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Study of Associations between ABO Blood Group and COVID-19 Infection, ICU Need and Death in a Tertiary Care Centre

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Abstract: ***Introduction: The world is experiencing COVID-19 pandemic. Earlier ABO and Rh blood group systems were associated with many infectious diseases. Currently a few studies have shown association between blood groups and COVID-19 infection. Objective of this study is to determine the associations between ABO blood group and COVID-19 infection, ICU need and death. Methods: A retrospective observational study was done at Emergency department, SDMMCH, Dharwad from March 2021 to July 2021. Clinical and ABO blood group data of patients were collected. Data was analyzed using chi-square test to determine the association between blood groups and COVID-19 susceptibility, need of ICU and mortality. Results: In our present study, out of 481 patients who fulfilled the inclusion criteria 158 cases (32.8%) were triaged as mild, 153 (31.8%) as moderate and 170 (35.3%) as severe. Among our study population 44.7% were of A blood group, 26.2% were O, 23.7% were B, and 5.4% were AB. Of 191 (39.7%) patients admitted in ICU, 131 (60.9%) were of blood group A. In our study 68 (14.1%) died of which 46 were of Blood group A and had highest mortality rate. Conclusions: In our study we observed that blood group A had more susceptibility for COVID-19 infection, required ICU care and had highest mortality compared to other ABO blood groups.***

Keywords: COVID-19, ABO blood groups, Intensive Care Unit

1. Introduction

The world is undergoing one of the most arduous pandemic by COVID-19 caused by SARS-CoV-2, a novel Corona Virus. COVID-19 has been burden to the healthcare and economic system , is global concern because it spreads easily via respiratory droplets containing virus particles and symptoms ranging from being asymptomatic to severe pneumonia[1]. Early diagnosis of serious illness and effective early intervention are the fundamental measures for the reducing mortality. There are various studies on biomarkers for detecting the susceptibility and severity of COVID-19 patients. ABO blood group system discovered by Karl Landsteiner is an inherited, non-modifiable trait whose antigens are glycoprotein's present on erythrocytes and are encoded by co-dominant alleles (A and B) present in Chromosome 9. Individuals can be A, B, AB, or O depending on the antigens present or absent on their erythrocyte surface[2]. Blood types are also characterized as positive or negative depending on the presence of the Rhesus (Rh) factor protein. Various studies have found an association between ABO blood group and number of non infectious and infectious diseases and their severity as in rheumatologic and cardiovascular diseases, cancers, and viral diseases including influenza A (H1N1), severe acute respiratory syndrome (SARS) [3-9]**.** The underlying mechanism is still inconclusive though several theories have been proposed to elaborate the mechanism of this association which need to be validated. In the cellular model, spike protein adhesion to ACE-2-expressing cell lines was

specifically inhibited by monoclonal or natural human anti-A antibodies. Thus, individuals with non-A blood types, i,e O or B blood type, which produce anti-A antibodies, may be less susceptible to SARS-CoV-2 infection due to the inhibitory effects of anti-A antibodies while blood group type A has high odds of getting infected [10,11]. Rh (D) positive blood group is also associated with increased COVID-19 infection and mortality. Many studies have been supported the finding that blood group A have higher risk of COVID-19 infection and mortality and blood group O had decreased risk [12 -17].Contradicting observations were observed by Latz et al, where higher risk of infection was observed with individuals of blood group B instead of A [18]. COVID-19 is a novel virus, and it is indefinite whether blood groups have any impact on COVID-19 susceptibility and severity .This recent conflict to the literature has added uncertainty to the field. Hence, our objective is to determine whether the risk of COVID-19 infection and severity of clinical outcomes are associated with ABO blood groups and antibodies.

2. Methods

Objective of this study: To determine the associations between ABO blood group and COVID-19 infection, ICU need and death.

Study design and participants

This study was a single centered retrospective observational study and was conducted in Emergency department at SDM college of medical sciences and hospital Dharwad, from March to July 2021. Data were retrieved from the medical records of adult patients who fulfilled the inclusion and exclusion criteria of the study. Informed consent was waived off. **Inclusion criteria:** Patients aged >18 years, of either sex, admitted to Emergency medicine department with confirmed COVID-19 infection by either reverse-transcriptase-polymerase chain reaction (RT-PCR) or rapid antigen testing (RAT) and who were tested for ABO blood grouping and typing. **Exclusion criteria:** Patients aged <18 years and who were not admitted to hospital. COVID positive patients with no data regarding ABO blood grouping. Patients with multiple contradictory ABO type, pregnant COVID-19 patients. After obtaining approval and clearance from the institutional ethics committee of SDM college of Medical Sciences and Hospital, the patients admitted during five months, fulfilling the inclusion criteria were identified from medical records and were enrolled into the study. Patients were categorized as mild, moderate or severe COVID-19 cases, based on the clinical features and the place of initial care facility was determined as per ICMR/AIIMS-COVID-19 National task force/joint monitoring group dated 22nd April 2021 (Figure 1) and treated as per standard of care.

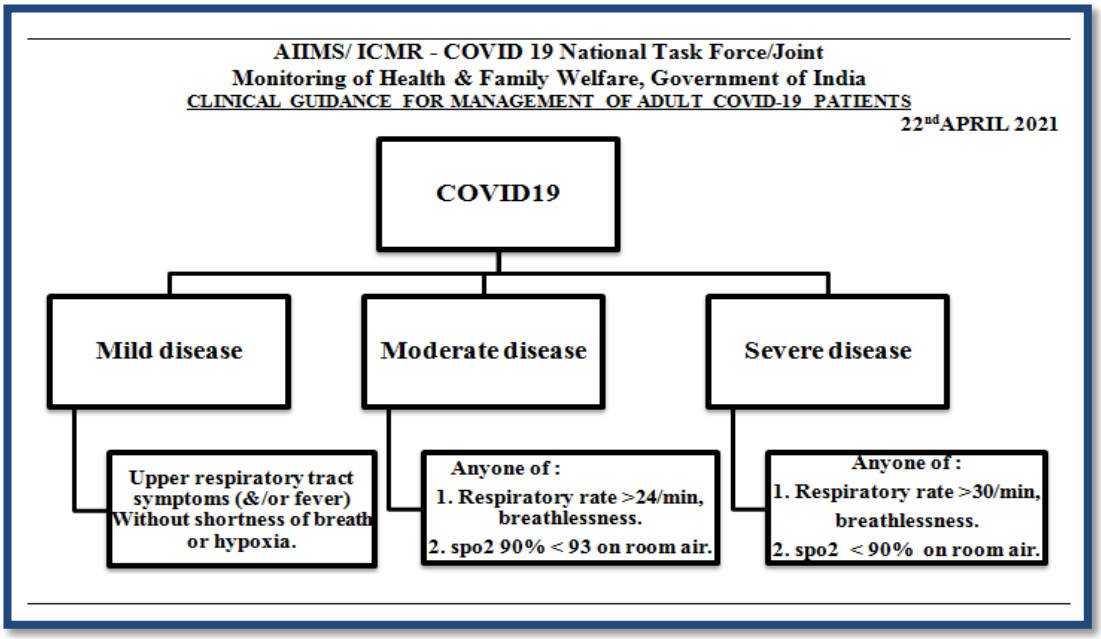

Figure 1: AIIMS/ICMR COVID-19 National task force [19]

3. Statistical Analysis

The data collected was entered into MS Excel sheet and was analyzed using SPSS 20.0 version. Socio demographic data such as age, gender, co-morbidities are presented as descriptive statistics namely mean, standard deviation, frequency and percentage. Association between two variables was analyzed using Pearson's Chi- square test. P-value <0.05 was considered as statistically significant. Data are presented in the form of tables, figures and graphs wherever necessary.

4. Results

This study was done from the data of patients admitted over a period of five months between March 2021 and July 2021. It was during the peak of the second wave in Dharwad, Karnataka, India. Total 1625 COVID-19 cases were admitted to our hospital during five months period, out of which 481 patients were admitted in Emergency medicine department and fulfilled our inclusion and exclusion criteria. Study flow chart as been described in Figure 2.

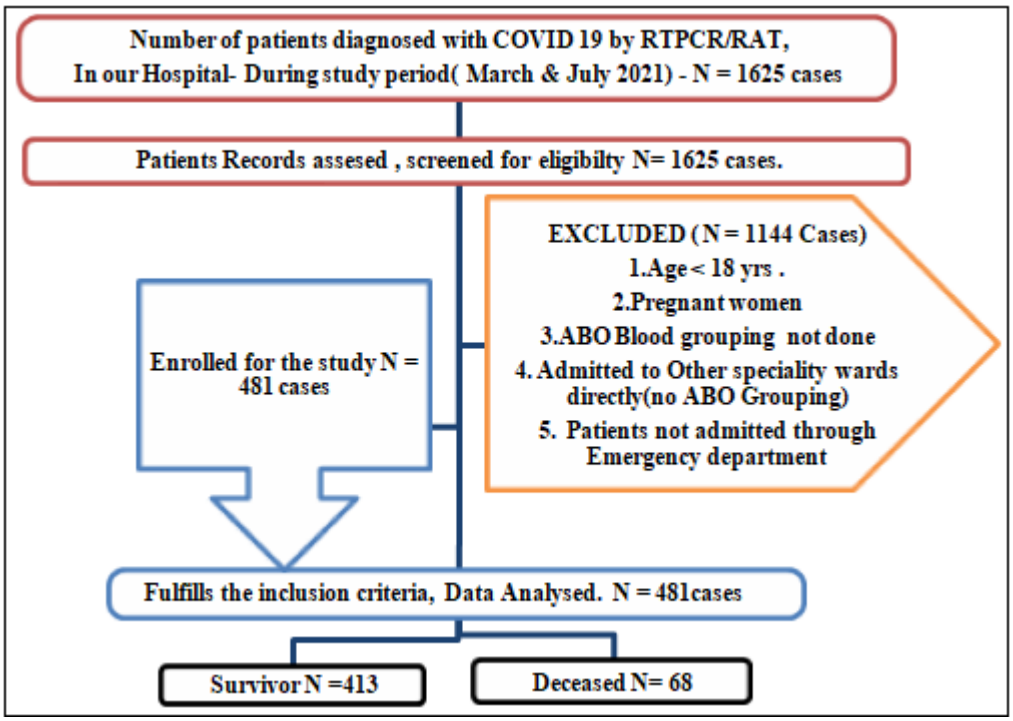

Figure 2: Study Flow Chart

Among 481 study patients, 315 (65.5%) were males and 166 (34.5%) were females, with mean age of 54.337±16.29 years. Common presenting complaints were fever (N=315, 65.5%), shortness of breath (N=257, 53.4%), cough (N=183, 38%), myalgia (N=154, 32 %), headache (N=36, 7.5%), sore throat (N=7, 1.5%), diarrhea (N=21, 4.4%). Most of our patients had one or other underlying comorbid condition, mostly diabetes mellitus (N=223, 46.4%), hypertension (N=210, 43.7%), obstructive airway disease (N=71,14.8%), ischemic heart disease (N=34, 7.1%), chronic kidney disease (N=28, 5.8%), cerebrovascular accident (N=16, 3.3%), chronic liver disease (N=4, 0.8%). On arrival, patients were categorized into mild, moderate or severe COVID cases, based on the clinical features and provided with standard of care respectively as per ICMR/AIIMS-COVID-19 national task force/joint monitoring group dated 22nd April 2021 (Figure 1). Out of 481 patients, 158 patients were mild case(32.8%),153 patients were moderate (31.8%), and 170 patients severe case(35.3%).Of which 290 (60.3%), 191 (39.7%) patients were admitted to ward, ICU respectively. In these 481 COVID-19-infected patients majority were blood group A, followed by O, B, and AB, which is depicted in the pie chart (figure 3). We found positive association between blood group A and risk of COVID-19 infection. As shown in Figure 4, Rh Positive were more predisposed to COVID-19 infection than Rh Negative.

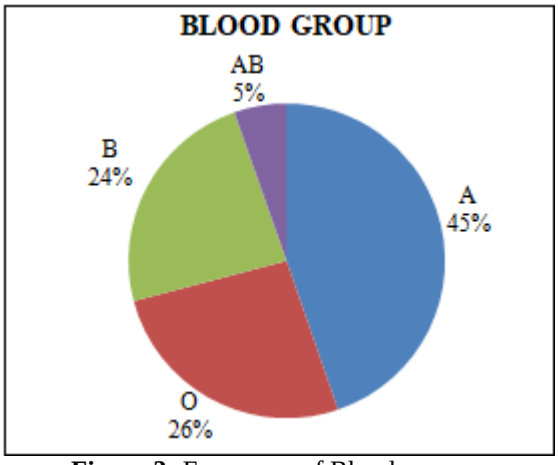

Figure 3: Frequency of Blood groups.

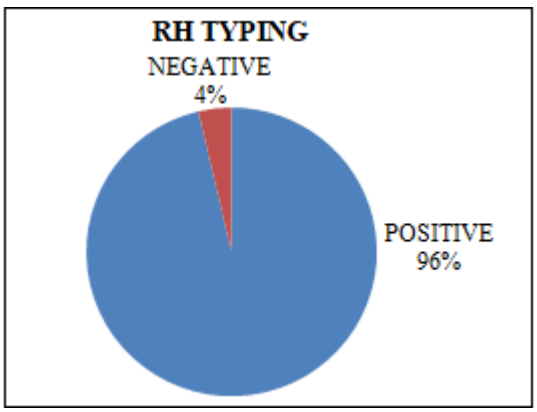

Figure 4: Frequency distributions of Rh Typing.

Chi-square test was used to compare the blood groups and the severity of the COVID-19 patients. Of 481 patients 170 (35.3%) belonged to Severe category, in that 116 (53.9%) were of Blood group A, 24 (21.1%) were of Blood group B, 25(19.8%) were Blood group O and 5 (19.2 %) were of Blood group AB. Hence blood group A patients were of

severe COVID-19 than other blood groups, therefore there is positive association between blood group and severity of COVID-19 (p value<0.001), as depicted in Table I.

Table I: Blood group distributions in Mild, Moderate , Severe COVID-19 patients.

COVID-19 Severity Grading	Blood Group				Total	Pearson Chi Square Value	P value
	A	AB	B	O			
	% Within Blood Group (N)	% Within Blood Group (N)	% Within Blood Group (N)	% Within Blood Group (N)	% Within Blood Group (N)		
Mild(N)	20.9% (45)	38.5% (10)	43.9% (50)	42.1% (53)	32.8% (152)	61.024[a]	<0.001
Moderate (N)	25.1% (54)	42.3% (11)	35.1% (40)	38.1% (48)	31.8% (153)		
Severe (N)	53.9% (116)	19.2% (5)	21.1% (24)	19.8% (25)	35.3% (170)		
Total (N)	100% (215)	100% (26)	100% (114)	100% (126)	100% (481)		

Of 481 patients, 191 (39.7%) were admitted to ICU while 290 (60.3%) towards. Patients with blood group AB, B and O were admitted more towards than ICU. Chi-square analysis was done to know the association of blood groups and their admission status. We found that blood group A was associated with highest number of ICU admission than compared to AB, B, O groups with statistical significance (p value <0.001) as depicted in Table II.

Table II: Blood group distributions in COVID-19 patients as per their admission status.

COVID-19 Severity Grading	BLOODGROUP				Total	Pearson Chi Square Value	P value
	A	AB	B	O			
	% Within Blood Group (N)	% Within Blood Group (N)	% Within Blood Group (N)	% Within Blood Group (N)	% Within Blood Group (N)		
Mild (N)	20.9%(45)	38.5%(10)	43.9%(50)	42.1%(53)	32.8%(152)	61.024[a]	<0.001
Moderate (N)	25.1%(54)	42.3%(11)	35.1%(40)	38.1%(48)	31.8%(153)		
Severe (N)	53.9%(116)	19.2%(5)	21.1%(24)	19.8%(25)	35.3%(170)		
Total (N)	100%(215)	100%(26)	100%(114)	100%(126)	100%(481)		

Also we aimed to find the association of ABO blood groups with deceased COVID-19 patients; blood group distribution was compared between deceased and recovered COVID-19-infected patients as shown in Table III. Of 481 patients, 413 (85.9%) recovered by the time of discharge, 68 (14.1%) succumbed. Among 68 deceased patients, 46 were of blood group A, 12 of B, 8 of O 2 of AB blood group. Blood group A patients had highest mortality rate than other blood groups (p Value<0.001).

Table III: Blood group distributions between deceased and recovered COVID-19-infected patients

Patient Condition at Discharge	Blood Group				Total	Pearson Chi Square Value	P value
	A	AB	B	O			
	% Within Blood Group (N)	% Within Blood Group (N)	% Within Blood Group (N)	%Within Blood Group (N)	% Within Blood Group (N)		
Dead(N)	21.4%(46)	7.7%(2)	10.5%(12)	6.3%(8)	14.1%(68)	17.741[a]	<0.001
Survivor(N)	78.6%(169)	92.3%(24)	89.5%(102)	93.6%(118)	85.9%(413)		
Total(N)	100%(215)	100%(26)	100%(114)	100%(126)	100.0%(481)		

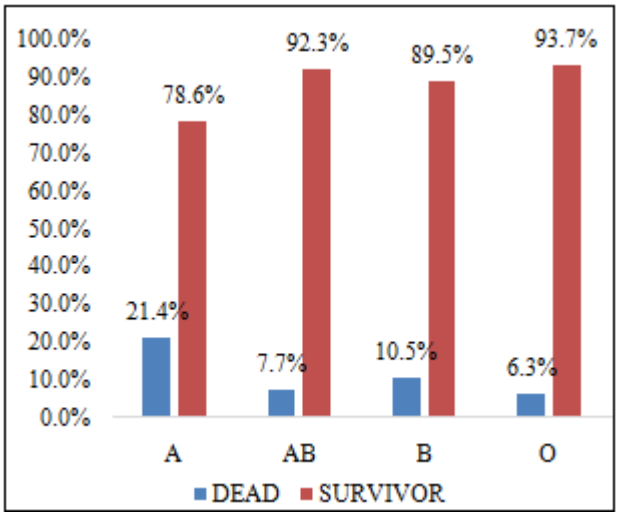

Figure 5: Blood group distributions between deceased and recovered COVID-19-infected patients.

5. Discussion

COVID-19 has developed as a pandemic with various number of mutations and spreading rampantly. Early identification of prognostic indicators is an essential foundation for any pandemic to promptly identify the severity of patients' condition and plan treatment. Hence a simple and elective prognosticator is important for triaging and to guide treatment strategies of potentially critical patients, with the aim of reducing the mortality in the pandemic. Currently no known single biological biomarker can predict the severity and risk of being infected by COVID-19. Several studies have been conducted across the globe to determine the correlation between COVID-19 severity with inflammatory markers and CT severity score. However these investigations are uneconomical, time consuming, not readily and easily available in the primary centers. As Emergency department is face of the hospitals, it is important for the emergency physicians to know about the biomarkers and its association with COVID-19 , which in turn helps them in triaging the patients, allocation of

resources and treatment of critical patients. Hence in our study we seek to analyze the association of ABO blood groups for risk of COVID-19 infection in Emergency medicine department. However, there are only limited number of Indian data and few ongoing studies across the world to determine the associations between ABO blood group and COVID-19 infection, ICU need and death. ABO and Rh blood group types are the most widely used blood groups in clinical studies. The ABO blood group system basically contains two antigens, namely, A and B. The antigen coding gene is located on chromosome 9q34.1 and 9q34.2. It consists of three alleles (A, B, and O) and is four phenotypes (A, B, O, and AB). Several mechanisms have been proposed to explain the association between ABO blood groups and COVID-19 susceptibility, these include anti- A antibodies, production of glycan antigens by SARS-CoV-2, influence of coagulation system and genetic variations in the ABO gene. The SARS-CoV-2 enters host cells by interacting with the angiotensin converting enzyme-2 receptor located on human cells. The virus binds to the ACE-2 through S1 glycoprotein, while the invasion is accomplished through the S2 glycoprotein [20]. Naturally occurring anti-A antibodies in group O individuals bind to SARS-CoV-2 S protein, blocking the interaction between the SARS-CoV-2 S protein and ACE-2 receptor, which may prevent viral entry into the lung epithelium. Group A individuals have increased Angiotensin converting enzyme-1 activity which may lead to increased COVID-19 severity[10]. A study by Gerard et al. reported that the COVID-19 infection was less prevalent among blood groups O and B, which have anti-A antibodies, while it was higher in the groups lacking the anti-A antibodies[11]. Another possible mechanism is that the SARS-CoV-2, while replicating in the host epithelium, produces glycan antigens similar to those of the host A or B antigens, according to the blood group of the host. SARS-CoV-2 S protein may express ABH glycans, which may enhance the affinity of SARS-CoV-2 for ACE-2 receptor. SARS-CoV-2 target cells that ABH glycans (not expressed by group O individuals) may serve as alternative, lower-affinity receptors for SARS-CoV-2 S protein or bind other viral envelope structures[21, 22]. Some factors of the coagulation system have also been proposed to influence the severity of COVID-19 by expressing A and B antigens to increase their concentration and life span .Group A individuals have increased von Willebrand factor (VWF) and factor VIII levels which may lead to increased COVID-19 severity [23].Up regulation of ACE-2 receptor activity due to the presence of ABH gene polymorphisms (rs495828, rs8176740, rs8176746 and rs12683493) present in non-O blood groups [24] . By contemplating these pathogenesis of COVID-19 infection and proposed Mechanisms for association between ABO blood groups and COVID-19,the current study was conducted to observe the association of ABO and Rh blood groups on susceptibility of COVID-19 infection, disease severity, need of ICU care and mortality, among the patients who were admitted to our SDM hospital, Dharwad Karnataka, India. 481 patients were recruited for the study , of these it was observed that blood group A were more affected by COVID-19, whereas blood group O , B and AB had significantly lower risk of infection(Figure 3). There is a positive association between blood group A and risk of COVID-19 infection. Our results are in congruence with the studies of Zhao et al, Wu et al, Fan et al [12,16,25]. Hospital based case control study by Fan et al, concluded that an individual with blood group A had high risk of COVID-19 infection [25] . A study by Zhao et al, on COVID-19-infected patients reported that blood group A was higher in COVID-19-infected patients, and blood group O was associated with low risk of infection [12]. Liu et al, concluded that blood group A was significantly higher in infected individuals than in the healthy control group population, while blood group O in COVID-19-infected patients was significantly less [17].

As shown in (Table I) Chi-square test was used to compare the blood groups and the severity of the COVID-19 patients. We found Blood group A patients suffered from severe COVID-19 than other blood groups, which was statistically significant. In a meta-analysis of 10 studies by Liu et al., 5 out of 10 studies have analyzed the association between ABO and mortality due to COVID-19[17]. It reported that blood group A was associated with significantly increased risk of mortality when compared to non-A blood group. Muniz-Diaz et al. found that blood group A has significantly high risk of mortality as compared to non-A blood groups, whereas blood group O is associated with significantly low risk of mortality[26]. As depicted in (Figure 5), we also found that blood group A patients had high mortality than other blood groups. Unlike our reports Zietz et al, a cohort study showed contradictory findings that risk of death was increased in type AB and decreased in type A and B[13]. Contrasting to our results Latz et al concluded that there is no correlation between blood group and COVID-19 death [18].

Furthermore, meta-analysis and larger prospective studies are necessary to validate the proposed mechanisms for association between ABO blood groups and COVID-19, to eliminate the various confounders and also to authenticate the contradictory results across the globe.

6. Limitations

We do acknowledge that our study has few limitations. It's single centered retrospective observational study. Results obtained were from small sample size and short duration period. Hindrances being age, comorbidities, secondary infections, complications, COVID-19 vaccine status, timely admission of the patients to hospital were not taken into consideration.

7. Conclusions

In our study we found that blood group A patients were more susceptible to COVID-19 infection than O,B,AB. Need of critical care and higher mortality rate were more in blood group A. Our results further added evidence to the previously discovered associations between blood types and COVID-19.However larger, multicenter, and prospective studies are needed to ascertain the relationship between blood groups and COVID-19, also to nullify the effect of comorbid conditions.

Conflict of Interest: Nil

References

[1] COVID-19(Coronavirus Disease). Centers for disease control and prevention. https://www.cdc.gov/coronavirus/2019-ncov/faq.html# Spread. Accessed November 16, 2020
[2] Bertsch T, Lüdecke J, Antl W, Nausch LW. Karl Landsteiner: The Discovery of the ABO Blood Group System and its Value for Teaching Medical Students. Clinical laboratory. 2019 Jun 1;65(6).
[3] Cheng Y, Cheng G, Chui CH, Lau FY, Chan PK, Ng MH, Sung JJ, Wong RS. ABO blood group and susceptibility to severe acute respiratory syndrome. Jama. 2005 Mar 23;293(12):1447-51.
[4] Lebiush M, Rannon L, Kark JD. The relationship between epidemic influenza A (H 1 N 1) and ABO blood groups. Epidemiology & Infection. 1981 Aug;87(1):139-46.
[5] Loscertales MP, Owens S, O'Donnell J, Bunn J, Bosch-Capblanch X, Brabin BJ. ABO blood group phenotypes and Plasmodium falciparum malaria: unlocking a pivotal mechanism. Advances in parasitology. 2007 Jan 1;65:1-50.
[6] Boren T, Falk P, Roth KA, Larson G, Normark S. Attachment of Helicobacter pylori to human gastric epithelium mediated by blood group antigens. Science. 1993 Dec 17;262(5141):1892-5.
[7] Lindesmith L, Moe C, Marionneau S, Ruvoen N, Jiang XI, Lindblad L, Stewart P, LePendu J, Baric R. Human susceptibility and resistance to Norwalk virus infection. Nature medicine. 2003 May;9(5):548-53
[8] Wang DS, Chen DL, Ren C, Wang ZQ, Qiu MZ, Luo HY, Zhang DS, Wang FH, Li YH, Xu RH. ABO blood group, hepatitis B viral infection and risk of pancreatic cancer. International journal of cancer. 2012 Jul 15;131(2):461-8.
[9] Foster Jr MT, Labrum AH. Relation of infection with Neisseria gonorrhoeae to ABO blood groups. Journal of Infectious Diseases. 1976 Feb 1;133(3):329-30.
[10] Guillon P, Clément M, Sébille V, Rivain JG, Chou CF, Ruvoën-Clouet N, Le Pendu J. Inhibition of the interaction between the SARS-CoV spike protein and its cellular receptor by anti-histo-blood group antibodies. Glycobiology. 2008 Dec 1;18(12):1085-93.
[11] Gérard C, Maggipinto G, Minon JM. COVID-19 and ABO blood group: another viewpoint. British journal of haematology. 2020 Jul 1.
[12] Zhao J, Yang Y, Huang H, Li D, Gu D, Lu X, Zhang Z, Liu L, Liu T, Liu Y, He Y. Relationship between the ABO blood group and the coronavirus disease 2019 (COVID-19) susceptibility. Clinical Infectious Diseases. 2021 Jul 15;73(2):328-31.
[13] Zietz M, Zucker J, Tatonetti NP. Associations between blood type and COVID-19 infection, intubation, and death. Nature communications. 2020 Nov 13;11(1):1-6.
[14] Li J, Wang X, Chen J, Cai Y, Deng A, Yang M. Association between ABO blood groups and risk of SARS-CoV-2 pneumonia. British journal of haematology. 2020 Jul 1.
[15] Göker H, Karakulak EA, Demiroğlu H, Ceylan ÇM, Büyükaşik Y, Inkaya AÇ, Aksu S, Sayinalp N, Haznedaroğlu IC, Uzun Ö, Akova M. The effects of blood group types on the risk of COVID-19 infection and its clinical outcome. Turkish journal of medical sciences. 2020 Jun 23;50(4):679-83.
[16] Wu Y, Feng Z, Li P, Yu Q. Relationship between ABO blood group distribution and clinical characteristics in patients with COVID-19. Clinica chimica acta. 2020 Oct 1;509:220-3.
[17] Liu N, Zhang T, Ma L, Zhang H, Wang H, Wei W, Pei H, Li H. The impact of ABO blood group on COVID-19 infection risk and mortality: A systematic review and meta-analysis. Blood reviews. 2021 Jul 1;48:100785.
[18] Latz CA, DeCarlo C, Boitano L, Png CY, Patell R, Conrad MF, Eagleton M, Dua A. Blood type and outcomes in patients with COVID-19. Annals of hematology. 2020 Sep;99(9):2113-8.
[19] Clinical Guidance for management of adult COVID-19 Pateints : https://covid.aiims.edu/ clinical-guidance-for-management-of-adult-covid-19-patients.
[20] Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell. 2020 Apr 16;181(2):281-92.
[21] Zaidi FZ, Zaidi AR, Abdullah SM, Zaidi SZ. COVID-19 and the ABO blood group connection. Transfusion and Apheresis Science. 2020 Oct;59(5):102838.
[22] Yamamoto F, Yamamoto M, Muñiz-Diaz E. Blood group ABO polymorphism inhibits SARS-CoV-2 infection and affects COVID-19 progression. Vox Sanguinis. 2020 Sep 23.
[23] Ewald DR, Sumner SC. Blood type biochemistry and human disease. Wiley Interdisciplinary Reviews: Systems Biology and Medicine. 2016 Nov;8(6):517-35.
[24] Severe Covid-19 GWAS Group. Genomewide association study of severe Covid-19 with respiratory failure. New England Journal of Medicine. 2020 Oct 15;383(16):1522-34.
[25] Fan Q, Zhang W, Li B, Li DJ, Zhang J, Zhao F. Association between ABO blood group system and COVID-19 susceptibility in Wuhan. Frontiers in cellular and infection microbiology. 2020 Jul 21;10:404.
[26] Muñiz-Diaz E, Llopis J, Parra R, Roig I, Ferrer G, Grifols J, Millán A, Ene G, Ramiro L, Maglio L, Garcia N. Relationship between the ABO blood group and COVID-19 susceptibility, severity and mortality in two cohorts of patients. Blood Transfusion. 2021 Jan;19(1):54.