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Association of ABO Blood Groups, D Antigen, and Comorbidities with COVID-19 Outcomes in Hospitalized Patients

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Abstract: Background/Objectives: The COVID-19 pandemic has highlighted the importance of identifying factors influencing disease susceptibility and severity. This study investigates the association of ABO blood groups, the D antigen, and comorbidities such as hypertension and diabetes with COVID-19 severity among hospitalized patients in one Croatian center. Methods: A retrospective observational study was performed on 1687 moderately and severely ill COVID-19 patients and 7086 voluntary blood donors. We used medical records from PCR-confirmed COVID-19 patients hospitalized at University Hospital Center Osijek in Osijek, Croatia, and compared their ABO, RhD, and comorbidity profiles with those of voluntary blood donors. Key clinical data and outcomes, such as mortality and comorbidities, were assessed. Results: Our findings reveal a statistically significant association between blood group A and severe COVID-19 outcome and mortality. Conversely, D antigen status showed no significant impact. The combined presence of hypertension and diabetes emerged as a significant predictor of mortality. Conclusions: These results suggest that blood group A and specific comorbidities may be associated with worse outcomes, but age remained the strongest independent predictor of mortality. Blood group typing could still support risk stratification when interpreted alongside other clinical factors.

Keywords: biomarkers; blood group antigens; ABO blood group system; COVID-19; patient acuity; RhD

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1. Introduction

Over the past four years, we have been confronted with one of the largest pandemics in modern times. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19), rapidly spread worldwide and became a serious threat to human lives. According to data provided by the World Health Organization (WHO), as of April 2025, approximately 1.4 million individuals had contracted COVID-19, accounting for an estimated 35% of Croatia's total population [1]. In the majority

of cases, patients experienced an asymptomatic to mild form of COVID-19, presenting with a variety of symptoms including fever, fatigue, headache, cough, loss of taste and smell, and pneumonia. These patients recovered relatively quickly and did not require hospitalization. In contrast, almost all patients with moderate illness were hospitalized, while severely and critically ill patients were admitted to the intensive care unit (ICU) and required high-flow oxygen therapy or mechanical ventilation support [2,3]. To date, statistics show that 1.44% of infected patients in Croatia have died [1].

Extensive studies have been conducted to identify and stratify the possible risks associated with SARS-CoV-2 infection and its outcome severity. Multiple studies have shown that age and comorbidities, such as cardiovascular disease and diabetes mellitus, increase the risk of severe courses with fatal outcomes [4,5]. Indeed, variability in clinical symptoms and outcomes, as well as uncertainties in viral pathogenesis, necessitates a quest for biological markers that could predict susceptibility to SARS-CoV-2 infection and the risk for severe and critical outcomes [6]. Since it has been known that blood group antigens and antibodies can directly or indirectly influence disease outcomes after infection by certain pathogens [7–9], one of the proposed ideas was that antigens of the ABO blood group system could have a strong influence on COVID-19 baseline severity [10].

Several pathophysiological mechanisms have been proposed to explain the association between ABO blood groups and SARS-CoV-2 infection [11–13]. Carbohydrate blood group antigens on the surface of erythrocytes and endothelial as well as epithelial cells in the respiratory and digestive tracts can act as receptors or co-receptors and affect disease progression [14] or serve as molecular mimicry agents if present on viruses, helping them to evade a host's innate immune system. Furthermore, immunoglobulins can bind or block different proteins; therefore, it is assumed that regular anti-A and anti-B antibodies, mostly of the IgM class, can have a significant role in protecting organisms from SARS-CoV-2 [15]. The proposed molecular mechanism suggests that pre-existing regular anti-ABO antibodies can recognize and target bacteria and viruses carrying blood group-like antigens [4]. Additionally, the binding rate of the SARS-CoV-2 spike protein to red blood cells was observed to be lowest in type O individuals and highest in type A, and it was hypothesized that this may be due to the competitive inhibition of spike protein binding to ACE2 by anti-A and anti-B antibodies present in type O individuals [16,17]. In addition to the presence of antibodies against A and B antigens of the ABO blood group system, it seems that their serum titer could also impact susceptibility to infection [18,19]. This may explain why some studies have shown that infected blood group O patients developed a severe form of COVID-19 less frequently and consequently had lower mortality compared to patients with other ABO blood groups [10,20–23].

Similarly, antigens of the Rh blood group system, particularly the D antigen, may also play a role in infectious diseases, although its association with COVID-19 is less studied. Some evidence suggests that D-negative individuals might have different immune responses, potentially affecting their susceptibility to infections [24]. A study by Zietz et al. [24] indicated that D-positive people might be associated with increased risk of SARS-CoV-2 infection and severe illness. Investigating both ABO blood groups and the D antigen could provide a more comprehensive understanding of the genetic factors influencing COVID-19 severity. In addition, factors such as von Willebrand factor (vWF) levels, which are affected by the ABO blood group, might play a role in COVID-19 severity [25–27]. Individuals with blood group O have lower vWF levels, which could potentially reduce the risk of thrombosis, a common complication in severe COVID-19 cases [26–28].

In light of previous knowledge about ABO groups and SARS-CoV-2 infection, we hypothesized that SARS-CoV-2-infected blood group A patients have a higher incidence of developing severe illness and higher mortality. We also aimed to explore the role of

the D antigen of the Rh blood group system in COVID-19 severity. Therefore, in this retrospective study, we aimed to investigate the frequency of ABO blood groups and D antigens among COVID-19 patients with mild, moderate, severe, and critical illness hospitalized at the University Hospital Center (UHC) Osijek, Croatia, during the two-year pandemic period. Given the quite conflicting results in the literature [21,29–35] and the lack of data specific to the eastern Croatian population, there is a need for further research in this area. Understanding the association between the ABO blood system and COVID-19 severity could have significant implications for risk stratification and management of patients. By analyzing a well-characterized cohort of patients, our study seeks to contribute valuable data to the ongoing discussion regarding blood group antigens and their potential influence on COVID-19 outcomes.

2. Materials and Methods

This retrospective study included all COVID-19 patients hospitalized at the UHC Osijek during the two-year pandemic period (March 2020 to March 2022) with a defined ABO blood group and RhD status.

2.1. COVID-19 Patients Stratification and Voluntary Blood Donors

The medical records of all enrolled patients were thoroughly reviewed, with a particular focus on clinical features related to the ABO blood groups and the D antigen, as well as comorbidities such as hypertension and diabetes. SARS-CoV-2 infection was confirmed in all patients by using quantitative polymerase chain reaction (qPCR) targeting both the viral E and RdRp genes. COVID-19-positive patients were classified into two distinct groups based on disease severity [2]. The first group consisted of patients with a moderate form of COVID-19 who were hospitalized at the Clinic for Infectious Diseases of the UHC Osijek, while the second group included patients with severe or critical forms of the illness who required admission to the ICU.

A group of voluntary healthy blood donors (n = 7086), residing in eastern Croatia, was also included in this study. These individuals donated blood at the Clinical Institute for Transfusion Medicine of the UHC Osijek during the study period. Upon reviewing the hospital information system, no recorded data on SARS-CoV-2 infection status were found for these donors, so we can clearly state that none of the blood donors experienced moderate, severe, or critical forms of COVID-19. However, information regarding possible recovery from asymptomatic, presymptomatic, or mild illness was not available. To ensure an accurate representation of the demographic distribution of ABO blood groups and the D antigen, data from multiple donations by the same individuals were excluded during study preparation, as were plasma donors and donors who were invited to donate due to emergency or specific blood shortages in the UHC Osijek.

Routine immunohematological determination of the ABO blood group and the D antigen in patients and blood donors was performed using blood samples collected in vacutainers containing dipotassium ethylenediaminetetraacetic acid (K_2EDTA). Automated platforms were employed to detect red blood cell surface antigens and serum antibodies. ABO blood group typing and D antigen detection were carried out using automatic analyzers ORTHO VISION (Ortho-Clinical Diagnostics, San Diego, CA, USA), IH-500, or IH-1000 (Bio-Rad, Hercules, CA, USA).

This retrospective study was approved by the Ethical Committee of the UHC Osijek, in Osijek, Croatia, and performed in accordance with the Declaration of Helsinki and the Principles of Good Laboratory Practice, as well as Croatian law governing healthcare and the Law on the Protection of Patients' Rights.

2.2. Statistical Analysis

Numerical data were presented as medians with interquartile ranges, while categorical data were presented as absolute and relative frequencies. The normality of data distribution was assessed using the Shapiro–Wilk test. Differences between continuous data were evaluated using the Mann–Whitney U test, while categorical data were analyzed using Pearson's chi-squared test. Binomial logistic regression was used to examine the impact of individual variables on COVID-19 treatment outcomes. Significance was set at alpha < 0.05, with all *p*-values being two-sided. Statistical analyses were performed using IBM SPSS software (IBM Corp. Released 2021. IBM SPSS Statistics for Macintosh, Version 28.0. Armonk, NY, USA: IBM Corp.).

3. Results

During the study period, 4576 patients were hospitalized at the UHC Osijek due to pneumonia caused by SARS-CoV-2. Among these, 1687 patients had their blood group determined and were included in this study. A total of 1157 (68.6%) patients had moderate forms of COVID-19, while 530 (31.4%) presented with severe or critical forms of the disease. A separate group of participants consisted of individual voluntary blood donors (n = 7086) who donated blood during the same study pandemic period. The study period was established based on the number of patients hospitalized at specific intervals throughout the pandemic. As the pandemic began to decline after March 2022, leading to a significant decrease in the number of patients with moderate and severe forms of COVID-19, the study period was concluded.

3.1. Demographic Characteristics

To assess the blood group frequency within the general population of eastern Croatia, the ABO blood groups of the present study population of blood donors were analyzed. The most frequent phenotypes of the ABO blood group system were A (39.1%) and O (35.4%), followed by B (18.3%) and AB (7.2%). The majority of participants across all ABO blood groups were D-positive, 82.4% (Figure 1).

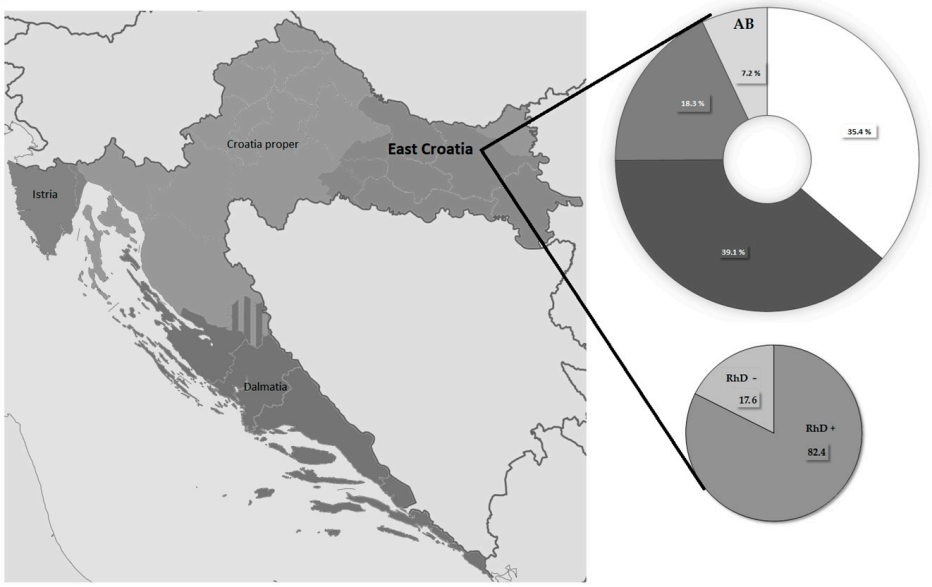


Figure 1. Distribution of ABO blood groups and the D antigen among blood donors in the region of eastern Croatia. Presence of the D antigen is denoted by "RhD+", and absence by "RhD−".

3.2. Distribution of ABO Blood Groups and the D Antigen Among Blood Donors and SARS-CoV-2-Infected Participants

The ratio of male to female participants among blood donors was 2.4:1, whereas in the COVID-19 patient group, the ratio was 1.1:1 (Table 1). The results indicated that the median age of the patients was significantly higher than that of the blood donor controls (71 vs. 36 years). This age difference reflects the expected demographic contrast between hospitalized patients and healthy blood donors commonly used in transfusion-related population studies.

Table 1. Comparison of demographic characteristics of the patient and blood donor groups.

	Blood Donors (*n* = 7086)	**COVID-19 Patients (*n* = 1687)**	***p* ***
Sex (male/female) [*n* (%)]	5051 (71.3)/ 2039 (28.7)	915 (54.2)/ 772 (45.8)	<0.001
Age [median (IQR)]	36 (28–46)	71 (63–79)	<0.001
ABO Blood Group [*n* (%)]			
O	2574 (36.3)	533 (31.6)	<0.001
A	2734 (38.6)	692 (41.0)	0.06
B	1282 (18.1)	318 (18.9)	0.48
AB	496 (7.0)	144 (8.5)	0.03
D antigen (positive/negative) [*n* (%)]	5820 (82.1)/ 1266 (17.9)	1418 (84.1)/ 269 (15.9)	0.06

Data are presented as the median (interquartile range (IQR)) or as *n* (frequency/%). * Mann–Whitney U test for continuous and Pearson's chi-squared test for categorical variables. Significance was set at $p < 0.05$.

Our data showed no significant distribution of ABO blood group combinations and the D antigen in patients with COVID-19 when stratified by disease outcome (discharged and deceased) (Figure 2). Not a single female patient with blood group A−, B−, or AB− was present in the group of discharged patients. In contrast, 35.7% (A−), 53.8% (B−), and 33.3% (AB−) of female patients were in the group of deceased patients. It is noteworthy that there were no male or female patients with blood group B− in the group of discharged patients. In our cohort, the lowest number of discharged and deceased patients had blood group AB.

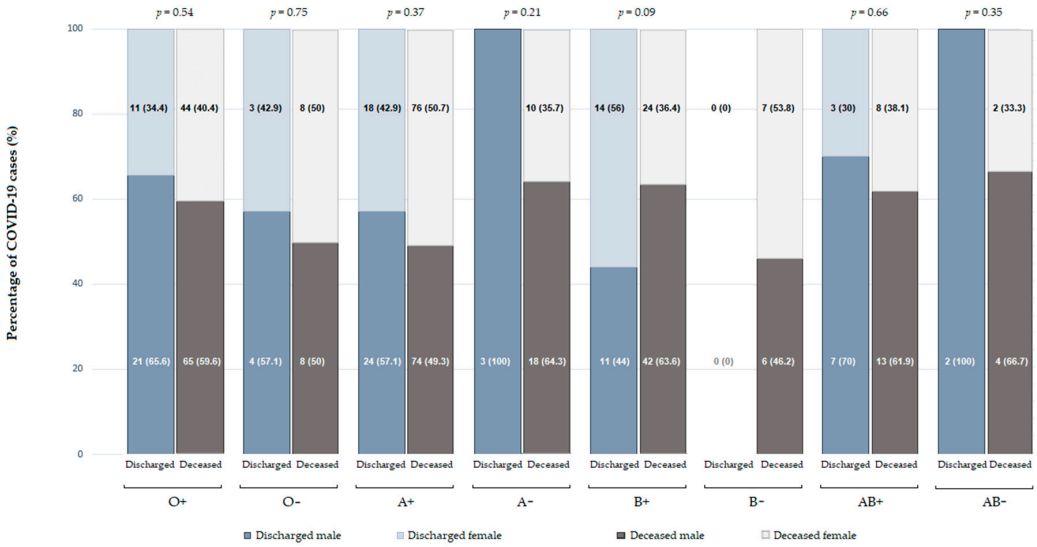


Figure 2. Outcome of severe and critically ill COVID-19 patients (*n* = 530) stratified by gender and blood group (ABO system and the D antigen). Presence of the D antigen is denoted by "+", and absence by "−"; values shown as *n* (%); *p*-values calculated by Pearson's chi-squared test.

3.3. The Influence of Blood Groups and Comorbidities on Patient Outcomes

When comparing COVID-19 outcomes in both groups, discharged and deceased, a significantly higher proportion ($p = 0.04$) of blood group A participants were among the deceased patients (44.6%) compared to the discharged patients (39.4%) (Table 2). There were no significant differences in the distribution of blood groups O, B, and AB, as well as the D antigen, between these two groups of patients.

Table 2. Characteristics of patients related to COVID-19 treatment outcome.

	COVID-19 Patient Outcomes (*n* = 1687)		
	Discharged (*n* = 1160)	**Deceased (*n* = 527)**	***p* ***
Age [median (IQR)]	70.5 (61–79)	73 (65–79)	<0.001
Sex (male/female) [*n* (%)]	625 (53.9)/535 (46.1)	290 (55.0)/237 (45.0)	0.66
Hypertension [*n* (%)]	583 (50.5)	281 (53.6)	0.24
Diabetes [*n* (%)]	34 (2.9)	15 (2.9)	0.92
Hypertension and diabetes [*n* (%)]	295 (25.6)	161 (30.7)	0.03
ABO blood group [*n* (%)]			
O	372 (32.1)	161 (30.6)	0.53
A	457 (39.4)	235 (44.6)	0.04
B	224 (19.3)	94 (17.8)	0.47
AB	107 (9.2)	37 (7.0)	0.13
D antigen (positive/negative) [*n* (%)]	975 (84.1)/185 (15.9)	443 (84.1)/84 (15.9)	0.99

Data are presented as the median (interquartile range) or as *n* (frequency/%). * Mann–Whitney U test for continuous and Pearson's chi-squared test for categorical variables. Significance was set at $p < 0.05$.

Among the hospitalized patients, 309 (18.4%) had neither hypertension nor diabetes, while 456 (27.2%) had both comorbidities. In addition, 864 (51.1%) and 49 (2.9%) patients had hypertension or diabetes, respectively. There was no significant difference with regard to gender ($\chi^2(1) = 2.342$, $p = 0.13$), the frequency of hypertension and diabetes ($\chi^2(1) = 0.344$, $p = 0.56$), ABO blood group ($\chi^2(3) = 1.790$, $p = 0.62$), and the D antigen ($\chi^2(1) = 1.857$, $p = 0.17$) between hospitalized patients with moderate and severe/critical clinical presentation of COVID-19 who required mechanical ventilation.

The patient characteristics related to COVID-19 treatment outcomes are shown in Table 2. The analysis of patient outcomes revealed a significant association of hypertension and diabetes ($\chi^2(1) = 4.852$, $p = 0.03$) as well as blood group A ($\chi^2(1) = 4.043$, $p = 0.04$) with the outcome of death for hospitalized patients. The median age was significantly higher among deceased patients compared to those discharged (73 (65–79) years vs. 70.5 (61–79) years, respectively).

Univariate binomial logistic regression was performed to determine the effects of age, sex, hypertension, diabetes, ABO blood group, and D antigen typing on the likelihood of death in hospitalized COVID-19 patients. Only age ($\beta = 0.021$, OR 1.02, CI 95% 1.01–1.03, $p < 0.001$), combined hypertension and diabetes ($\beta = 0.256$, OR 1.29, CI 95% 1.03–1.62, $p = 0.03$), and blood group A ($\beta = 0.214$, OR 1.24, CI 95% 1.01–1.53, $p = 0.04$) were significant predictors of the outcome of death (Table 3).

Table 3. Univariate regression in the prediction of the outcome of death.

Independent Variables	β	Wald	p	OR	95% CI	
					Lower	Upper
Age	0.02	24.994	<0.001	1.02	1.01	1.03
Sex (male)	0.05	0.193	0.66	1.05	0.85	1.29
Hypertension only	0.12	1.391	0.24	1.13	0.92	1.39
Diabetes only	−0.03	0.009	0.92	0.97	0.52	1.79
Hypertension and diabetes	0.25	4.480	0.03	1.29	1.03	1.62
Blood group O	−0.07	0.387	0.53	0.93	0.75	1.16
Blood group A	0.21	4.037	0.04	1.24	1.01	1.52
Blood group B	−0.09	0.514	0.47	0.91	0.69	1.18
Blood group AB	−0.29	2.240	0.14	0.74	0.51	1.09
D antigen-positive	0.001	0.000	0.99	1.00	0.75	1.33

β: regression coefficient; OR: odds ratio; and CI: confidence interval.

In the multivariate regression model with age, hypertension, diabetes, and blood group A as independent variables, only age made a significant contribution to the prediction of death. The model was statistically significant ($\chi^2(3) = 31.145$, $p < 0.001$), and the results are shown in Table 4.

Table 4. Multivariate regression model of the prediction of the outcome of death.

Independent Variables	β	Wald	p	OR	95% CI	
					Lower	Upper
Age	0.019	20.935	<0.001	1.02	1.01	1.03
Hypertension and diabetes	0.205	3.062	0.08	1.23	0.98	1.54
Blood group A	0.188	3.068	0.08	1.21	0.98	1.49
Constant *	−2.283	56.159	<0.001	0.10		

β: regression coefficient; OR: odds ratio; and CI: confidence interval. * The constant represents the model intercept (log odds of death when all predictors are zero).

To enhance the interpretability of logistic regression results from Tables 3 and 4, a forest plot (Figure 3) visualizes the odds ratios and 95% confidence intervals from both univariate and multivariate models.

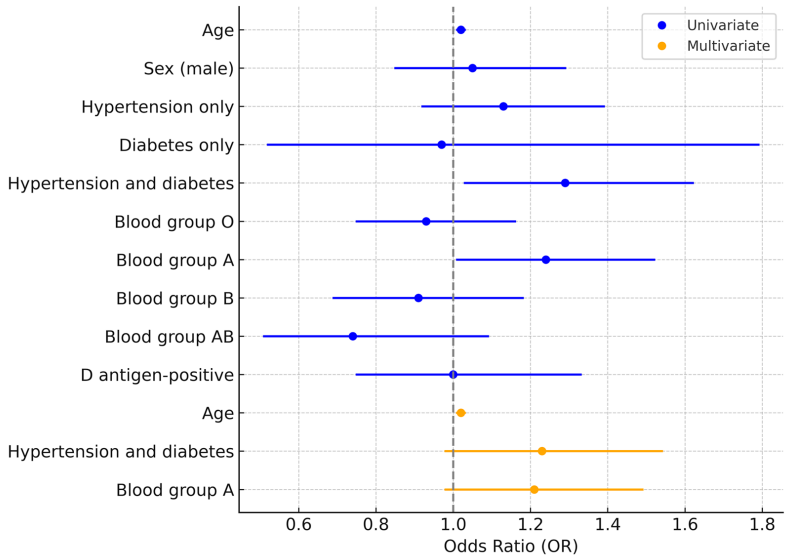


Figure 3. Forest plot showing univariate and multivariate logistic regression odds ratios (ORs) for predictors of in-hospital mortality among COVID-19 patients. Horizontal lines represent 95% confidence intervals. A vertical dashed line at OR = 1 indicates no effect. Multivariate ORs reflect the independent contribution of each variable when analyzed together.

4. Discussion

The aim of this study was to explore the relationship between ABO blood groups and the D antigen with the severity of clinical outcomes of COVID-19 in a cohort of patients from eastern Croatia hospitalized at the UHC Osijek. Our findings highlight several significant associations that contribute to the growing body of literature about COVID-19.

4.1. Association of ABO Blood Groups with COVID-19 Severity

Previous studies have consistently reported a higher risk of SARS-CoV-2 infection and severe outcomes in blood group A individuals, while blood group O appears to offer some protection, or at least a reduced risk of severe disease [35–39].

For example, Zhao et al. [36] and Wu et al. [37] identified blood group A as a risk factor for more severe illness, potentially due to its significant association with increased susceptibility to COVID-19 and worse clinical outcomes. This was further supported by Ellinghaus et al. [38], a European study focusing on respiratory failure, a key determinant of severity. However, many of these studies examined initial infection risk or admission severity. In our cohort of already hospitalized patients with confirmed COVID-19, we observed no significant difference in the frequency of blood group A between those with moderate and severe COVID-19, suggesting that ABO blood group may be more relevant to susceptibility than to intra-hospital disease progression. The conflicting findings in the literature underscore the complexity of interpreting blood group associations, especially across different populations and healthcare systems [39–41].

In the present study, one of the most significant observations was the higher prevalence of blood group A among deceased patients. Specifically, 44.6% of deceased patients had blood group A, compared to 39.4% of those who were discharged, a significant difference ($p = 0.04$), supporting the hypothesis that blood group A may be associated with an increased risk of severe outcomes. This aligns with prior studies [36–38], including recent findings that suggest the A antigen could facilitate viral binding, further enhancing susceptibility [42]. Similarly, Jukić et al. reported a significantly higher frequency of blood group A among hospitalized patients with severe COVID-19 compared to the general population [35]. These findings add relevance to the results in the eastern Croatian cohort, where specific genetic and environmental features may modulate these associations.

On the other hand, we observed a significantly lower frequency of blood group O in hospitalized patients than in blood donors ($p < 0.001$), which aligns with reports that individuals with blood group O may be less susceptible to severe COVID-19 outcomes [17,18,20]. This finding is consistent with the previous Croatian report, which also showed a significantly lower frequency of blood group O among hospitalized COVID-19 patients compared to the general population [35]. However, in that study, the control group, referred to as the general population, was predominantly composed of blood donors, which may have contributed to a higher observed frequency of group O, similar to the distribution observed in the present study's donor cohort. Although the difference between deceased and discharged patients in our cohort was not statistically significant ($p = 0.53$), the trend toward a protective effect for blood group O was consistent with earlier findings [15,16,37,38]. This pattern was particularly shown as the under-representation of blood group O patients among those with severe or fatal outcomes, consistent with reports from Ellinghaus et al. [38]. Studies propose that regular anti-A and anti-B antibodies in blood group O individuals, mostly of the IgG class, may play a role in neutralizing the virus or preventing its entry into host cells [11,17], thus contributing to the observed protective effect [37,38]. In addition, lower levels of vWF and, consequently, factor VIII in blood group O individuals [25–27] could reduce the risk of thrombotic complications, a common feature of severe COVID-19. Though our study did not directly measure vWF levels, the observed

protective effect of blood group O could be partly explained by this mechanism [17]. Still, this result should be viewed in light of potential confounding factors, as group O is known to be overrepresented in blood donor populations due to transfusion policy preferences, which may contribute to the observed difference. These transfusion-driven factors, such as the prioritized recruitment of group O D-negative donors, can influence the ABO and D antigen distribution in the donor population. However, in this study, plasma donors and group-specific call-up donors were excluded during study preparation, which helped reduce this type of selection bias.

The higher frequency of blood group AB hospitalized patients observed in our study aligns with reports suggesting that this blood group may be more susceptible to severe disease [19]. A previous Croatian study also observed a slight increase in blood group AB among hospitalized COVID-19 patients, though it was not statistically significant [35]. While both the present study and the study by Jukić et al. [35] suggest the potential susceptibility of blood group AB to severe COVID-19, the lack of statistical significance in their study may be due to variations in patient sample size between studies. Since blood group AB individuals possess the A antigen, which may facilitate viral binding to host cells [42], they could be at higher risk for severe outcomes. Additionally, lacking both anti-A and anti-B antibodies may impair the ability to mount an effective immune response against SARS-CoV-2, contributing to worse outcomes [16]. However, further research is needed to fully understand the mechanisms underlying these observations.

While some discrepancies with other studies exist, such as those conducted by Latz et al. [39] and Hoiland et al. [40], which did not find significant associations between ABO blood groups and COVID-19 severity, these differences might be attributed to variations in population genetics, healthcare practices, or environmental factors [41]. The present study, focused on the eastern Croatian population, reflects the role of ABO blood groups in this region, but further research is necessary to explore the underlying mechanisms more thoroughly.

4.2. ABO Blood Groups and COVID-19 Mortality

When comparing patient outcomes based on ABO blood groups, we found that blood group A was significantly ($p = 0.04$) more frequent among deceased patients than among those who were discharged. This finding aligns with previous studies reporting higher mortality rates in blood group A individuals [17,38]. Hoiland et al. [40] reported that blood group A or AB is associated with severe clinical outcomes, such as mechanical ventilation and continuous renal replacement therapy. In contrast, Kerbage et al. [43] did not find that blood group A individuals were associated with severe outcomes, although it increased the susceptibility for the disease. Recent findings suggest that the A antigen, expressed on epithelial cells in the respiratory tract, may facilitate SARS-CoV-2 infection by enhancing viral binding to host cells, thereby increasing susceptibility to severe outcomes [42]. This interaction may be related to the role of ABO antigens in inflammation and coagulation, which are critical in the pathophysiology of severe COVID-19. Additionally, blood group A individuals may have a heightened immune response, increasing their risk of cytokine storms and related severe inflammatory complications [24].

Interestingly, we did not observe significant associations between blood groups O, B, and AB and COVID-19 mortality. Although some studies have suggested a protective effect for blood group O, particularly in terms of reduced mortality and less severe disease [14,20,43], our data did not confirm this, potentially due to the older age of our patient cohort, which might have mitigated any protective effect associated with blood group O.

4.3. D Antigen and COVID-19 Outcomes

The role of the D antigen of the Rh blood group system in COVID-19 severity has been less thoroughly studied compared to the ABO system. There is a general notion that the influence of the D antigen on infectious disease outcomes may be specific to certain populations or subtler overall [23]. Some studies hypothesize that the D antigen may play a subtle or indirect role in influencing disease outcomes, yet limited research exists on this in the context of COVID-19 [18,40]. Zietz et al. [24] reported that D-negative individuals had a lower risk of SARS-CoV-2 infection, intubation, and death, suggesting a possible protective effect. Given the genetic variability of the *RHD* gene across populations [23,44], further investigation is warranted into the potential impact of the D antigen on COVID-19 severity, particularly in populations where its influence may be more nuanced.

Our results did not show significant differences in the distribution of the D antigen between COVID-19 patients and blood donors (84.1% vs. 82.1%, respectively, $p = 0.06$). Moreover, the frequency of D-positive individuals was identical in both the discharged and deceased groups (84.1%). While Zietz et al. [24] suggested that D-positive individuals may be at a higher risk of infection, our findings do not support this association. Nonetheless, the absence of a statistically significant association in our cohort does not exclude the possibility of population-specific effects, which future studies with larger sample sizes may clarify.

4.4. ABO Blood Groups and the D Antigen Distribution in COVID-19 Patients and Blood Donors

We compared the ABO blood groups and D antigen distributions between hospitalized COVID-19 patients and blood donors from eastern Croatia. A significant over-representation of blood group O (31.6% vs. 36.3%, $p < 0.001$) and an under-representation of blood group AB (8.5% vs. 7.0%, $p = 0.03$) were observed among hospitalized patients. This suggests that individuals with blood group O are less likely to be hospitalized for severe COVID-19, consistent with the protective effect observed in other studies [19,20]. Conversely, those with blood group AB were more likely to experience severe illness.

The higher proportion of D-negative individuals in the donor population (17.9%) compared to patients (15.9%) was not statistically significant ($p = 0.06$). This trend may reflect the possibility that individuals lacking D-variant-expressing alleles of the *RHD* gene are often preemptively provided with D-negative blood products [23,44]. While the observed trend could be explained by the higher percentage of D-negative individuals in the blood donor population, it remains possible that D-negative individuals are under-represented among hospitalized COVID-19 patients due to a different immune response. This can imply that D-negative individuals might experience milder symptoms, although this did not reach significance in the study cohort ($p = 0.06$). This aligns with the hypothesis that D-negative individuals may have a unique immune reaction that could influence their susceptibility to severe disease [17,24,40], though further research is needed to confirm this.

Although the blood donor population may have a higher percentage of D-negative individuals compared to the general population, they can still serve as a useful comparison group for understanding blood group distributions and their implications for clinical outcomes in COVID-19. Because blood donors are generally younger and healthier than hospitalized patients, it is advised that differences in blood group frequencies between these groups be interpreted with caution. In addition, the sex distribution significantly differed between the two groups, with blood donors being predominantly male (71.3%) and patients more balanced (54.2% male), likely reflecting the male predominance in the donor population and the broader representativeness of the hospitalized cohort.

4.5. Influence of Comorbidities on COVID-19 Outcomes

The present study confirmed that comorbidities, particularly hypertension and diabetes, had a significant impact on COVID-19 outcomes. Patients with both conditions were more likely to experience severe disease and higher mortality, which is consistent with findings from other studies [4,5,7]. These comorbidities may exacerbate the proinflammatory state observed in severe COVID-19, contributing to worse clinical outcomes [17]. In our cohort, the combination of hypertension and diabetes also emerged as an independent predictor of mortality.

A significantly higher proportion of deceased patients had both hypertension and diabetes (30.7%) compared to those who were discharged (25.6%) ($p = 0.03$), consistent with global data showing that these comorbidities increase the risk of severe COVID-19 outcomes [5,41]. These findings highlight the need for targeted interventions for and the close monitoring of high-risk patients with these conditions.

Interestingly, when comparing the influence of blood group and comorbidities on patient outcomes, blood group A and the combination of hypertension and diabetes were both associated with severe outcomes. However, in the multivariate regression model, age remained as the significant predictor of mortality. This suggests that while blood group A and comorbidities such as hypertension and diabetes are important risk factors, age is the most significant independent predictor of poor outcomes. This finding mirrors research by Dede et al. [4], which found that older patients, independent of their comorbid conditions or blood group, were at a higher risk of severe disease and death.

4.6. Gender Differences in COVID-19 Outcomes

We observed differences in blood group distribution and gender among patients with severe COVID-19 outcomes. No female patients with blood groups A-negative, B-negative, or AB-negative were discharged, while numerically higher proportions of females with these blood groups died compared to men. For instance, 35.7% of women with blood group A-negative were in the deceased group, while none were discharged. These patterns may reflect a potential gender interaction with the ABO blood group and the D antigen in COVID-19 severity but should be interpreted with caution. This is supported by studies suggesting gender-related differences in COVID-19 outcomes [45,46]. Additionally, blood group B-negative was observed only among deceased male patients, with no male patients with this blood group discharged. However, the number of individuals in several of these gender–blood group subcategories was very small. Although these trends did not reach significance in this cohort, they highlight an area for further research on the interplay between gender, blood group, and immune response to SARS-CoV-2.

4.7. Implications for Risk Stratification

Our data provide several valuable implications for COVID-19 risk stratification and patient management. Blood group typing, being a routine and inexpensive procedure, could be used to help identify individuals at a higher risk of severe COVID-19. The increased risk of worse outcomes associated with blood group A may guide healthcare professionals in prioritizing these patients for closer monitoring, early interventions, and intensive treatment approaches. Although blood group O might confer some protection, it is crucial not to overlook or lessen the attention given to comorbidities, such as hypertension and diabetes, which remain significant risk factors.

In addition, while blood group and comorbidities are significant risk factors, age emerged as the most independent predictor of mortality in our study. This finding underscores the need for healthcare providers to prioritize older patients for intensive monitoring

and early interventions, irrespective of their blood group or comorbidities, while still accounting for these factors in a comprehensive risk assessment approach.

4.8. Limitations of This Study

One of the strengths of our study is the inclusion of a well-defined cohort of COVID-19 patients and blood donors, allowing for a direct comparison of blood group distribution between these groups. While this study provides valuable insights, there are several limitations that should be acknowledged. First, as a retrospective study based on hospital data, confounding factors—such as age, comorbidities, vaccination status, and healthcare access—may not have been fully accounted for, potentially influencing the results. Although healthcare access or vaccination status were not specifically addressed in this study, they could have impacted patient outcomes. The relatively small geographic area and lack of detailed genetic information on the study population may also, to an extent, limit the generalizability of our findings beyond the eastern Croatian population. Second, we did not have detailed data on the severity of SARS-CoV-2 infection in blood donors (who were, presumably, healthy), which could have affected comparisons with hospitalized patients.

COVID-19 vaccination in Croatia began in December 2020, which coincided with our peak monthly hospital admissions of 418 patients. All patients hospitalized before that date were unvaccinated. Vaccination data are not available for this cohort and could not be retrieved. As vaccination could reduce the likelihood of severe disease, the absence of these data introduces uncertainty when evaluating associations between blood group category and clinical outcomes. However, the majority of severe cases and deaths in our study occurred before widespread vaccine uptake, suggesting that the findings primarily reflect disease behavior in unvaccinated individuals.

Finally, while we focused on ABO blood groups and the D antigen, other genetic and immunological factors likely contribute to COVID-19 severity. We were unable to obtain serological data on antibody titers, which could have provided direct evidence of the protective effects of anti-A and anti-B antibodies. This limitation, combined with the absence of detailed genetic data, restricted our ability to better explore the potential protective role of blood group O and its related immunological responses.

5. Conclusions

In conclusion, the present study provides important insights into the role of ABO blood groups and the D antigen in COVID-19 severity and mortality in the eastern Croatian population.

It was observed that blood group A was associated with higher mortality in univariate analysis, but this association was not retained in the multivariate model, where only age remained a significant independent predictor. Blood group O was significantly less frequent among hospitalized COVID-19 patients, suggesting a protective effect, although not in terms of mortality. The role of RhD status remains unclear, and further research is needed to better understand its potential impact on disease severity.

In examination of existing comorbidities, the combined occurrence of hypertension and diabetes was a significant predictor of worse outcomes in univariate analysis but also lost significance in the multivariate model. Moreover, the strong association between comorbidities and poor outcomes underscores the importance of comprehensive risk assessment in managing COVID-19. This should include both genetic factors, such as blood groups, and health-related factors, such as hypertension and diabetes. As COVID-19 continues to affect populations, understanding these associations can be critical for improving patient care, enhancing outcomes, and guiding public health strategies. Additionally, exploring the interactions between blood groups and immune responses could provide further insight

into the complexity of COVID-19 pathophysiology and inform targeted interventions for those at higher risk.

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Abbreviations

The following abbreviations are used in this manuscript:

COVID-19	Coronavirus disease 2019
ICU	Intensive care unit
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
UHC	University Hospital Center
vWF	von Willebrand factor

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