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INVESTIGATING THE ASSOCIATION BETWEEN BLOOD GROUPS, D-DIMER, AND NEUTROPHIL TO LYMPHOCYTE RATIO IN RELATION TO DISEASE SEVERITY AND OUTCOME: RETROSPECTIVE COHORT STUDY ON COVID-19 PATIENTS

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Abstract

Introduction: chronic obstructive pulmonary disease, asthma and tuberculosis are well known fatal disorders. Corona-virus disease of 2019 (COVID-19) caused worldwide pandemic and it affected lungs and caused deaths more than other causes combined in one year. Research has been focused on different aspects of COVID-19 since it emerged. Blood groups and inflammatory markers are being investigated. The thromboembolism marker D-dimer and other coagulation markers are intensively being studied.

Methodology: We conducted a retrospective cohort study in Azad Jammu Kashmir, Pakistan to explore the relationship between blood groups and neutrophil to lymphocyte ratio (NLR) and D-dimers in relation to disease severity and outcomes.
Results: The blood groups A and B+ve are more affected than other blood groups (58%) and NLR and D-dimer predict disease severity ($p<-0.05$). D-dimer is associated with blood groups, but NLR is not.

Conclusion: The present study gave good insight into role of blood groups, NLR and D-Dimer values in COVID-19 disease severity and outcomes. We recommend that further studies should be done, and more inflammatory markers must be explored as the present study represents only one area of our country.

Keywords: COVID-19, D-dimer, NLR, ABO blood group system

Introduction

Respiratory disorders primarily account for five of the top 30 causes of mortality worldwide. Chronic obstructive pulmonary disease (COPD) is the third leading cause, followed by lower respiratory tract infections, tracheal, bronchial, and lung cancers, tuberculosis, and asthma (1). The SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2) is the cause of the outbreak of COVID-19 (Coronavirus disease 2019), which was later classified as a pandemic. It spreads quickly and can cause severe acute respiratory failure (2). Over 100 million cases of COVID-19 have burdened global governments and healthcare systems globally (3). The pandemic has long-lasting effects on the health of populations and remains a threat (4). People around the world are affected differently by the SARS-COV2 virus; those who are older and have comorbid conditions, including cardiovascular disease, diabetes, and pulmonary disorders, are more susceptible to serious illness. Given the high morbidity and mortality rates associated with COVID-19, research has been interested in gathering information about the traits that make people more likely to contract the virus and determining what risk factors might be connected to the onset and severity of the disease. ACE-2 expression in airway epithelia is one of the mechanistic hypotheses underlying susceptibility and severity of illness (5).

Since December 2019, research has focused on treating the infected, identifying risk factors, and avoiding transmission. No biological biomarker has yet been identified to predict the risk of infection (3). Environmental and socioeconomic factors, such as smoking and air pollution, as well as genetic susceptibility, are the main causes of respiratory disorders. Both COPD and asthma have been linked to the ABO system; however, this linkage has only been hinted at in earlier studies, which found no statistically significant correlation. One study examined the relationship between blood type and acute respiratory distress syndrome (ARDS), and it indicated that blood type A is linked to a higher risk for ARDS in white people who have undergone substantial trauma or who have severe sepsis (6). Inherent polymorphic features in people and populations are represented by blood-type antigens. There are currently 34 recognized blood types in humans as well as hundreds of other blood group antigens and alleles. Variations in blood group antigen expression can affect the susceptibility of a host to a variety of illnesses. Blood-type antigens may affect disease susceptibility through a variety of mechanisms, including acting as immune system modifiers in the form of anti-ABO antibodies and as reporters for pathogenic agents (7). Several studies have linked blood ABO group to COVID-19 risk (3). However, it is still unclear how certain variables affect COVID-19 severity. An ABO blood type has been linked to a higher risk of major COVID-19 issues, and anti-T may help moderate the thrombotic tendency, as it was also linked to an increase in D-dimer levels (1). There were approximately 35 thousand reported cases of COVID-19 in Azad Kashmir, Pakistan, with 741 deaths (8). Research has focused on COVID-19 since its emergence. This study aimed to explain the relationship between ABO blood groups and inflammatory markers in relation to COVID-19 disease severity and outcomes. To the best of our knowledge, this relationship has not been studied in Azad Kashmir.

Methodology

The potential relationship between blood groups and inflammatory markers regarding disease severity and outcomes was investigated in this study using a retrospective cohort methodology. The study participants were patients who sought medical care in isolation wards associated with territorial care facilities in Muzaffarabad from January 2020 to June 2021. The analysis included patients whose blood group histories, pertinent inflammatory indicators (obtained from laboratory investigations), and complete clinical records were available.

The following formula was used to calculate the sample size to provide sufficient statistical power: $n=(Za/2)^2*P(1-p)/(d^2)$, which yielded a minimum data size of 384. Prior ethical permission was sought from the applicable institutional review board or ethics committee to ensure adherence to ethical standards and guard the rights and privacy of the patients. Necessary information was obtained from the patients' medical records, including blood group details, inflammatory markers, and clinical outcomes. This includes the results of diagnostic imaging tests, laboratory reports, progress notes, and discharge summaries. The dates of admission and discharge, disease severity scores, and other important clinical data were obtained from hospital registries for the entire time.

The blood group, divided into distinct categories (A, B, AB, and O), which was ascertained from the patient's medical records, is the key exposure variable of interest. The Patients' hospital stays included laboratory testing, which was used to calculate inflammatory markers. To evaluate the severity of the underlying disease, the presence of symptoms was evaluated, and the number of symptoms was calculated.

To assess the effect of blood group and inflammatory markers on patient outcomes and clinical outcomes such as duration of hospital stay, requirement for intensive care, complications, duration of hospital stay, requirement for intensive care, complications, duration of hospital stay, requirement for intensive care complications, and mortality. The acquired data will be subjected to appropriate statistical analysis using the relevant statistical software (IBM SPSS, R, Stata). The characteristics of the study population were enumerated using descriptive statistics. Using suitable statistical tests (such as the chi-square test, t-test, and analysis of variance), regression models, and consideration of potential confounding factors, the relationship between blood group, inflammatory markers, disease severity, and clinical outcomes will be evaluated.

Potential study flaws include the use of secondary data sources, and the retrospective nature of the design will be highlighted. Measures are taken to overcome or lessen these constraints, including data acquisition and processing, suitable statistical correction for confounding variables, and judicious interpretation of the results. Ethical considerations: The study will adhere to ethical principles and regulations, guarantee patient confidentiality, provide informed consent when necessary, and preserve professional information. The possible dangers and benefits of the study will be thoroughly assessed and addressed.

Results

The total number of participants is 932 and majority are males (65.9%). B+ve blood group was the most frequent and B-ve blood group the least frequent finding (Figure 1). History for Hypertension (60.4%), Diabetes (39.5%), ischemic heart disease (IHC), presence of other comorbid like chronic obstructive pulmonary disease (COPD) was also noted down (Table 1). Fever (72.6%), cough (67.6%) and shortness of breath (65.5%) were the most common symptoms presented in the study population (Table 2).

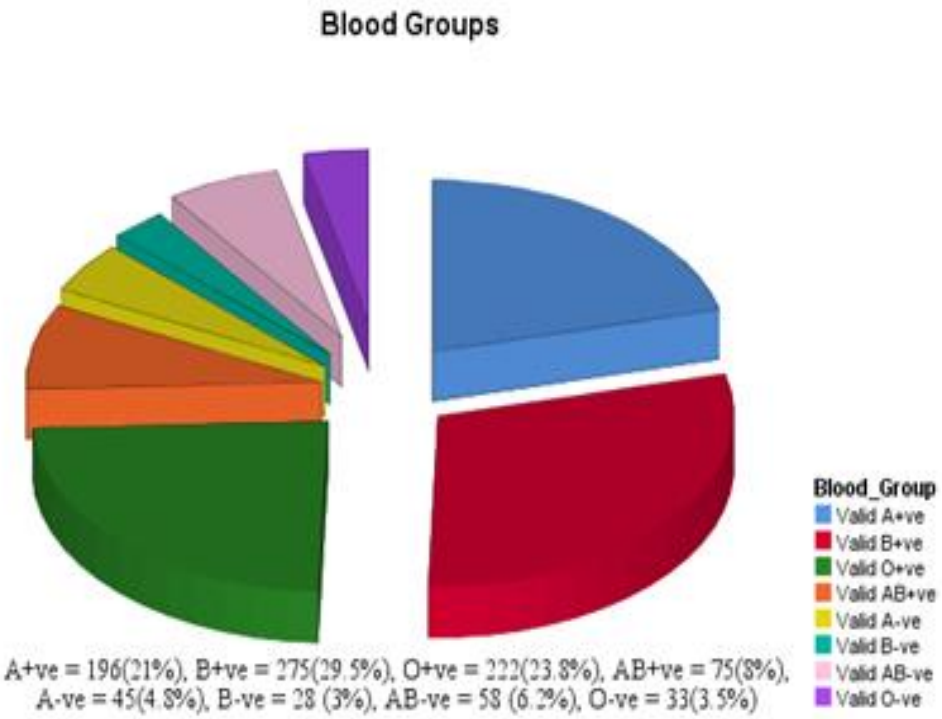

Figure 1: Blood groups

Table 1: Descriptive statistics (Demographics and comorbid)

Variable		Frequency (Percentage)
Gender	Male	614 (65.9
	Female	318 (34.1)
Marital status	Never Married/Divorced/Widowed	440 (47.2)
	Married	492 (52.8)
Household	Joint	709 (76.1)
	Nuclear	223 (23.9)
ICU Admission	No	294 (31.5)
	Yes	638 (68.5)
Hypertension	Non-hypertensive	369 (39.6)
	Hypertensive	563 (60.4)
Diabetes	Non-diabetic	564 (60.5)
	Diabetic	368 (39.5)
Ischemic Heart Disease	Not Present	782 (83.9)
	Present	150 (16.1)
COPD/asthma	Not Present	856 (91.8)
	Present	76 (8.2)
Other Comorbid	Not Present	787 (84.4)
	Present	145 (15.6)
Smoking	Non-smoker	759 (81.4)
	Smoker	173 (18.6)

ICU: intensive care unit, COPD: chronic obstructive pulmonary disease

Table 2: Symptoms of COVID-19, disease severity, lung involvement and outcomes

Variables		Frequency (Percentage)
Fever	Absent	255 (27.4)
	Present	677 (72.6)
Cough	Absent	302 (32.4)
	Present	630 (67.6)
Shortness of Breath	Absent	322 (34.5)
	Present	610 (65.5)
Muscle ache	Absent	733 (78.6)
	Present	199 (21.4)
Headache/Confusion	Absent	882 (94.6)
	Present	50 (5.4)
Sore Throat	Absent	872 (93.6)
	Present	60 (6.4)
Runny Nose	Absent	890 (95.5)
	Present	42 (4.5)
Chest Pain	Absent	844 (90.6)
	Present	88 (9.4)
GIT upset	Absent	814 (87.3)
	Present	118 (12.7)
Lethargy	Absent	851 (91.3)
	Present	81 (8.7)
Disease Severity	Mild	76 (8.2)
	Mild To Moderate	170 (18.2)
	Moderate	283 (30.4)
	Moderate To Severe	326 (35.0)
	Severe	77 (8.3)
Lung Involvement	None	111 (11.9)
	Unilateral	596 (63.9)
	Bilateral	225 (24.1)
Outcome	Recovered	834 (89.5)
	Death	59 (6.3)
	Referred	39 (4.2)
Recovery	Not Recovered	98 (10.5)
	Recovered	834 (89.5)

GIT: Gastrointestinal tract

Most of the patients developed mild to moderate, moderate, or moderate to severe symptoms. Disease severity was mild in only 8.7% (n=76) patients. Disease severity was calculated by considering respiratory rate and SpO_2. The outcomes were calculated in two different parameters. First considered the number of cases recovered, referrals and number of deaths. The second category was made on basis of how many patients were recovered or not recovered. In our cohort of COVID-19 patients selected for this study, 89.5% (n=834) patients were recovered and were symptom free when discharged from the hospital.

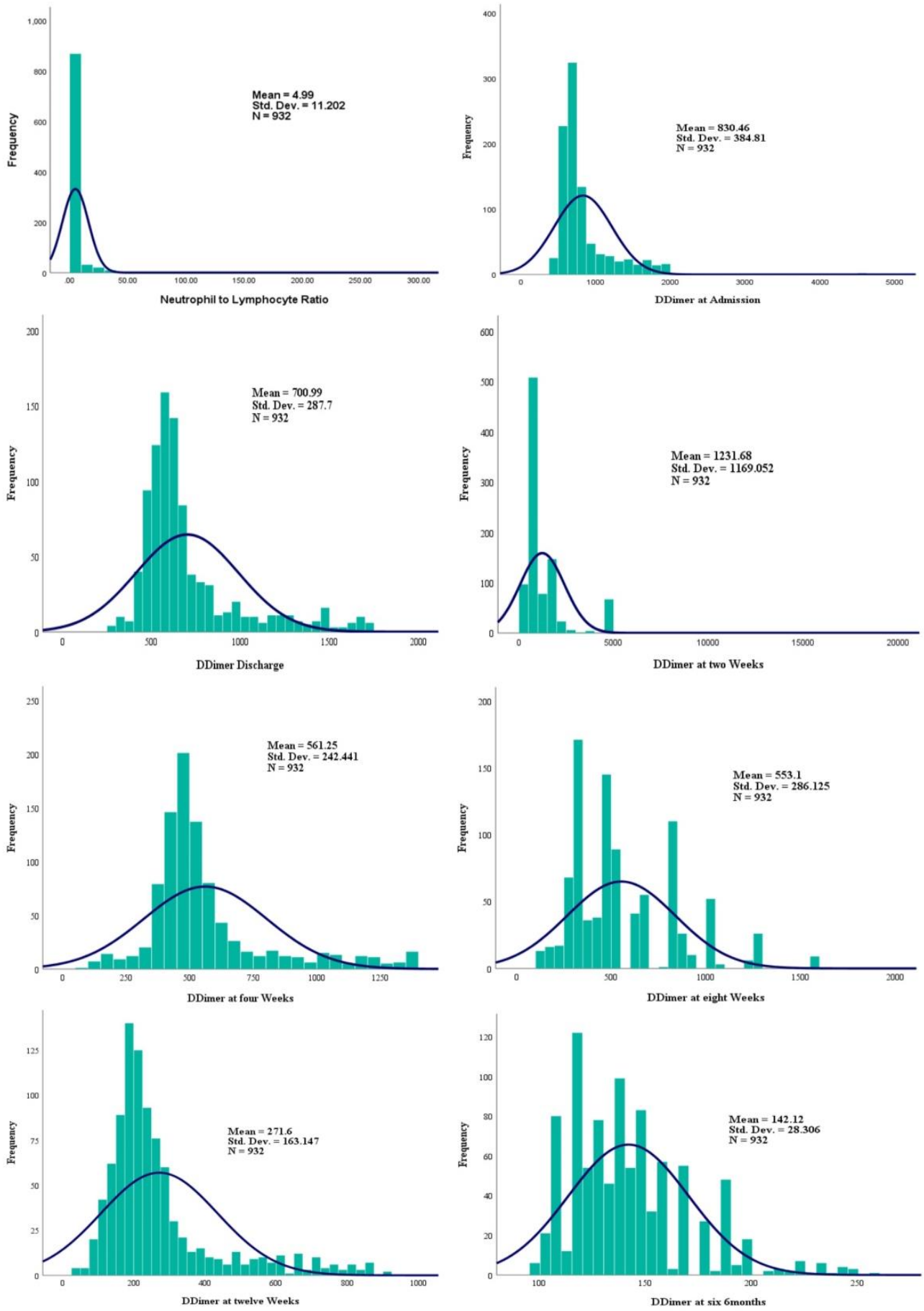

Figure 2: Means Inflammatory Markers

Table 3: Correlation of disease severity and outcomes with blood groups and inflammatory markers

	Spearman's rho	Pearson Correlation	Paired sample Correlation
Blood Group* Disease Severity	0.048	0.026	
Blood Group* Outcome	0.001	0.007	
Disease Severity*Outcome	0.000	0.002	
Blood group*Days symptomatic			0.054 (p<0.000)
NLR*Blood Group	0.646	0.182	
NLR*Disease Severity	0.009	0.316	
NLR*Outcome	0.665	0.657	
NLR*Days symptomatic			0.706 (p<0.000)
DD_Admission*Blood Group	0.337	0.119	
DD_Admission*Disease Severity	0.019	0.000	
DD_Admission*Outcome	0.309	0.323	
DD_Admission*Days symptomatic			0.000 (p<0.000)
DD_Discharge*Blood Group	0.373	0.455	
DD_Discharge*Disease Severity	0.030	0.001	
DD_Discharge*Outcome	0.280	0.052	
DD_Discharge*Days symptomatic			0.000 (p<0.000)
DD_02 weeks*Blood Group	0.188	0.375	
DD_02 weeks*Disease Severity	0.717	0.694	
DD_02 weeks*Outcome	0.608	0.575	
DD_02 weeks*Days symptomatic			0.494 (p<0.000)
DD_04 weeks*Blood Group	0.897	0.936	
DD_04 weeks*Disease Severity	0.075	0.004	
DD_04 weeks*Outcome	0.186	0.024	
DD_04 weeks*Days symptomatic			0.000 (p<0.000)
DD_08 weeks*Blood Group	0.072	0.070	
DD_08 weeks*Disease Severity	0.927	0.871	
DD_08 weeks*Outcome	0.961	0.988	
DD_08 weeks*Days symptomatic			0.634 (p<0.000)
DD_12 weeks *Blood Group	0.934	0.905	
DD_12 weeks *Disease Severity	0.104	0.003	
DD_12 weeks*Outcome	0.052	0.015	
DD_12 weeks*Days symptomatic			0.000 (p<0.000)
DD_06 months*Blood Group	0.040	0.024	
DD_06 months*Disease Severity	0.550	0.372	
DD_06 months*Outcome	0.205	0.188	
DD_06 months*Days symptomatic			0.016 (p<0.000)

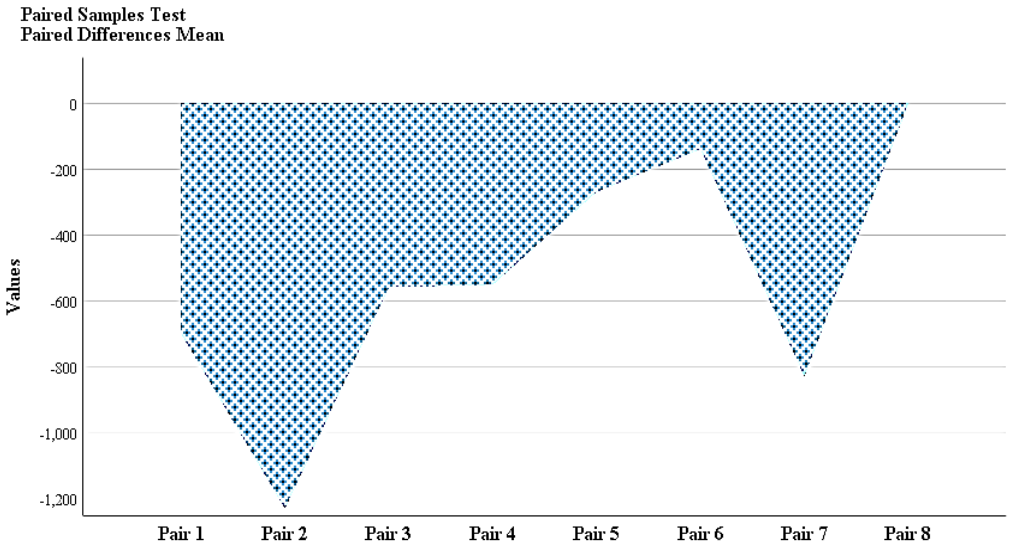

Figure 3: Paired Mean Differences for Inflammatory markers and Days Symptomatic

Inflammatory markers were paired with number of days patients were symptomatic to obtain association between symptomatic days and inflammatory markers.
*Pair 1 includes D-Dimer (DD) at discharge, pair 2: DD two weeks, pair 3: DD four weeks, pair 4: DD eight weeks, pair 5: DD twelve weeks, pair 6: DD 06 months, pair 7: DD at admission and pair 8: NLR (neutrophil to lymphocyte ratio)

Table 4: Association between "symptoms, disease severity and outcomes" and "blood groups and comorbid conditions"

Test Variables	Blood Group	HTN	Diabetes	IHD	COPD	Smoking	Comorbid
ICU admission	0.055	0.604	0.656	0.276	0.792	0.058	0.796
Fever	0.546	0.768	0.618	0.027	0.000	0.735	0.006
Cough	0.442	0.623	0.142	0.067	0.380	0.012	0.153
Shortness of Breath	0.002	0.359	0.095	0.683	0.001	0.835	0.005
Muscle ache	0.502	0.067	0.161	0.083	0.271	0.008	0.529
Headache/Confusion	0.288	0.952	0.825	0.706	0.567	0.000	0.001
Sore Throat	0.072	0.024	0.933	0.395	0.356	0.806	0.078
Runny Nose	0.137	0.007	0.609	0.594	0.137	0.131	0.000
Chest Pain	0.057	0.621	0.964	0.060	0.087	0.024	0.068
GIT upset	0.318	0.796	0.492	0.181	0.053	0.071	0.080
Lethargy	0.001	0.486	0.637	0.348	0.000	0.654	0.236
Disease Severity	0.320	0.379	0.755	0.063	0.525	0.840	0.777
Lung Involvement	0.782	0.174	0.899	0.059	0.383	0.817	0.507
Outcome	0.106	0.016	0.884	0.360	0.560	0.038	0.574
Recovery	0.021	0.018	0.879	0.165	0.433	0.090	0.295

Discussion

Landsteiner's ABO carbohydrate moieties are genetically inherited, and prior studies have linked ABO blood type, cardiovascular disease, and cancer and infection susceptibility, including SARS coronavirus (5). The environment may have an impact on which blood types in a population are passed on to the next generation more frequently, even if the blood types are genetically inherited. ABO blood groups have been shown to be associated with susceptibility to viral infection. For instance, there is a distinct blood group vulnerability to the Norwalk virus and hepatitis B (9,10). These studies on blood group and COVID should be criticized for not including all forms of the disease and not providing data on patients' viral exposure before acquiring COVID-19. Therefore, it is crucial to study ABO blood groups and SARS-C0V-2 infection. It is also important to determine whether different infection rates reflect infection prevention methods or a sharp increase in silent or mid-forms (without seeking medical help), which might impair communal immunity (11). We conducted this study to determine association of COVID-19 severity and outcomes with ABO blood group system based on blood groups, NLR and D-Dimer values.

Previous studies on blood groups have shown varying results. A or AB groups are more susceptible to need for mechanical ventilation, and prolonged ICU admission (12). Blood group O is associated with slightly lower risk of severe symptoms (13), (14). Blood group B is associated with mild to moderate symptoms (15). The Rh antigen is associated with higher inflammatory response to infection (16). Blood counts and coagulation profile can help predict the course of disease (17).

Patients with blood types) O and B had higher resistance to severe COVID-19 than those with blood types A and AB. This may be related to blood group A people having more anti-T than non-blood group A people (4). Similar results were observed when blood type stratification was used. In the case of severe COVID-19, the aHR was 0.27 among O blood groups after the first mRNA immunization in comparison to individuals who had not received the vaccine (18). In an observational review of healthcare data in New York, ABO and Rh blood types were found to be associated with infection, intubation, and death in an observational review of healthcare data in New York (14,1112) people

tested for SARS-CoV-2 who had known blood types). The Non-O types had somewhat higher infection prevalence. In comparison to type O, there was a lower risk of intubation for type A and a higher risk for types of AB and B, whereas type AB had a higher risk of death than types A and B. We predicted that having an Rh-negative blood type would be protective for each of the three outcomes (19).

A previous study determined whether there is a connection between patient blood types, risk of SARS-Cov-2 infection and clinical outcomes in COVID-19 patients. The Blood group A was most frequently found (57 %) in COVID-19 individuals. This was followed by Blood group O (24.8%) Blood group A was more prevalent in COVID-19 patients than in controls (75% vs. 38%, P 0.001: OR: 2.1) and was statically significantly more common overall. Contrarily, there was a substantially reduced prevalence of blood group O in COVID-19 patients compared to the control group (24.8% vs. 37.2%, P 0.001: OR 1.8). Current research suggests that blood group O may be relatively protective against COVID-19 infection, but blood group A may contribute to an increased susceptibility to infection. The blood group type does not seem to affect clinical outcomes, although once an infection has occurred (2). In our cohort, blood group B+ve was the most and blood group B-ve was the least prevalent blood type. Blood group A+, B+, AB+ were present in 546 patients in our cohort that makes 58.6% of the total study population. We may conclude that these three groups were more affected than A-ve, B-ve and AB-ve.

A retrospective study on Danish individuals tested for SARS-CoV-2 between February 27, 2020, and July 30, 2020. Real-time polymerase chain reaction testing was used to screen 473,654 individuals for SARS-CoV-2, with 7422 testing positive and 466,232 testing negatives. This represented 38% of the Danish population (blood groups are not evenly distributed) (20). We studied a cohort of 932 patients retrospectively in the present investigation. The blood groups distribution was not uniform. Positive blood groups were more prevalent among COVID-19 positive patients (Figure 1).

Higher neutrophil and lower lymphocyte count is associated with disease severity (21). In present study means of inflammatory markers (NLR) and d-dimer were determined (Figure 2). NLR (neutrophil to lymphocyte ratio) was associated with disease severity in our cohort too, but its association was independent of the blood group of the patient (Table 3).

D-dimer is a marker for thromboembolism and pulmonary embolism (22). D-dimer levels are higher is severe COVID-19 disease compared to mild to moderate disease (23). DD levels higher than 1360 ng/ml recorded on day five can help clinicians to predict COVID-19 disease stage and prognosis (24). Elevated levels can predict disease severity and mortality (25). Fatigue, shortness of breath and reduced tolerance for physical activity persists for months in patients who contracted COVID-19. D-dimer levels remain high which indicates that the symptoms persist because of immuno-thrombosis of microvasculature of lungs (26). These patients can present with lower mean SpO_2 even after three months (27). Early measurement of D-dimer levels and risk stratification based on the obtained values may help to design management protocols for COVID-19 patients (28).

We used bivariate correlation and paired sample t-test to determine correlation among the variables included in the study. Blood groups are associated with disease severity, number of days the patient was symptomatic and outcomes. Blood groups A+ve and B+ve were more affected than other blood groups. D-dimer values were calculated at seven different points of time that are: admission, discharge, two weeks, four, eight and twelve weeks and finally at six months. D-dimer was tested for correlation with disease severity, symptomatic days, and outcomes. The d-dimer values exhibited correlation with disease severity, it was more intense during early period that is admission to discharge time. And the association faded with time observing no association at six months. Association between blood groups and d-dimer was not established until six months. At six months, the blood groups showed correlation with d-dimer values (Table 3). Paired sample t-test also showed relationship between d-dimer and number of days symptomatic (Figure 3). Chi-square test 2 * 2 contingency exhibited association of blood groups and disease severity and outcomes. Blood groups were associated with outcomes and the symptom “shortness of breath”. Blood groups were also associated with the need of admission to ICU (Table 4).

The present study gave good insight into role of blood groups, NLR and D-Dimer values in COVID-19 disease severity and outcomes. The blood groups A and B+ve are more affected than other blood groups and NLR and D-dimer predict disease severity. D-dimer is associated with blood groups, but NLR is not.

The study was a retrospective study and from small area in Pakistan (Muzaffarabad, AJK) and the sample size is not too big. It also did not include all the inflammatory markers. So, the study results cannot be generalized. We recommend that further studies should be done and more inflammatory markers must be explored.

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