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Original Article

Internal Medicine Section

Association of ABO and Rhesus Blood Groups with the Severity of SARS-CoV-2 Infection: A Cross-sectional Analytical Study

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ABSTRACT

Introduction: Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), a new strain of RNA viruses causes coronavirus disease in human. Though some studies suggested different blood group types as risk factors for Coronavirus Disease 2019 (COVID-19) infection, the association between blood groups and the COVID-19 infection may not be the same in various societies with different genetic statuses. Also, no studies so far have investigated the relationship between COVID-19 severity and ABO blood groups in Iran and developing countries according to the World Health Organisation (WHO) criteria.

Aim: To evaluate the association between blood types and the severity of COVID-19 infection.

Materials and Methods: This cross-sectional study enrolled 171 patients infected with SARS-CoV-2 {49 severe (severe or critical) and 122 non severe (mild to moderate)}, who were admitted to hospitals of Mazandaran University of Medical Sciences, Sari, Iran from April 2020 to June 2020. To evaluate the distribution of the blood group, 171 COVID-19 patients were compared with the reported data of Iranian population blood groups. The severity of COVID-19 infection was determined based on WHO criteria including clinical symptoms, radiological findings, and signs of organ dysfunction. The associations between ABO blood groups and the severity of COVID-19, were evaluated using Pearson's Chi-square.

Results: The distribution of the blood group in 171 patients with COVID-19 was not different compared to the reported general Iranian population blood group (p-value=0.344). Evaluation of the association between ABO blood groups and the severity of COVID-19 showed that patients with blood group type B developed severe COVID-19 infection compared to other blood types who showed mild or moderate conditions (p-value=0.048). Mortality due to COVID-19 was not statistically different between the ABO blood group and Rh (p-value=0.96, p-value=0.27 respectively), but the frequency of patients with Rh-negative that needed intubation and mechanical ventilation was higher compared to Rh-positive patients (p-value=0.003).

Conclusion: A positive correlation was found between blood type B and COVID-19 severity. Also, mechanical ventilation was significantly more in Rh-negative patients.

Keywords: Intubation, Iran, Severity, Severe acute respiratory syndrome coronavirus 2

INTRODUCTION

The new Coronavirus Disease 2019 (COVID-19) belongs to the RNA viruses family is a zoonotic beta coronavirus that can cause a lethal and Severe acute respiratory syndrome coronavirus 2. The COVID-19 pneumonia was first identified in Wuhan, China, and then spreaded worldwide [1]. Since the beginning of the COVID-19 pandemic, a considerable amount of research has been done to evaluate the related risk factors for the contraction of COVID-19 and the severity of the infection. The findings up to now show the related risk factors for the severity of infection to be older age, male sex, lymphopenia, smoking, and co-morbidities such as hypertension obesity, and diabetes [2-5].

There are different antigens on the surface of Red Blood Cells (RBCs). These antigens have a role in human bacterial and viral infections [6]. The ABO and Rhesus antigen (Rh) are two important blood group systems and the blood group of every person is identified according to the type of these RBC surface antigens. Blood groups are classified into four types A, B, AB, and O, which can be positive or negative for Rh [7].

Blood groups have been evaluated in patients with COVID-19 in some studies and non O blood groups (A, B, or AB) were found to have a higher risk to SARS-CoV-2 [8-10] compared to the blood type O [11,12]. The molecular mechanisms suggesting that blood group O contains both antibodies (anti-A and anti-B) that can inhibit the binding of the virus's spike (S) protein to the cells [13]. Cheng Y et al., found an association between blood groups and SARS-CoV infections [14].

Various studies have shown the association between blood groups and several diseases such as cardiovascular diseases, neurological disorders, malignancy, and infections [15,16]. Also, blood groups may affect the outcomes of diseases. Gotsman I et al., showed that blood groups are relevant to the development and outcomes of chronic heart failure [17].

The findings of various studies on SARS-CoV-2 showed that different blood groups can affect the susceptibility to the SARS-CoV-2 or even the severity of COVID-19 [8,18-20]. In a study aimed to investigate the association between SARS-CoV-2, vulnerability and blood type with ABO blood types, a higher rate of infection was observed among patients with the AB blood group, while patients with the O blood group have shown a lower rate of infection [8]. A retrospective cohort analysis of all Danish individuals determined the influence of blood groups on SARS-CoV-2 susceptibility and demonstrated that blood group O is significantly associated with reduced susceptibility to SARS-CoV-2 infection [8,21].

Although the random-effect meta-analysis revealed a large heterogeneity among studies, The results indicated that the COVID-19 infection rate in persons with blood group A>O>B>AB. Overall, The COVID-19 infects all ABO blood groups at different rates. These findings also suggested that people with blood group A more infected with COVID-19 and blood group AB is linked to a lower risk of COVID-19 infection [22]. However, the exact molecular and clinical mechanism of association between different blood groups and COVID-19 infection is unclear. Therefore, more studies are needed to better understand how ABO blood type affects COVID-19

infection and whether blood type-based infection control measures can reduce the risk of COVID-19. Until now no study has examined the relationship between COVID-19 severity, according to the World Health Organisation criteria, and ABO blood types in Iran. Therefore, the present study was designed to investigate the association between ABO blood groups and the severity of COVID-19 infection among Iranian patients.

MATERIALS AND METHODS

This cross-sectional study was conducted on 171 patients with COVID-19 who referred to teaching hospitals of Mazandaran University of Medical Sciences, Sari, Iran, from April 2020 to June 2020. The study was approved by the Ethics Committee of the Mazandaran University of Medical Sciences (Code: IR.MAZUMS.REC.1399.7456), and informed consent was obtained from all participants.

Inclusion criteria: The study population included all patients who were referred to the study hospital during the mentioned period and consented to participate in the study.

Exclusion criteria: Considering that some patients were referred from other hospitals affiliated with Mazandaran University of Medical Sciences, their complete information was not available. Therefore, patients whose information was not accessible, were excluded from the study.

Diagnosis and Severity Definitions

The COVID-19 was confirmed in patients according to their clinical symptoms, chest imaging findings, laboratory, and molecular evidence {Reverse Transcription-Polymerase Chain Reaction (RT-PCR) assay of viral nucleic acid from nasal and throat swab samples}. According to the World Health Organisation (WHO) [23], the severity of COVID-19 infection was divided into four phases: phase 1 (mild), phase 2 (moderate), phase 3 (severe), and phase 4 (critical).

- Phase 1: Patients in phase 1 (mild) experience fever, cough, fatigue, anorexia, shortness of breath, myalgias. Other non specific symptoms, such as sore throat, nasal congestion, headache, diarrhoea, nausea, and vomiting, have also been reported [24]. Loss of smell (anosmia) or loss of taste (ageusia) preceding the onset of respiratory symptoms has also been reported in this phase [25,26].
- Phase 2: Patients in phase 2 (moderate) are diagnosed with clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) but no signs of severe pneumonia, including SpO_2 ≥90% on room air [27].
- Phase 3: Patients with clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) plus one of the following: respiratory rate >30 breaths/min; severe respiratory distress; or SpO_2 <90% on room air, classified in the phase 3 (severe) [27].
- Phase 4: Patients are considered to be in phase 4 (critical) if they have acute life-threatening organ dysfunction caused by a dysregulated host response to suspected or proven infection. Signs of organ dysfunction include altered mental status, difficult or fast breathing, low oxygen saturation, reduced urine output, fast heart rate, weak pulse, cold extremities or low blood pressure, skin mottling, laboratory evidence of coagulopathy, thrombocytopenia, acidosis, high lactate, or hyperbilirubinemia [28].

In the present study, the patients were classified into two groups based on severity, group1: severe (severe or critical) and group 2 non severe (mild to moderate).

Laboratory Testing and Data Collection

Demographic traits (age, sex, height, weight, signs and symptoms, history of other chronic diseases, co-morbidities), were interviewed from patients, and information related to diagnostic findings {Computed Tomography (CT) scan of lungs and laboratory results} and disease severity were extracted from electronic medical records and recorded in a questionnaire. The effect of confounding risk factors {including age, gender, Body Mass Index (BMI), and co-morbidities} on associations between blood group and COVID-19 severity was evaluated. ABO+Rh blood groups were determined using Blood Type Test Kit (CinnaGen) in the study population.

The distribution of the blood group in 171 patients with COVID-19 was compared to the Iranian general population. These people were 3475 individuals referred for paternity testing from 1998 to 2008 to the Immunohematology Reference Laboratory (IRL) of the Iranian Blood Transfusion Organisation (IBTO), Tehran, Iran, to derive information on the population prevalence of antigens and phenotypes in ABO, Rh, and seven other major blood group systems. The relationship between demographic, laboratory and clinical characteristics of patients with Blood groups (ABO+Rh) was evaluated. The association between blood groups (ABO+Rh) and COVID-19 severity intubation and death in the study population were investigated.

STATISTICAL ANALYSIS

Weight by count [5] and Chi-square methods were used to compare the COVID-19 patients with the general population. First, the unadjusted associations of ABO blood group and COVID-19 severity were analysed separately among the patients using the Pearson test. Then multiple logistic regression analysis was used to adjust the potential confounders on disease severity, including age, gender, BMI, smoking, and history of chronic diseases such as hypertension, diabetes mellitus, cardiovascular disease. Statistical Package for the Social Sciences (SPSS) (version 16.0) was used for all the statistical analyses. A p-value of <0.05 was considered significant. Pearson's Chi-square tests or Fisher's-exact tests were used to comparing various groups of study populations. Odds Ratios (ORs) and 95% Confidence Intervals (CIs) were calculated to describe the possible effect on the development of COVID-19.

RESULTS

Characteristics of the Study Populations

A total of 171 patients infected with SARS-CoV-2, including 49 severe and 122 non severe were studied. The demographic, and clinico-pathological characteristics of the patients based on blood groups are shown in [Table/Fig-1]. There was no significant difference in age (p-value=0.62) and gender {94 (55%) male, 77 (45%) female, p-value=0.72} among blood groups. Also, the result showed no statistically significant difference in the history of smoking between patients based on ABO blood groups and Rh^+ (A: 2.3%, B: 11.1 %, AB: 0, and O: 14.1%, Rh^+: 9.6%, p=0.06, likelihood ratio).

There was no significant relationship between ABO/Rh blood groups and co-morbidities including hypertension, diabetes mellitus, cardiovascular disease, chronic lung diseases, and malignancy in these patients (p>0.05) [Table/Fig-2].

As shown in [Table/Fig-3], the study group was compared with a general population whose information had already been recorded to compare the distribution of blood types. The distribution of the ABO blood group in 171 patients with COVID-19 was not different compared to the reported general Iranian population blood group (p-value=0.344, Chi-square test). The distribution of A, B, AB, O, and Rh^+ blood groups among 171 patients with COVID-19 were 45 (26.3%), 48 (28.1%), 12 (7%), 66 (38.6%), and 167 (97.7%), respectively.

Association of ABO Blood Groups with Laboratory Markers and Disease Severity in COVID-19

Evaluation of the COVID-19 severity of 171 patients (49 severe and 122 non severe) according to the WHO classification [23], showed the potential relationship between ABO blood types and severity of COVID-19 infection. Distribution of blood types in the severe phase of disease was A: 10 (22%), B: 19 (40%), AB: 2 (17%), O: 18 (27%), and Rh^+: 44 (29%) and in the non severe phase for A, B, AB, O, and Rh^+ was as follows respectively: 35 (78%), 29 (60%), 10 (83%), 48 (73%), and 108 (71%). The patients with blood type B were significantly developed the severe disease compared to other blood types; 40%

Characteristics	Type A (n=45)	Type B (n=48)	Type AB (n=12)	Type O (n=66)	Total (N=171)	p-value (Student's t-test)	Rh+	Rh-	p-value (Student's t-test)
Age (years)	53.11±2.2	56.93±2.2	54.08±3.9	54.9±2.1	54.9±1.2	0.712	54.67±1.27	56.80±4.99	0.623
Body mass index (kg/m^2)	28.17±0.8	27.67±0.7	25.64±1.0	27.39±0.5	27.5±0.4	0.450	27.57±0.41	28.42±1.49	0.555
Partial pressure of oxygen (mmHg)	91.07±2.2	87.82±2.5	94.1±1.1	92.77±0.7	37.25±0.9	0.188	91.23±0.98	87.36±5.3	0.273
Body temprature (°C)	37.26±0.07	37.1±0.08	37.2±0.2	37.25±0.09	37.25±0.04	0.753	3.18±0.09	3.14±0.32	0.903
Respiration rate (per minute)	20.43±0.5	19.76±0.4	18.5±0.6	20.35±0.5	37.25±0.2	0.406	37.22±0.05	37.16±0.17	0.701
C-Reactive protein (mg/dL)	37.86±5.9	53.21±8.9	70.71±17.3	43.99±4.7	37.25±3.7	0.186	19.95±0.32	21.20±0.70	0.211
Erythrocyte sedimentation rate (mm/hrs)	49.75±4.3	45.94±3.2	60.37±16.8	46.42±4.5	37.25±2.4	0.574	47.73±4.0	28.79±7.5	0.138
Lymphocyte count (per mm^3)	1438.24±269	1535.11±143	2003.44±621	1523.47±113	37.25±99	0.65	47.82±2.6	51.50±10.1	0.698
Feritin (ng/mL)	254.61±88	1377.66±535	504.85±179	511.15±223	37.25±193	0.135	18.74±1.05	18.32±2.2	0.902
Alanine transaminase (U/L)	36.15±7.0	30.40±4.4	35.16±7.1	25.25±2.7	37.25±2.6	0.409	687.88±204.8	1054.40±755.1	0.599
Aspartate aminotransferase (U/L)	48.96±11.3	55.05±11.1	65.16±23.3	35.97±4.3	37.25±5	0.354	31.17±2.9	23.92±3.3	0.409
Alkaline phosphatase (IU/L)	272.5±32	378.78±48	324.83±78	303.60±43	37.25±23	0.376	49.70±5.6	24.18±4.3	0.144
Creatine phosphokinase (U/L)	103.92±20	240.10±49	764.83±674	302.58±112	37.25±60	0.09	309.76±21.4	400.08±147.3	0.556
Lactate dehydrogenase (U/L)	901.13±314	854.94±180	689.66±191	631.35±118	37.25±109	0.76	273.01±66.6	113.13±35.6	0.474
Data are shown as Mean±SEM Normal range:	Feritin: 12-300 ng/mL (male) 12-150 ng/mL (female) Alanine transaminase: 7-56 U/L Aspartate aminotransferase: 10-40 U/L Alkaline phosphatase: 20-140 U/L Creatine phosphokinase: 39-308 U/L (male), 26-192 U/L (female) Lactate dehydrogenase: 140-280 U/L								

[Table/Fig-1]: The demographic, clinical, and laboratory characteristics of the patients with different blood groups type (Student t-test).

Co-morbidities	Type A	Type B	Type AB	Type O	p-value (Chi-square test)	Rh+	Rh-	p-value (Chi-square test)
Hypertension	19 (45.2%)	18 (38.3%)	3 (25.0%)	28 (43.8%)	0.59	57 (38.8%)	9 (64.3%)	0.064
Diabetes	17 (40.5%)	14 (29.8%)	1 (8.3%)	21 (32.8%)	0.2	45 (30.6%)	6 (42.9%)	0.34
Cardiovascular disease	10 (23.8%)	9 (19.1%)	0	16 (25.0%)	0.25	30 (20.4%)	5 (35.7%)	0.18
Pulmonary disease	1 (2.4%)	1 (2.1%)	0	3 (4.7%)	0.76	4 (2.7%)	0	0.532
Cerebrovascular disease	1 (2.4%)	3 (6.4%)	0	4 (6.2%)	0.64	6 (4.1%)	2 (14.3%)	0.09
Liver disease	1 (2.4%)	0	0	1 (1.6%)	0.73	2 (1.4%)	0 (0.0%)	0.66
Malignancy	4 (9.5%)	4 (8.7%)	1 (8.3%)	6 (9.2%)	0.99	12 (8.2%)	2 (4.3%)	0.437

[Table/Fig-2]: Co-morbidities in patients with COVID-19 based on blood group.

Blood group	Iranian general population N=3475	COVID-19 patients N=171	p-value
A	1115 (32.1%)	45 (26.3%)	0.344
B	823 (23.7%)	48 (28.1%)	
AB	269 (7.7%)	12 (7.0%)	
O	1268 (36.5%)	66 (38.6%)	
Rh+	3152 (90.7%)	167 (97.7%)	0.02
Rh-	323 (9.3%)	4 (2.3%)	

[Table/Fig-3]: Distribution of the ABO blood group and Rhesus antigens among COVID-19 patients compared to the Iranian general population.

vs 24% (p-value=0.048) [Table/Fig-4]. The result was the same after adjustment for other important risk factors such as age (OR: 1.043, 95% CI: 1.015 to 1.072), gender (OR: 1.408, 95% CI: 0.625 to 3.175), and BMI (OR: 1.102, 95% CI: 1.012 to 1.20) in regression analysis.

To evaluate the possible reason for the severity of COVID-19 infection in patients with blood type B, the inflammatory markers such as CRP and ESR were compared between severe and non severe groups that there was not a significant association between blood group and inflammatory markers (p-value=0.211 and p-value=0.138 respectively) [Table/Fig-1].

As shown in [Table/Fig-5], mortality due to COVID-19 was not different between patients with ABO blood groups and Rh (p-value=0.96,

Blood group	A (n=45)	Non A (n=126)	B (n=48)	Non B (n=123)	AB (n=12)	Non AB (n=159)	O (n=66)	Non O (n=105)	Rh+ (n=156)	Rh- (n=15)
Non severe	35 (78%)	87 (69%)	29 (60%)	93 (76%)	10 (83%)	112 (70%)	48 (73%)	74 (71%)	112 (71.8%)	10 (67%)
Severe	10 (22(%	35 (31%)	19 (40%)	30 (24%)	2 (17%)	47 (30%)	18 (27%)	31 (30%)	44 (28.2%)	5 (33%)
p-value (Chi-square tests)	0.266		0.048*		0.512		0.751		0.76	

[Table/Fig-4]: Association of COVID-19 severity with the ABO/Rh blood group in COVID-19 patients.

COVID-19 outcome	Type A	Type B	Type AB	Type O	p-value (Chi-square tests)	Rh+	Rh-	p-value (Chi-square tests)
Intensive Care Unit hospitalisation	8 (30.8%)	10 (26.3%)	3 (50.0%)	13 (30.2%)	0.7	29 (29%)	4 (36.4%)	0.61
Acute Respiratory Distress Syndrome (ARDS)	0	1 (2.6%)	1 (16.7%)	1 (2.1%)	0.11	3 (2.7%)	0	0.58
Ventilation	3 (9.1%)	3 (7.3%)	1 (14.3%)	7 (12.5%)	0.83	10 (8%)	4 (36.4%)	0.003*
Discharge	32 (88.9%)	31 (86.1%)	8 (80%)	44 (88%)	0.89	101 (87.1%)	10 (83.3%)	0.71
Death	5 (16.1%)	5 (14.7%)	2 (20.0%)	8 (18.2%)	0.96	17 (16.2%)	3 (30%)	0.27

[Table/Fig-5]: Outcome in patients with COVID-19 according to blood group.

p-value=0.27, respectively); however, the Rh$^-$negative patients significantly needed more intubation and mechanical ventilation (p-value=0.003).

DISCUSSION

The COVID-19 pandemic has led to the demise of thousands of people worldwide over the recent years. The important risk factors for this disease, especially in its severe forms, are still unknown. Age, diabetes, hypertension, and history of cardiovascular and respiratory disease have been reported as risk factors. The blood group antigens may also play a role in microorganisms receptor recognition and affect host susceptibility to many infections [11].

In the present study, the distribution of the blood group in patients with COVID-19 was not different compared to the general population. The inflammatory markers and COVID-19 severity correlation with blood group (A, B, AB, and O) in addition to Rh were compared. Patients in all four blood groups were similar in mean age, gender, history of diabetes mellitus, cardiovascular disease, respiratory disease, and cancer. There was no association between blood type and the risk of COVID-19 infection.

Some studies have already identified a possible role for blood groups in COVID-19 infection [11,29]. Wu Y et al., and Zhao J et al., found that blood group type A is a risk factor for COVID-19 infection [11,30]. Latz CA et al., found that B and AB blood groups correlate with COVID-19 infection [31]. Franchini M et al., reported that O blood type subjects (donors of convalescent plasma) have a reduced predisposition to become infected with SARS-CoV-2 compared to healthy uninfected periodic volunteer blood donors [32].

Zeng X et al., in a meta-analysis found a lower risk of COVID-19 among O blood types individuals but they suggested lower odds of mechanical ventilation for all non O types [10].

Studies on other infectious diseases also found a correlation between infection and blood types. Hutson AM et al., investigated the relationship between ABO blood group and the risk of Norwalk virus (NV) infection. They showed that individuals with an O phenotype have an increased susceptibility to NV, whereas persons expressing the type B antigen had a decreased risk of infection [33].

The discrepancies between our results and previous studies that identified different blood groups as severity factors can be explained by COVID-19 infection confirmation methods. Most of the above studies confirmed COVID-19 infection only by PCR test. However, in our study COVID-19 infection was confirmed by clinical symptoms, positive PCR test, and chest CT scan. Although our method may lead to over-diagnosis of COVID-19 cases, relying solely on the PCR test may lead to under-diagnosis of the disease.

In the current study, patients with blood type B were significantly more prone to develop severe to critical illness when compared to other blood types. The result was the same after adjustment for other important risk factors such as age, gender, and BMI in regression analysis. The mortality rate due to COVID-19 infection was not different between patients according to blood groups but patients with Rh$^-$ needed more intubation and mechanical ventilation.

In the study by Zhao J et al., blood group A correlated with severe COVID-19 disease condition [30]. Latz CA et al., and Göker H et al., did not report a correlation between blood group type and COVID-19 severity [29,31]. In the study by Latz CA et al., the COVID PCR positive patients had a higher percentage of blood Rh antigen [31]. The debatable element is that there is surely a racial factor in ABO blood grouping. In studies, the factors that confuse race and primary language should be evaluated through multivariate models, which may have isolated the influence of ABO blood type, regardless of ethnicity. However, the effects of ethnicity on the susceptibility and severity of COVID-19 require further investigation.

The potential of the risk factor of blood group B against disease aggravation found in our study and some previous studies [31,34]. can be explained by RBC surface antigens and their ability to produce antibodies. Mackenzie JS et al., reported the low ability of blood type B to produce antibodies against some viral infections as influenza A [35]. Also, blood group B has a role in some bacterial infections caused by salmonella, gonorrhoea, tuberculosis, *Streptococcus pneumoniae,* and *E.coli* [36].

Histo-Blood Group Antigen (HBGAs) are complex carbohydrates that are expressed on the surface of RBC membranes as well as on a large number of human cells and tissues such as platelets, vascular endothelia, and mucosal epithelia [37]. These antigens are specified by the presence or absence of particular sugar molecules that are added to proteins or lipids of mentioned cells and tissues. H antigen is a precursor of the HBGAs and in its absence, ABO blood group antigens will not be produced. Depending on the ABO blood types, the H antigen is converted into either the A antigen, B antigen, or both. A and B antigens by enzymatic addition of N-acetyl-D-galactosamine and D-galactose to the H antigen precursor respectively. The H antigen remains unmodified in a person with blood type O [33].

In this research, type B antigen increased the severity of COVID-19 infection. One possibility is the biochemical structural difference between blood groups. SARS-CoV-2 spike protein (S), which is heavily glycosylated, is a key molecule for infecting cells. Viruses put sugars together using host enzymes (glycosyl-transferase) and the S protein carries infected host cell blood group sugar antigens, so SARS-CoV-2 can replicate in cells that express blood type antigens [10]. This study showed patients with blood type B get more severe COVID-19 infection. Maybe type B has more sugar components in addition to the basic-O-oligosaccharide of type O and also there is a link between the "glycosylated" spike protein requiring glucosyl-transferase which are highly expressed in B blood types compared to other types.

Another possibility is ABO antibody production in the body. The immune system of people with blood group A (antigen A) makes antibodies against B, people with blood group B (antigen B) make anti-A antibodies, and people with blood group O (antigen O) produces antibodies for both [38]. Therefore, patients with blood types A or B may be more vulnerable to infections like SARS-CoV-2.

One of the points of in the present study is that patients with blood type B showed more severe disease compare to patients with other blood types, while mortality was not different between patients with various blood groups. Here, the role of different types of therapies can be considered.

Interestingly, unlike other studies [12,18-20], that showed the protective effect of Rh$^-$, the patients with Rh$^-$ needed more ventilation. More studies are needed to investigate the role of drugs, according to patients' genetics, or "personalised medicine" in the treatment of patients.

Moreover in the present study, other risk factors for COVID-19 infection aggravation such as older age, hypertension, and diabetes were matched between blood groups, and the results between severe and non severe COVID-19 groups were unaffected after these adjustments. While the aforementioned studies did not consider other risk factors for COVID-19 infection aggravation.

Finding of the current study provides some new information about blood types' correlation with COVID-19 infection severity. However, more molecular research is needed to discover the relationship between the virus and the structure of blood groups and also the influence of treatment in each patient.

Limitation(s)

The present study had some limitations. First, authors did not have access to all patient's Polymerase Chain Reaction (PCR) results. Though COVID-19 infection was confirmed in the clinical setting as a sum of laboratory results (CRP, lymphopenia), recent contact of the subject with an infected individual, and chest CT scan. Second,

the sample size of the study was not very large, due to the limited COVID-19 patients with disease severity data. Regional selection and gender stratification need to be considered. More studies are needed to confirm these findings with a larger sample size and among individuals of different ethnicities.

CONCLUSION(S)

Results of the present study suggested that patients with blood type B were significantly more prone to develop severe to critical illness when compared to other blood types. To reach a definite conclusion regarding the role of blood groups and the incidence of COVID-19, especially its protective effect, more studies are needed in our country, Iran, as well as other countries with a high prevalence of this virus.

Author contributions: All authors contributed to the study. ZK designed and conducted the research and contributed to data analysis and manuscript preparation. MK carried out the assays and contributed to data collection. ZHK contributed to data collection and writing the manuscript. NM contributed to samples and data collection. RG and ME provided the samples. All authors read and approved the final manuscript.

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