected when compared with non-O participants (OR: 0.18; 95% CI: 0.04-0.81). For this reason, only qualitative ABO group analysis will not be able to give precise information about infection risk, and the findings cannot be extrapolated to all populations. The studies that each country will conduct on its own population will be more valuable about blood groups and infections.

In the Turkish population, studies examining this risk were conducted [15-17]. The joint results found in these studies; people with group A are more likely to be infected, but the blood group does not have a significant effect on the course of the disease except for the study of Sertbas et al., which showed that the risk of intubation increased in the AB group [16]. It is seen in this study that the risk in group A, which we also confirmed before, is not valid for the period in which the current waves with delta and omicron variants. This difference can be hypothesized that the new variants contain lesser A-antigen-like structures than the alpha.

On the other hand, the low infection risk of group O, shown in many studies in the literature, was also confirmed in the Turkish population by Yanardag et al. in a study of 823 people [18]. Similarly, although the risk of infection with the alpha variant

decreased in group O, this protection seems to have disappeared in the delta and omicron dominant pandemic waves, according to the present study findings.

The most important limitation of this study is that it includes patient groups that can be considered somewhat small for the pandemic period with a high incidence of COVID-19.

In conclusion, apart from ABO group antigens, there are many individual blood group factors, such as antibody titers, and it is impossible to determine all of them for each individual. In cases of outbreaks where antigenic changes are common, such as viral pandemics, cross-sectional results cannot be generalized to the whole period. Nevertheless, these results provide evidence that anti-infective approaches such as using masks, social distancing, hygiene, and especially vaccination should not change for the ABO blood groups.

Author contribution

Study conception and design: HG, OEÇ, and RI; data collection: RI, EÖ, and ÜYM; analysis and interpretation of results: HG, OEÇ, RI, EAK, YB, NS, İCH, OÖ, and GTD; draft manuscript preparation: RI, OEÇ, MÇS, AÇİ and HD. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

This study was approved by the Hacettepe University Non-interventional Clinical Researches Ethics Board (Project no: GO 22/180; Decision no: 2022/03-44; Date: 15.02.2022). Approval was also obtained from the General Directorate of Health Services of the Ministry of Health of the Republic of Turkey.

Funding

The authors declare that the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

- [1] Organization, W.H. WHO Coronavirus (COVID-19) Dashboard. Date: 22.02.2022 Available from: <https://covid19.who.int>.
- [2] Ejaz H, Alsrhani A, Zafar A, et al. COVID-19 and comorbidities: Deleterious impact on infected patients. *J Infect Public Health* 2020; 13(12): 1833-1839.
- [3] Galván-Román JM, Rodríguez-García SC, Roy-Vallejo E, et al. IL-6 serum levels predict severity and response to tocilizumab in COVID-19: An observational study. *J Allergy Clin Immunol* 2021; 147(1): 72-80 e8.
- [4] Halim C, Mirza AF, Sari MI. The Association between TNF-alpha, IL-6, and Vitamin D Levels and COVID-19 Severity and Mortality: A Systematic Review and Meta-Analysis. *Pathogens* 2022; 11(2).
- [5] Hippisley-Cox J, Ac Coupland C, Mehta N, et al. Risk prediction of covid-19 related death and hospital admission in adults after covid-19 vaccination: national prospective cohort study. *BMJ* 2021; 374: n2244.
- [6] Xie W, Wu N, Wang B, et al. Fasting plasma glucose and glucose fluctuation are associated with COVID-19 prognosis regardless of pre-existing diabetes. *Diabetes Res Clin Pract* 2021; 180: 109041.
- [7] Farhud DD, Yeganeh MZ. A brief history of human blood groups. *Iran J Public Health* 2013; 42(1): 1-6.
- [8] Cooling L. Blood Groups in Infection and Host Susceptibility. *Clin Microbiol Rev* 2015; 28(3): 801-870.
- [9] Howe C. The influenza virus receptor and blood group antigens of human erythrocyte stroma. *J Immunol* 1951; 66(1): 9-35.
- [10] Cheng Y, Cheng G, Chui CH, et al. ABO Blood Group and Susceptibility to Severe Acute Respiratory Syndrome. *JAMA* 2005; 293(12): 1447-1451.
- [11] Guillon P, Clément M, Sébille V, et al. Inhibition of the interaction between the SARS-CoV Spike protein and its cellular receptor by anti-histo-blood group antibodies. *Glycobiology* 2008; 18(12): 1085-1093.
- [12] Göker H, Aladağ Karakulak E, Demiroğlu H, et al. The effects of blood group types on the risk of COVID-19 infection and its clinical outcome. *Turk J Med Sci* 2020; 50(4): 679-683.
- [13] Organization, W.H. Tracking SARS-CoV-2 Variants. Date: 28.02.2022. Available from: <https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/>.
- [14] Mazda T, Yabe R, NaThalang O, et al. Differences in ABO antibody levels among blood donors: a comparison between past and present Japanese, Laotian, and Thai populations. *Immunohematology* 2007; 23(1): 38-41.
- [15] Çakır M. The Relationship Between Blood Groups and COVID-19 Patients. *Erciyes Medical Journal* 2020; 43(2): 142-145.
- [16] Sertbas M, Kizilay V, Dagci S, et al. Association of blood groups on the risk of COVID-19 infection, morbidity, and mortality. *North Clin Istanbul* 2021; 8(3): 298-305.
- [17] Gursoy V, Avci S. Effect of ABO blood groups on length of hospital stay according to age in Covid-19 patients. *Hematol Transfus Cell Ther* 2022; 44(1): 7-12.
- [18] Yanardag Acik D, Bankir M. Relationship of SARS-CoV-2 Pandemic with Blood Groups. *Transfus Med Hemother* 2021; 48(3): 161-167.