AIMS Medical Science

AIMS Medical Science, 10(1): 1–13.
DOI: 10.3934/medsci.2023001
Received: 03 September 2022
Revised: 21 November 2022
Accepted: 22 December 2022
Published: 16 January 2023

http://www.aimspress.com/journal/medicalScience

Research article

The correlation between severe complications and blood group types in COVID-19 patients; with possible role of T polyagglutination in promoting thrombotic tendencies

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Abstract: Introduction: Coronavirus disease-19 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is still posing detrimental effects on people. An association between contracting COVID-19 and the ABO blood group type has been determined. However, factors that determine the severity of COVID-19 are not yet fully understood. Thus, the current study aimed to investigate whether the ABO blood group type has a role in the severity of complications due to COVID-19. **Materials and methods:** Eighty-Six ICU-admitted COVID-19 patients and 80 matched-healthy controls were recruited in the study from Baish general hospital, Saudi Arabia. ABO blood grouping, complete blood count (CBC), CBC-derived inflammatory markers, coagulation profile, D-

Dimer and anti-T antigen were reported. **Results:** Our data showed that patients with blood groups O and B are more protective against severe complications from COVID-19, as compared to patients with blood groups A and AB. This could be partially attributed to the presence of anti-T in blood group A individuals, compared to non-blood group A. **Conclusion:** The current study reports an association between the ABO blood group and the susceptibility to severe complications from COVID-19, with a possible role of anti-T in driving the mechanism of the thrombotic tendency, as it was also correlated with an elevation in D-dimer levels.

Keywords: COVID-19; ABO blood group; D-dimer; anti-T; severity

1. Introduction

The rapid spread of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), at the end of 2019, still exhibits a huge burden and challenges on healthcare systems and economies including testing resources and patients' management. The novel coronavirus disease 2019 (COVID-19) might lead to severe acute respiratory syndrome and has shown association with increased morbidity and mortality especially among elderly patients and patients with commodities such as diabetes, hypertension, obesity, and cardiovascular diseases [1–3]. In addition, COVID-19 has several non-respiratory complications such as systematic complications including thrombosis, septic shock, and disseminated intravascular coagulopathy (DIC) [4].

Studies have suggested that ABO blood group system is not only a potential risk factor for the susceptibility and severity of COVID-19 [5,6], but also for (i) viral infections such as Hepatitis B virus, Middle Eastern respiratory syndrome coronavirus (MERS) and severe acute respiratory syndrome coronavirus (SARS) [6,7] and (ii) other non-viral diseases such as myocardial infarction, cancer, acute renal injury, and venous thromboembolism [7,8].

The current study aimed to (i) determine and correlate the ABO blood group type with D-dimer levels among intensive care unit (ICU)-admitted COVID-19 patients, and (ii) correlate the ABO blood group type with the T polyagglutination in Jazan city, Saudi Arabia.

2. Materials and methods

The current study was a case-control study, which involved a total of 86 ICU-admitted COVID-19 patients (42 males and 44 females) and 92 healthy individuals (47 males and 45 females). The patients and controls were recruited from Baish General Hospital, Jazan region, Saudi Arabia. All COVID-19 patients were confirmed positive for SARS-COV-2 using RT-polymerase chain reaction (RT-PCR). The ICU admission of the patients was based on the Saudi Arabia ICU-admission criteria [9].

2.1. Sample collection

Venous blood samples were collected from patients and control in ethylenediaminetetraacetic acid (EDTA) and sodium citrate anticoagulated tubes. The EDTA tube was used for determining complete blood count (CBC) and ABO blood typing. The sodium citrate tube was used for coagulation profile and D-dimer analysis.

2.2. Complete blood count analysis

The CBC was obtained by analyzing the EDTA tube using Sysmex XN–1000 Hematology Analyzer (Kobe, Japan).

2.3. Complete blood count-derived inflammatory markers

The CBC-derived inflammatory markers, including neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and platelet/neutrophil ratio (PNR), were calculated as previously described [10,11].

2.4. Coagulation profile and D-dimer measurement

Coagulation profile (prothrombin time [PT], activated partial thromboplastin [aPTT]) and D-dimer levels were measured using the Stago compact analyzer (Diagnostica Stago, Asnieres sur Seine, France).

2.5. ABO blood group typing

Red cell suspension prepared from samples collected from COVID-19 patients were reacted with antisera A & B and were observed for agglutination indicating the presence or absence of corresponding antigen. ABO blood group antisera were obtained from Crescent Diagnostics (Jeddah, KSA).

2.6. Anti-T testing

The anti-T test was performed by mixing one drop of anti-T (Arachis hypogaea lectin) with one drop of 3–5% suspension of the patient's RBCs. After 15 minutes of incubation at room temperature and centrifugation at 1000 rpm for one minute, agglutination was observed macroscopically indicating positive results.

2.7. Ethical approval

The study was approved by the Jazan Health Ethics Committee "Jazan IRB", Ministry of Health (project no. 2053) and carried out according to the Declaration of Helsinki.

2.8. Statistical analysis

GraphPad Prism version 9 (San Diego, USA) was used for the statistical analysis. A chi-squared test was performed to test non-parametric data, and student's unpaired t-test was applied for group comparison of parametric data. The CBC data were presented as mean ± standard deviation (SD). *P*-value of less than 0.05 was considered statistically significant.

3. Results

3.1. Demographic data

Eighty-six ICU-admitted COVID-19 patients (42 males and 44 females; patient group) and ninety-two healthy controls (47 males and 45 females; control group) were recruited. The male to female ratio was almost 1:1 in both groups. The demographic data of the patients and control groups are shown in Table 1. There were no significant differences between the two groups in number, gender and age ($P > 0.05$).

Table 1. Complete blood count and CBC-derived inflammatory markers in the study cohort. Data are presented as mean ± SD. Unpaired student t-test was used to assess the significant differences between the patients and control groups.

Parameters	Patients	Controls	*P* value
	Mean ± SD	Mean ± SD	
Number (male/female)	86(42/44)	92(47/45)	>0.05
Age (years)	59.6 ± 18.5	55.1 ± 25.3	>0.05
WBCs ($\times 10^9$/L)	12.8 ± 10.3	6.6 ± 1.8	<0.0001
Neutrophils ($\times 10^9$/L)	9.9 ± 20.2	2.9 ± 1.3	0.0002
Lymphocytes ($\times 10^9$/L)	1.6 ± 1.4	2.7 ± 0.8	<0.0001
Monocytes ($\times 10^9$/L)	0.6 ± 0.9	0.6 ± 0.2	>0.05
Eosinophils ($\times 10^9$/L)	0.1 ± 0.1	0.3 ± 0.2	<0.0001
Basophils ($\times 10^9$/L)	0.05 ± 0.07	0.04 ± 0.02	>0.05
RBCs ($\times 10^{12}$/L)	3.9 ± 0.8	5.1 ± 0.5	<0.0001
Hemoglobin (g/dL)	10.6 ± 2.0	13.7 ± 1.9	<0.0001
Hematocrit (%)	33.5 ± 6.4	42.1 ± 5.8	<0.0001
MCV (fL)	84.9 ± 9.0	82.3 ± 6.6	0.0176
MCH (pg)	26.9 ± 3.3	26.9 ± 2.6	>0.05
MCHC (g/dL)	31.7 ± 1.8	32.6 ± 0.9	<0.0001
RDW (%)	15.2 ± 2.9	16.8 ± 1.9	<0.0001
Platelets ($\times 10^9$/L)	215 ± 115	286 ± 67	<0.0001
NLR	6.2 ± 5.5	1.1 ± 1.5	<0.0001
PLR	134 ± 215	104 ± 79	>0.05
PNR	21.7 ± 19	98 ± 51	>0.05

Note: WBCs: White blood cells; RBCs: Red blood cells; MCV: Mean cell volume; MCH: Mean cell hemoglobin; MCHC: Mean cell hemoglobin concentration; RDW: Red cell distribution width; NLR: Neutrophil/lymphocyte ratio; PLR: Platelet/lymphocyte ratio; PNR: Platelet/neutrophil ratio.

The overall CBC parameters showed an abnormal pattern in the patient group (Table 1). Patients had higher WBC, neutrophils ($P < 0.05$) and basophils ($P > 0.05$) counts as compared to the control group. The lymophcytes, eosinophils, ($P < 0.05$) and monocytes ($P > 0.05$) were low in patient group

as compared to the control group. Furthermore, the RBCs, hemoglobin, hematocrit, red cell distribution width (RDW) and mean cell hemoglobin concentration (MCHC) were significantly low in the patient group as compared to control group ($P < 0.0001$; Table 1). On the other hand, the mean cell volume (MCV) was significantly high in patients as compared to control (Table 1).

3.2. Complete blood count-derived inflammatory markers

The inflammatory markers i.e., NLR ($P < 0.0001$) and PLR ($P > 0.05$) were high in patients compared to controls (Table 1). PNR values were less in patient group compared to control group ($P > 0.05$; Table 1).

3.3. Coagulation profile and D-dimer measurement

The coagulation profile tests (PT and aPTT) were markedly prolonged in the patient group as compared to the control group ($P < 0.0001$; Table 2). The D-dimer levels were elevated in patients (Table 2).

Table 2. Coagulation profile and D-dimer in the study cohort. Data are presented as mean ± SD. Unpaired student t-test was used to assess the significant differences between the patients and control groups.

Parameters	Patients	Controls	*P* value
	Mean ± SD	Mean ± SD	
Prothrombin time (seconds)	18.1 ± 7.7	12.5 ± 1.9	<0.0001
Activated partial thromboplastin time (seconds)	42.6 ± 12.8	31.7 ± 5.2	<0.0001
D-Dimer (ng/mL)	4.1 ± 6.5	NA	

Note: NA: Not available.

3.4. ABO blood group in the study cohort

The ABO group typing analysis revealed the following sequence A > O > B > AB in the patient group (Table 3). Out of 86 patients, 34 (39.5%) had blood group A, 22 (25.6%) blood group O, 17 (19.8%) blood group AB, and 13 (15.1%) patients had blood group B. On the other hand, in the control group the blood group is in 55 out of 92 representing 59.8%, followed by blood group A (28.3%), blood group B (10.9%) and blood group AB (1.1%).

Table 3. Distribution of ABO group systems in the study cohorts.

Blood group	Patients number (%)	Controls number (%)
O	22 (25.6)	55 (59.8)
A	34 (39.5)	26 (28.3)
B	13 (15.1)	10 (10.9)
AB	17 (19.8)	1 (1.1)
Total number	86 (100)	92 (100)

3.5. Anti-T analysis

The anti-T analysis was positive in 28 out the 86 patients and negative in 58 patients as well as healthy controls (Table 4).

Table 4. Anti-T in the studied population.

Anti-T	Patients (n = 86)	Controls
Positive	28	0
Negative	58	92

3.6. Association of ABO blood grouping and anti-T analysis

Twelve patients out of the 34 with blood group A were anti-T positive, followed by 9 out of 22 patients with blood group O (Figure 1).

3.7. Association of ABO blood grouping vs D-dimer levels

The D-dimer levels were found to be more elevated in patients with blood group A. This elevation was twice the D-dimer levels found in blood O, B, and AB (Figure 1).

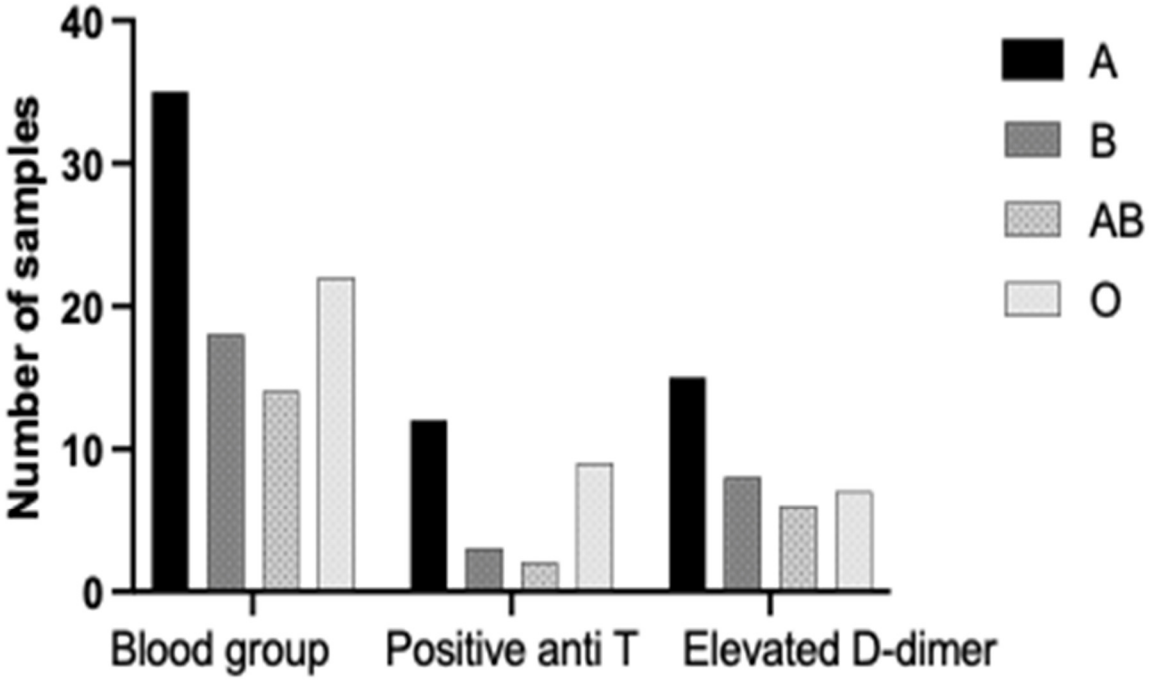

Figure 1. Distribution of ABO blood types, positive anti T antibodies and D-dimers levels in patients with COVID-19.

4. Discussion

The current study investigated the prevalence of ABO blood group system in ICU-admitted COVID-19 patients and correlated each ABO blood group system with other biochemical parameters including D-dimer, anti-T polyaggulintation.

The current study reported abnormalities in the CBC parameters, including increased WBC (leukocytosis), which is a feature of COVID-19 infection. These finding are in agreement with previous reports [10–12]. The WBC count have been reported to be high in COVID-19 patients. In addition, several studies also reported high WBC count in severely, ICU, infected COVID-19 patients as compared with mild infected COVID-19 patients [12]. Our data showed high neutrophil count (neutrophilia), low count of lymphocytes, RBC count, and low hemoglobin concentration in the ICU-admitted COVID-19 patients as compared to the matched healthy controls. Indeed, neutrophilia and lymphopenia have been suggested to be associated with severity and mortality in COVID-19 patients [10,13,14]. Similarly, the inflammatory markers, NLR and PLR were found to be elevated and lower PNR in the patients cohort, similar to other reported studies [10,11]. The inflammatory response is a hallmark of COVID-19 infection and have been associated with the cytokine storm [15].

The current study showed that majority of the patients who were shifted to ICU due to COVID-19 were patients with blood group A (39.5%) followed by O (25.6%) as compared to those with other ABO blood group types (Figure 1). It is worth mentioning that O and A blood group types are most common blood group system among the Saudi population with frequencies of ~59% O and ~29% A

in Jazan area respectively [16–18]. The above data are consistent with the previous studies suggesting a link between the susceptibility to SARS-CoV-2 infection and ABO blood group types [19–21]. A recent study by Muñoz-Diaz et al. (2021) reported a strong association between susceptibility to COVID-19 and the ABO blood group types [5]. Individuals with blood group A had higher risk of acquiring COVID-19 while those with blood group O had lower susceptibility [21]. Similarly, SARS has also been found to be more frequent in individuals with blood group A [22].

Furthermore, it has also been reported that the severity of COVID-19 and mortality risk, as well as the risk of hospitalization, are higher in patients with blood group A as compared to those with non-blood group A [5]. Importantly, ICU admitted patients with blood group O were reported to be less susceptible to severe complications/manifestations of COVID-19, as indicated by current data and others [23]. Similar findings have also been observed among females with COVID-19 [24]. It was suggested that anti-A antibody, found in persons with blood group O or B, appears to antagonize the link between SARS-CoV-1 and the receptor for angiotensin-converting enzyme 2 (ACE2), which is expressed by the target cells of the host [25]. This could explain the reason behind the correlation between the ABO blood type and COVID-19 severity as shown in the current study.

It is reasonable to consider and address that ABO blood types may also be possible determinants of susceptibility to SARS-CoV-2 infection and its severity, as the virus, SARS-CoV-2, also binds to ACE2 [26,27]. Moreover, it has also been found that critically ill COVID-19 patients with blood group type A or AB are linked with an increased risk of requiring mechanical ventilation, continuous renal replacement therapy (CRRT), and prolonged stay in ICU, as compared to patients with blood group B or O [28]. However, further studies are required to identify the biological mechanisms underpinning these findings. Kibler et al. (2020) declared that patients with A blood group were especially prone to develop the disease and showed unfavorable outcomes [29]; which is consistent with the findings of our study. Furthermore, Zhao et al. (2020) found that the incidence, severity, and mortality of COVID-19 were more common in non-blood group O, while individuals with blood group O were protected from contracting COVID-19 [19].

Several studies have been linked between blood group types and susceptibility and severity to bacterial, parasitic and viral infection including severe acute respiratory syndrome (SARS-CoV-1) [22,30,31]. The susceptibility to SARS-CoV-1 infection (which is up to 70% similar to SARS-CoV-2 [32], has been linked to ABO polymorphism [22]. Other investigators have found the presence of anti-A antibodies could be a protective against SARS-CoV-1 [25,33]. This is mainly driven by anti-A antibody inhibiting the binding of angiotensin converting enzyme-2 to angiotensin converting enzyme-2—expressing on the cells [22].

Although, the exact mechanism of the interaction of ABO blood group and SARS-Cov2 is not fully understood and needs to be elucidated, several studies have postulated different mechanism for the influence of ABO blood groups on modulating COVID-19 infection and SARS-CoV-2 binding to the cells [34]. Silva-Filho et al. (2020) have linked the influence of ABO blood group on COVID-19 infection mainly blood group A through the modification of sialic acid containing receptors mainly modulation of the carbohydrate-carbohydrate interactions with host cells allowing potentially more binding of the virus (SARS-CoV-2) with host cell [34].

Other studies have suggested that receptor binding domain SARS-CoV-2, which is main part responsible for the COVID-19 infection [35] could bind to blood group A [36]. Moreover, a possible mechanism in reducing the susceptibility and severity of COVID-19 infection is attributed to the anti-A and anti-B antibodies in non-blood group A, non-blood group B and non-blood group AB, which

can inhibit the interaction between the spike protein of SARD-CoV-2 and the receptor on the target cells [25], or could be due to their ability to opsonize the virus [37]. Furthermore, the levels of anti-A and anti-B play a key role in the COVID-19 infection, as those will high levels of anti-A and anti-B antibodies lower COVID-19 infection [38–40]. COVID-19 infection could be also modulated by the host transmembrane protease serine subtype 2 [41,42].

The current study also showed elevated D-dimer levels in COVID-19 patients with prolonged PT and aPTT; consistent with the findings of previous studies [11,43]. Elevated D-dimer levels have been linked to severity and mortality in COVID-19 patients [44]. As D-dimers are produced through fibrinolysis by degrading the fibrin clots, hence its elevated levels indicates thrombotic tendency in COVID-19 patients [11]. Elevated D-dimer levels are suggested to be associated with disease complications, including COVID-19 severity. Elevated D-dimer levels have been proposed to be a surrogate and reliable prognostic marker of increased mortality among COVID-19 in hospitals and aiding in early intervention regimes among COVID-19 patients [45,46]. In the current study elevated D-dimer levels were more pronounced in blood group A as compared to non-blood group A.

The role of coagulation system in thrombotic tendency and manifestations of COVID-19 is not fully understood and needs to be elucidated. Furthermore, hypercoagulability is multifactorial, and RBC hemolysis is a known risk factor. RBC hemolysis contributes to hypercoagulability and the subsequent prothrombotic tendency in COVID-19. Our findings show the presence of anti-T antibody in patients with blood group A. Anti-T is a naturally occurring antibody against T-antigen on the RBC's membrane, renal endothelium and platelets [47]. In normal individuals with a normal physiological mechanism, the T-antigen has hidden receptors (crypt antigens) on the RBC's membrane. In several clinical conditions such as severe infections, malignancies, and due to some idiopathic reasons [19], the T-antigen on the RBC membrane is unmasked and exposed. RBC hemolysis externalizes the inner negatively charged membrane phospholipids to the outer surface, mainly phosphatidylserine (PS) [48]. RBCs with exposed PS have the ability to adhere to endothelial cells [49]. Furthermore, they enhance and support thrombin generation and tissue factor expression in many disorders including beta-thalassemia and sickle cell disease [50,51]. Thrombin is known to be a key player not only in haemostasis and thrombosis but also in driving inflammation, vascular endothelium regulation, and blood cells activation [52].

All of these conditions, we hypothesized, set a platform for thrombin to orchestrate fibrin formation. Once fibrin clot formation is initiated, the counterpart mechanism in human body; fibrinolysis, dissociates and breaks down the fibrin clot into fibrin degradation products (FDPs), where the D-dimer is part of these FDPs derived from cross linked fibrin.

The current study is a preliminary study that investigated the possible role of anti-T in driving the thrombotic tendency in COVID-19 and its link to ABO blood group types. However, similar to other studies, the study has some limitations to it, such as small sample size and lack of details related with co-morbidities.

5. **Conclusions**

Our data suggest that patients with blood group A are more susceptible to serious complications due to COVID-19, whereas patients with blood group O or B are less likely to suffer from severe complications due to COVID-19 as per their admissions in ICU. It is worthwhile to conduct this study

on a large number of patients and look at affected markers and possible correlations with the ABO blood group type.

Acknowledgments

The authors extend their appreciation to the Deputyship for Research and Innovation, Ministry of Education in Saudi Arabia for funding this research work through the project number ISP22-1.

Conflict of interest

All authors have no conflict of interest in this manuscript.

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