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Clinical characteristics of COVID-19 patients in ABO blood groups

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Abstract:

BACKGROUND AND AIM: Coronavirus Disease 2019 (COVID-19) is a novel respiratory infection caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Recent studies have suggested that certain blood groups may be associated with different risks of COVID-19 infection and mortality.

METHODS: We conducted a retrospective case-control study to determine if ABO blood groups are associated with different clinical outcomes. Our study involved 286 COVID-19 patients.

RESULTS: We found that patients with the AB blood group had a higher risk of COVID-19 compared to the control group (OR=3.63, 95% CI=2.76-4.76, p<0.0001). Conversely, patients with the O blood group had a higher risk of death (OR=9.56, 95% CI=3.059-27.89, p=0.001). White blood cell (WBC) counts, C-reactive protein (CRP) levels, and the Neutrophil to Lymphocyte ratio (NLR) varied among ABO blood groups. Comparing fatal to survival cases, we observed that fatal cases had higher levels of WBC, CRP, and NLR in comparison to survivors. Multiple logistic regression analysis revealed that age, O blood group, and NLR were independent factors for mortality.

CONCLUSIONS: ABO blood groups can exhibit different clinical characteristics. Nonetheless, it is crucial to emphasize that elevated inflammation markers and advanced age are also independent risk factors for mortality. Further studies with larger populations are essential to fully comprehend the relationship between ABO blood groups and COVID-19 outcomes.

Keywords:

Coronavirus Disease 2019 (COVID-19), ABO blood group system, mortality

Introduction

Coronavirus Disease 2019 (COVID-19) is caused by the novel coronavirus, the Severe Acute Respiratory Syndrome

Coronavirus 2 (SARS-CoV-2). It first emerged as a cluster of pneumonia cases in Wuhan, China, in December 2019. [1,2] The spectrum of COVID-19 severity ranges from asymptomatic cases to se-

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vere illness.^[3,4] Severe manifestations have been linked to comorbidities including cardiovascular diseases, diabetes mellitus, hypertension, chronic lung disease, cancer, chronic kidney disease, obesity, and smoking.^[5-7] The virus spread rapidly throughout the world, prompting the World Health Organization (WHO) to declare it a global pandemic in March 2020. To date, there have been a cumulative 767,972,961 reported cases and 6,950,655 deaths since the onset of the outbreak.^[8] Blood groups are inherited traits that display varied frequencies across populations. Established associations exist between certain infectious diseases – like *Helicobacter pylori*, *Plasmodium falciparum*, hepatitis B virus, and rotavirus – and certain blood groups.^[9-12] Some studies have suggested that there is a heightened susceptibility to COVID-19 in individuals with blood group A, while others have found no such correlation.^[13-16] Other studies have found differences in intubation and mortality risks among ABO blood groups.^[16-18] The aim of this study is to investigate the distribution of ABO blood groups in COVID-19 patients and to compare the clinical characteristics of patients across each ABO blood group.

Materials and Methods

Design and data source

This study is a retrospective case-control study. We retrospectively reviewed the medical records of inpatients with COVID-19 who were admitted to a tertiary-level hospital designated for COVID-19 treatment between March 2 and May 31, 2020. The hospital information management system was used to document patients' medical records. The study was approved by the Turkish Health Ministry Scientific Research Platform and the Institutional Review Board.

Subjects

Patients who had both a positive COVID-19 test and a recorded blood type were included in the study. Patients under 18 years of age were excluded. We aimed to compare our blood group distribution with that of our population. We believed that this approach could yield more accurate results for risk evaluation among different blood groups. To achieve this, we conducted a comparison between the blood group distribution in our study and the findings from a study encompassing 389,362 patients. This study outlined the ABO blood frequencies within our city's population before the onset of the COVID-19 pandemic.^[19]

Association analysis

The ABO blood group frequencies in both the control and study groups, as well as in fatal and surviving COVID-19 patients, were compared. We also recorded demographics, comorbidities, Intensive Care Unit (ICU) requirements, Computed Tomography (CT) involvement, and inflammation markers. Comorbidities included hypertension, cardiovascular comorbidities (coronary artery disease, congestive heart disease, stroke), diabetes mellitus, cancer, chronic lung disease, chronic kidney disease, chronic liver disease, and venous thromboembolism. If patients had at least one of these chronic diseases, it was recorded. Inflammation markers included C-reactive protein (CRP), white blood cell count (WBC), and the neutrophil/leukocyte ratio (NLR). Age, sex, CT involvement, ICU requirements, death frequencies, and inflammation marker levels were compared between both ABO blood groups and fatal and surviving patients.

Statistical analysis

Statistical analysis was performed using IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp. One-Way Analysis of Variance (ANOVA) tests were used for continuous parameters such as age, WBC, CRP, and NLR. The Chi-square test was used to compare CT involvement, the existence of chronic diseases, gender, ICU requirement frequencies between ABO blood groups, and fatal/survival groups. The frequencies of the ABO blood groups in COVID-19 and control groups, as well as in fatal and surviving patients within these blood groups, were tested using a Chi-square test. The Receiver Operating Characteristics (ROC)-Area Under the Curve (AUC) was calculated to assess inflammatory markers' ability to predict mortality. The cutoff value for inflammatory markers was defined based on ROC curve analysis. Multiple logistic regression analysis was conducted to identify factors independently associated with death in the study group. A p-value of <0.05 was considered statistically significant.

Results

Table 1 presents the demographics, clinical characteristics, and inflammation levels of 286 COVID-19 patients based on their ABO blood groups. The frequencies of blood types A, B, AB, and O in the study and control groups were 41.2%, 20.6%, 23.4%, 14.6%, and 42.9%, 16.2%, 7.7%, 33.3%, respectively (p=0.000). COVID-19

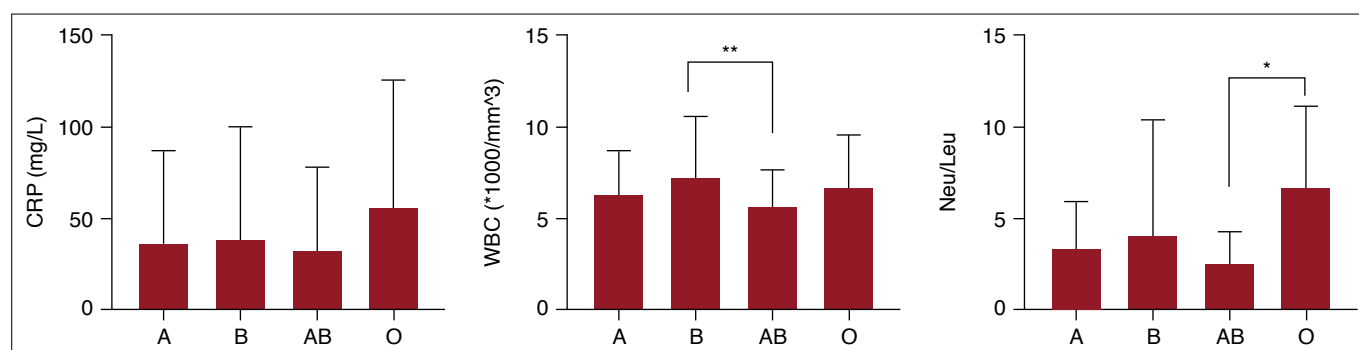
Table 1: Demographics, clinical characteristics, and inflammation marker levels of COVID-19 patients based on their ABO blood groups

	A		B		AB		O		p
	n	%	n	%	n	%	n	%	
Control group	167,131	42.92	63,225	16.24	30,226	7.76	128,780	33.7	
COVID-19 patients	118	41.2	59	20.6	67	23.4	42	14.6	0.000
OR, (CI) p	0.93 (0.73–1.18) 0.59		1.34 (1.00–1.78) 0.044		3.63 (2.76–4.76) 0.0001		0.34 (0.25–0.48) 0.0001		
Age	53.4±17.8		56.7±18.8		50.2±19.9		56.6±17.3		0.05
Sex (male)	69	58.5	34	58.6	43	63.2	22	52.4	0.05
Comorbidities	61	51.6	29	50	22	32.3	20	47.6	0.05
CT involvement	92	77.9	36	61	50	74.6	34	80.9	0.05
ICU admission	15	12.7	8	13.5	6	8.9	10	23	0.05
Death, OR (95% CI)	3 (2.5), 0.46 (0.1322–1.729)		2 (3.3), 0.76 (0.1631–3.448)		0 (0)		7 (16.6), 9.56 (3.059–27.89)		0.05
WBC	6.24±2.48		7.216±3.32		5.61±2.01		6.67±2.89		0.01
CRP	36.77±50.02		37.46±62.37		32.24±45.49		55.89±69.96		0.05
NLR	3.361±2.49		4.017±6.27		2.546±1.67		4.741±6.33		0.05

One-Way Analysis of Variance (ANOVA) tests were used for continuous variables: Age, WBC, CRP, NLR. The Chi-square test was used for categorical variables: sex, comorbidities, CT involvement, death, ICU admission. ABO: A, B, O blood groups, OR: Odds ratio, CI: Confidence interval, CT: Computed tomography, ICU: Intensive care unit, WBC: White blood cell, CRP: C-reactive protein, NLR: Neutrophil-to-lymphocyte ratio

patients with the AB blood group displayed a significantly higher frequency than the control group, while the O blood group's frequency was lower. The risk of contracting COVID-19 was higher for patients with the AB blood group (OR=3.63, 95% CI=2.76–4.76, $p<0.0001$). The rates of comorbidities in blood groups A, B, AB, and O were 51.6%, 50%, 32.3%, and 47.6%, respectively ($p=0.07$). The rates of thorax CT involvement in blood groups A, B, AB, and O were 77.9%, 61%, 74.6%, and 80.9%, respectively ($p>0.05$). ICU admission rates for blood types A, B, AB, and O were 12.7%, 13.5%, 8.9%, and 23%, respectively ($p>0.05$). Mortality rates for blood types A, B, AB, and O were 2.5%, 3.3%, 0%, and 16%, respectively ($p=0.000$). The mortality rate for the O blood group was significantly higher, whereas the AB blood group had no fatal cases ($p=0.000$). The risk

of death was higher in patients with the O blood group (OR=9.56, 95% CI=3.059–27.89, $p<0.0001$). The CRP levels were higher in the O blood group, but the difference was not statistically significant. The WBC levels were lower in the AB blood group ($p<0.01$). The NLR ratio was higher in the O blood group ($p<0.05$) [Fig. 1]. When comparing fatal and surviving patients, those who were fatal had higher WBC, CRP, and NLR levels than survivors ($p<0.000$). The ROC-AUC for inflammatory markers to predict mortality and the cutoff values for these markers are illustrated in Figure 2 and Table 2. Multiple logistic regression analysis revealed that only age (OR=1.076, 95% CI=1.001–1.176, $p=0.047$), O blood group (OR=2.734, 95% CI=1.474–16.774, $p=0.022$), and NLR (OR=1.191, 95% CI=0.182–2.648, $p=0.007$) were independent factors for death.

**Figure 1:** The association of WBC, CRP and Neu/Leu ratio in between ABO blood groups

*: $p<0.05$, **: $p<0.01$. CRP: C-reactive protein, WBC: White blood cell, Neu: Neutrophil, Leu: Lymphocyte, ABO: A, B, O

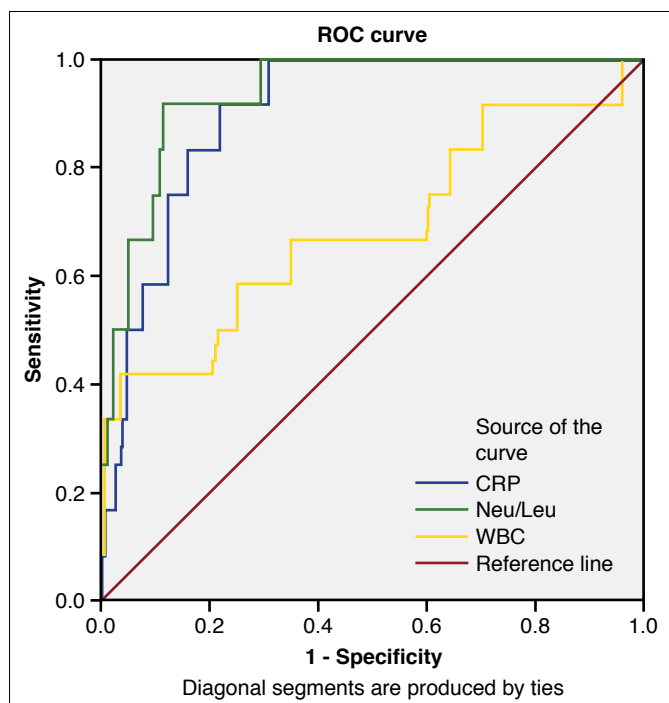


Figure 2: ROC curves of COVID-19 mortality and predictors
CRP: C-reactive protein, WBC: White blood cell, Neu: Neutrophil, Leu: Lymphocyte

Discussion

Although most studies conducted in China and the United States of America (USA) have found that the A blood group has an increased risk for COVID-19 infection, our study discovered that the AB blood group faces the highest risk for COVID-19 infection when compared with population blood group distribution. These studies assessed the risk using mostly small local control groups. They did not account for population blood group distribution, which may lead to misinterpretation of the results. To address this, we took a different approach. We compared our blood group distribution with recent findings from another study, which used our city's blood group distribution as a control group and encompassed 389,362 cases. Fan et al.^[14] found that the A blood group was associated with a higher risk of COVID-19 infection in females but not in males. Li et al.^[20] reported that the proportion of COVID-19 patients with the A blood group is higher than in the healthy control group,

while the proportion with the O blood group is lower than in the healthy control group. Zhao et al.^[6] determined that the A blood group has an increased risk, while the O blood group has a decreased risk for COVID-19 infection. It is suggested that natural anti-A and anti-B antibodies inhibit the adhesion of SARS-CoV-2 to receptors. This may explain why individuals with the A blood group exhibit higher susceptibility to COVID-19 infection. However, this does not align with our findings.^[21] Boudin et al.^[22] investigated the COVID-19 outbreak among 1,769 healthy young crew members of the French navy and found no correlation between ABO blood groups and COVID-19 infection in this demographic. Similarly, Abdollahi et al.^[15] identified a heightened risk for individuals with the AB blood group and a lower risk for those with the O blood group regarding COVID-19 infection, aligning with our observations. An interesting genetic study by Ellinghaus et al.^[23] delved into the genetic factors associated with the development of severe COVID-19. They conducted a genome-wide association study on DNA samples from 8,582,968 single nucleotide polymorphisms of COVID-19 patients and compared them to samples from 950 healthy individuals. Their study indicated a potential link between severe COVID-19 manifestations and certain genetic variants in the ABO blood group locus, responsible for determining one's blood type. The proportion of CT involvement at admission for COVID-19 patients with the O blood group was found to be the highest (80%), whereas those with the B blood group showed the lowest frequency (61%). However, this difference was not statistically significant. No study to date has specifically investigated the frequency of CT lung involvement in COVID-19 patients based on their blood groups. Nonetheless, Ding et al.^[24] analyzed 348 thorax CT scans from 112 COVID-19 positive patients and discovered that nearly all had lung involvement by day 28. Additionally, 78.8% exhibited lung involvement at symptom onset, consistent with our findings.

In the aforementioned study, there was no marked difference in ICU requirement frequency between ABO blood groups. This observation aligns with findings from other studies, including those conducted by Ab-

Table 2: Cutoff values, sensitivity, and specificity of inflammation markers.

	AUC (95%)	Cut off	p	Sensitivity (%)	Specificity (%)
CRP	0.901 (0.845–0.957)	72.6	0.000	83.3	83.9
NLR	0.936 (0.887–0.985)	4.96	0.000	91.7	88.7
WBC	0.684 (0.500–0.868)	6.47	0.031	66.7	65.0

AUC: Area under the curve, CRP: C-reactive protein, NLR: Neutrophil-to-lymphocyte ratio, WBC: White blood cell

dollahi and Latz.^[15,17] Leaf et al.^[18] reported that among individuals of White ethnicity, the A blood group was overrepresented, while the O blood group was underrepresented among COVID-19 patients admitted to the ICU. The difference in ICU admission rates across blood groups may have been obscured during the early stages of the pandemic when numerous patients were admitted to the ICU irrespective of their clinical severity.

The study identified a significant difference in death frequency among ABO blood groups, with the O blood group exhibiting the highest frequency, while the AB group reported no fatalities. However, some studies found no correlation between ABO blood groups and mortality.^[17,18] Multiple logistic regression analysis highlighted that age, the O blood group, and NLR were independent predictors of death.^[17,18,25]

Our study revealed that patients with blood type O had slightly higher CRP values compared to those of other blood types, though this difference was not statistically significant. Individuals with blood type B had significantly higher WBC values than those of other blood types, whereas individuals with blood type AB demonstrated significantly lower WBC values ($p < 0.01$). There was also a pronounced increase in the NLR for individuals with blood type O compared to those with blood type AB. Still, no significant differences were observed among other blood groups. However, we did find that these biomarker levels were significantly higher in fatal cases compared to survivors. Several studies have indicated that severe and fatal cases tend to exhibit elevated levels of WBC, CRP, and NLR compared to milder cases and those who survive.^[26–29] These findings suggest that unidentified genetic or individual factors may amplify inflammation levels in patients, thereby affecting disease outcomes.

A strength of our study is that our control group encompasses a broad sample size, accurately representing the blood group distribution of the population. However, the study has several limitations. Not all COVID-19 patients had recorded ABO group information, which limited our sample size. Additionally, the study was conducted at a single center in just one city, so there might be other potential factors that could influence the results.

In conclusion, ABO blood groups can exhibit different clinical characteristics. However, it is crucial to highlight that increased inflammation marker levels and advanced

age are also independent risk factors for mortality. Further studies involving larger populations are needed to fully understand the relationship between ABO blood groups and COVID-19 clinical outcomes.

Conflicts of interest

There are no conflicts of interest.

Ethics Committee Approval

The study was approved by the İzmir Katip Celebi University Non-invasive Clinical Research Ethics Committee (No: 757, Date: 18/06/2020).

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Nil.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept – C.D., M.O.T., C.A., B.U., B.S., S.S.; Design – S.S., B.S., C.D., M.O.T., C.A., B.U.; Supervision – B.S., M.O.T., C.A., S.S.; Data collection &/or processing – C.D.; Analysis and/or interpretation – C.D., B.S., S.S.; Literature search – C.D., B.S.; Writing – C.D., B.S.; Critical review – M.O.T., C.A., B.S., S.S.

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