Original research

Association of COVID-19 severity with vitamin D and blood group

Ariej M. Mustafa[1*], Halla Elshwekh[1], Afaf Shebani[1], Marwa Attayeb[1], Alauldin A. Makhlouf[2], Omnia Edaali[3], Hafsa Al-Emam[1], Nesrein Bendala[1]

[1]Libyan Centre for Biotechnology, Tripoli, Libya
[2]Aldahmani COVID Filtration Center, Tripoli, Libya
[3]Abushusha Polyclinic, Ministry of Health, Tripoli, Libya

*Corresponding author: arigealmahmudi@yahoo.com
https://orcid.org/: 0000-0001-9678-2243

Received: 11-02-2022, **Revised:** 09-03-2022, **Accepted:** 15-03-2022, **Published:** 31-03-2022

HOW TO CITE THIS: *Mustafa et al. (2022) Association of COVID-19 severity with vitamin D and blood group. Mediterr J Pharm Pharm Sci. 2 (1): 65-72. https://doi.org/10.5281/zenodo.6399538*

Abstract: Vitamin D is a hormone which plays a vital role in immune response regulation, including the prevention of inflammation and autoimmunity. Insufficient vitamin D may increase the risk of infection. Vitamin D deficiency is not the only factor linked to an elevated risk of COVID-19 infection. Recent studies have discovered a link between SARS-COV-2 infection risk and blood type. This study was aimed to examine the association of vitamin D and blood groups with the severity of COVID-19. A retrospective study was conducted on 224 confirmed COVID-19 patients, aged between 18 and 89 years old. Patients were divided into three groups (asymptomatic, moderate, and severe cases), and serum 25(OH)D concentration and blood group were analyzed for all the patients. Data of the severe cases were obtained from Souq Althalath Isolation Center, Tripoli, Libya, while moderate and asymptomatic cases were obtained from Abushusha Polyclinic and Aldahmani COVID Filtration Center, during 22nd February 2021 and 28th April 2021 and serum 25(OH)D concentration and blood group were statistically analyzed for all the patients. The percentages of males and females were found to be 47.3% and 52.7%, respectively. Disease severity was distributed as follows: 12.5% asymptomatic, 44.6 % moderate and 42.9% severe. Most of the severe cases had vitamin D deficiency (88.5%). Among the severely ill patients, 39.6% had blood group A and 09.4% had group O, while 22.9%, and 28.1% had blood group B and AB, respectively. In contrast, among the asymptomatic patients, only 7.1% had group A and 85.7% had group O. Overall, the difference in the distribution pattern of blood group in the three severity categories was highly significant ($p < 0.001$). The prevalence of Rh positivity among asymptomatic, moderate and severe cases was 78.6%, 76.0%, and 60.4%, respectively. This study concludes that insufficient vitamin D levels might influence the severity of COVID-19. COVID-19 patients with blood group A and those who are Rh-positive could be more vulnerable to developing COVID-19 severity.

Keywords: Blood group, COVID-19, disease severity, Libya, vitamin D

Introduction

In December 2019, several cases of pneumonia with unknown etiology have been reported in Wuhan, China [1, 2]. Later on, the causative agent was identified as a novel coronavirus denominated severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and the disease was called COVID-19 [1, 3]. The severity of COVID-19

ranges from mild respiratory symptoms to severe lung injury, multiple organ failure and death, while many cases are asymptomatic [3]. In the beginning, the disease spread through China and then started to reach other countries [1]. On March 11th, 2020, World Health Organization (WHO) declared the COVID-19 outbreak as a global pandemic [3]. The first case of COVID-19 in Libya was identified on March 24th, 2020 and a couple of months later the incidence of the disease started to increase notably [4]. Several studies have reported that advanced age, sex, smoking and presence of comorbidity such as hypertension, diabetes mellitus and chronic cardiovascular and respiratory diseases increase the risk of infection and severity of COVID-19 [5, 6].

Vitamin D is a hormone with important functions in the regulation of immune responses and prevention of inflammation and autoimmunity. The connection between vitamin D deficiency and increased risk of infection was suggested over a century ago and interest in its use as an adjunctive therapy continued into modern times [7]. Serum levels of 25-hydroxyvitamin D (25(OH)D) less than 50 nmol per l are defined as vitamin D deficiency. Several studies have connected low 25(OH)D with the severity of infectious respiratory diseases such as pharyngotonsillitis, bronchiolitis, pneumonia, and influenza [8 - 10]. In clinical trials, supplementation of vitamin D resulted in the reduction of illness severity in patients with respiratory infections such as influenza [8, 9]. People who are categorized as highly susceptible to COVID-19 exhibit vitamin D deficiency. Persons who are considered at higher risk of COVID-19 usually have chronic diseases such as diabetes mellitus and cardiovascular diseases, as well as, those who are obese or elderly, are generally vitamin D deficient [10]. Higher morbidity and mortality rate are found in aged populations with COVID-19 disease than in younger patients and this strengthens the association between COVID-19 and vitamin D [11 - 13]. On the other hand, the relationship of vitamin D deficiency to the mortality rate from COVID-19 is controversial, as explained by two different studies published in 2020. Thus, one study showed that patients with vitamin D deficiency are more likely to die from COVID-19 in comparison to others with sufficient vitamin D levels [11]. The other study, conducted in Spain, showed that vitamin D deficiency is not connected to COVID-19 severity or death [14].

Vitamin D might be protective against COVID-19 because 1,25-dihydroxy vitamin D stimulates the production of surfactants in type II pneumocytes and reduces the surface tension caused by surfactant exhaustion in COVID-19 patients [10]. In addition, vitamin D prevents excessive release of pro-inflammatory cytokines and chemokines and increases the expression of anti-inflammatory cytokines by modulating the activity of macrophages, thereby, preventing tissue damage and reducing the severe immune response that is the main cause of COVID-19 complications [9 - 11]. Vitamin D deficiency is not the only factor connected to the increased risk of COVID-[19]. Several studies have found a relation between infection risk of the novel coronavirus and blood group [5, 6]. Another reports connect certain blood groups to increased susceptibility to cardiovascular diseases and cancer, as well as, to infections, including SARS coronavirus [15]. In particular, susceptibility to viral infection has been found to be related to ABO blood groups. For example, the Norwalk virus and Hepatitis B virus have clear blood group susceptibility [16]. Several studies reported that blood group A was associated with a higher risk of COVID- 19 infection, whereas blood group O was related to a lower risk of infection [2, 5, 16]. On the other hand, Other study carried out in the USA revealed that blood groups B and AB were associated with higher odds of testing positive for COVID-19 while blood group O was associated with lower odds [15]. Although the apparent protective effect of some blood groups against COVID-19 was also observed in the SARS outbreak [17], the mechanism of this protection is not fully understood. Natural antibodies of the ABO system blocking the interaction between the SARS-CoV spike (S) protein and the angiotensin-converting enzyme II (ACE-II) receptor may be one of the mechanisms [18]. A study on the SARS-CoV virus obtained evidence that monoclonal anti-A antibodies and natural anti-A antibodies could block the interaction between the ACE-II receptor

and the SARS CoV spike (S) protein, thereby protecting against this virus [17]. This study is aimed to examine the association between 25(OH)D and COVID-19 severity, as well as, the relationship between the patient's blood group and COVID-19 susceptibility in Libya.

Patients and methods

This study is a retrospective study conducted on 250 patients confirmed COVID-19 by PCR. The data of the severe cases were collected from Souq Althalath Isolation Center in Tripoli, Libya. Moderate and asymptomatic cases were collected from Abushusha Polyclinic and Aldahmani COVID Filtration Center during 22th February 2021 and 28th April 2021. These patients were isolated and treated at home and did not require hospital care. Patients were, nevertheless, under the care of two of the authors (OE and AA). All collected data based on ethics approval (BTC committee and personal link to patients or their relatives for collecting data).

Demographics, home isolation, intensive care unit stay and the results of serum 25(OH)D and blood group testing were obtained from the medical records. Of the 250 patients recruited initially, 224 were enrolled in the study after excluding 26 patients whose data were incomplete. The patients were divided into three groups according to their symptoms. Group A (asymptomatic) were PCR-positive for COVID-19 but had no symptoms. Group B (moderate disease) were PCR-positive for COVID-19 and were symptomatic but they did not need hospitalization and were isolated and treated at home. Group C (severe disease) were PCR-positive for COVID-19 and were admitted to intensive care due to the severity of the disease symptoms. Vitamin D was analyzed at the time of diagnosis and confirmation of infection with COVID-19 but before initiating treatment. As the data were collected retrospectively, and all the vitamin D analyses were done in private certified laboratories, the kits that were used are not known to us. Vitamin D status was classified according to serum 25(OH)D level into: deficient (< 25 nmol per l, < 10 ng per ml), insufficient (25-50 nmol per l, 10 - 20 ng per ml) or sufficient (> 75 nmol per l, > 20 ng per ml) [19].

Statistical analysis: Data analyses were performed using SPSS software version 26.0. Frequency and percentage were calculated for all the variables. Chi-squared test was used to estimate the difference between the data obtained (vitamin D, blood group (A, B, or O) and Rh factor) and the severity of the disease. Fisher's exact test was used for cells in the contingency table that had expected frequencies < 5%. A $P < 0.05$ was accepted as statistically significant. Correlation between the severity category and vitamin D status was assessed using the Spearman correlation test.

Results

All 224 patients were from Tripoli and their demographics are shown in **Table 1**. The male to female ratio is 0.9 : 1. The patients' clinical status varied, and 28 were asymptomatic (12.5%). The symptoms of the symptomatic patients included fever, cough, chest tightness, chest discomfort, and diarrhea that varied in severity. Moderate cases were 100 (44.6 %) and severe cases (inpatients) were 96 (42.9%). There are 106 males (47.3%) and 118 females (52.7%). The overall mean age is 47.7 years. There are no significant differences between asymptomatic, moderate, and severe cases in terms of sex-related distribution. The mean serum 25(OH)D level for all the patients is 11.4 µg/L (range 2.0 - 61.3 µg per l). For asymptomatic, moderate, and severe cases, it is 15.4 ± 12.3 µg per l, 16.3 ± 14.7 µg per l and, 5.2 ± 6.4 µg per l, respectively.

Table 1: Demographical data of Libyan patients with COVID-19 disease

	asymptomatic	moderate	severe
Male [n, %]	11 (10.4)	44 (41.5)	51 (48.1)
Female [n, %]	17 (14.4)	56 (47.5)	45 (38.1)
Age (years, mean ± SD)	43.5 ± 14.6	45.75 ± 13.6	50.95 ± 14.8
Vitamin D (µg/l, mean ± SD)	15.36 ± 12.3	16.33 ± 14.7	5.20 ± 6.4

Overall, the patients with severe disease were characterized by vitamin D deficiency, whereas those who were asymptomatic were characterized by insufficiency. While most of the severe cases had vitamin D deficiency (88.5%), only 21.4% of the asymptomatic patients are vitamin D deficient (**Table 2**). Therefore, it is not surprising that 67.9% of the asymptomatic patients had insufficient vitamin D levels versus 7.3% of the severely ill patients. Importantly, there is a highly significant association between vitamin D level and the severity of COVID-19 ($P < 0.001$).

Table 2: Vitamin D in patients according to the disease severity

Disease severity	*n (%)*				*R*	*P value*
	deficient	**insufficient**	**sufficient**	**Total**		
asymptomatic	06 (21.4)	19 (67.9)	03 (10.7)	28 (100.0)		
moderate	47 (47.0)	19 (19.0)	34 (34.0)	100 (100.0)	- 0.472	**0.01****
severe	85 (88.5)	07 (7.3)	04 (4.2)	96 (100.0)		
Total	138 (61.6)	45 (20.1)	41 (18.3)	224 (100.0)		

*Significant at the 0.01 level (2-tailed), r: Spearman correlation coefficient.

Concerning blood groups, the most frequently detected blood groups were groups A and O with each group representing 30.4% of all patients. Blood group O was found in 85.7% of the asymptomatic patients and only 9.4% of the severe COVID-19 group. In contrast, the prevalence rates of the other three blood groups were higher in the severely ill patients than in the asymptomatic patients. The association of disease severity with the blood group was highly significant ($P < 0.001$) (**Table 3**).

Table 3: Distribution of blood group according to disease severity

	n (%)				*Total*	*P value*
	A	**B**	**AB**	**O**		
Asymptomatic	02 (7.1)	00 (0.0)	02 (7.1)	24 (85.7)	28 (100.0)	
Moderate	28 (28.0)	27 (27.0)	10 (10.0)	35 (35.0)	100 (100.0)	**0.001*****
Severe	38 (39.6)	22 (22.9)	27 (28.1)	09 (09.4)	96 (100.0)	
Total	68 (30.4)	49 (21.9)	39 (17.4)	68 (30.4)	224 (100.0)	

The Rh positivity was found in 156 patients (69.6%). Most of the asymptomatic and moderate cases were Rh positive (78.6% and 75.2%, respectively), whereas the prevalence rate among the severe cases was lower at 60.4% (**Table 4**). The association between Rh and the severity of the disease is statistically significant ($P < 0.05$). In patients with blood groups A, B, and AB, vitamin

D deficiency is found in 32.6%, 29.0%, and 25.4% of the patients, respectively. In contrast, vitamin D deficiency was seen in only 13.0% of the patients with blood group O. Consequently, vitamin D insufficiency and sufficiency are higher in patients with blood group O (**Table 5**). Overall, the association between vitamin D level and blood group is very highly significant (P < 0.001).

Table 4: Distribution of Rh factor by COVID-19 disease severity

	n	Positive (n, %)	P value
Asymptomatic	28	22 (78.6)	**0.05***
Moderate	100	76 (76.0)	
Severe	96	58 (60.4)	
Total	224	156 (69.6)	

Of the 95 patients with severe disease, 11 died during hospitalization (mean age is 63 years, range 43 - 92 years). Eight of them were males (72.7%) and three were females (27.3%), though the overall male to female ratio is 0.9 : 1. All of them had severe vitamin D deficiency (< 25 nmol per l, < 10 ng per ml). The highest mortality rate is in patients with blood group A (7.4%) and the lowest in blood group O (1.5%), while 6.1% and 5.1% were in blood group B and group AB, respectively. There is a significant association between the patients' outcome (survival or death) and vitamin D level (P < 0.05). On the other hand, there is no significant association between the patient's outcome and blood group (P = 0.402).

Discussion

In this study, serum vitamin D in individuals with confirmed COVID-19 infection was categorized into asymptomatic, moderately ill, or severely ill. The distribution of vitamin D levels across the spectrum of COVID-19 severity in the study sample is found in agreement with the previous studies [3, 11, 19]. Vitamin D deficiency is significantly more prevalent among severely and moderately ill patients than those who are asymptomatic. The severity of the disease is negatively associated with serum vitamin D levels. Moreover, about 75% of the asymptomatic patients had low vitamin D levels compared to about 10% of the severely ill patients. This association is likely due to the role of vitamin D in the regulation of the immune response and its prevention of inflammation [8]. Vitamin D helps to reduce the risk of microbial infection and mortality by promoting physical barriers, cellular natural immunity, and adaptive immunity. It regulates the innate and acquired immune systems, generation of anti-microbial peptides such as cathelicidin and human-defensin-2, and genes involved in the destruction of the intracellular pathogen [14]. Vitamin D deficiency raises the risk of mortality in COVID-19 patients [9]. On the other hand, about 90% of the severe cases had vitamin D deficiency which indicates that disease severity is associated with lower vitamin D levels differs from those in several studies, which indicates no strong evidence for such a relationship [14, 20 - 22].

Blood groups A and O are the most common among the patients with an equal frequency, whereas blood group AB is the least frequently detected. The overall distribution of the blood group is similar to that previously reported in Libya [23 - 26]. However, notable differences are seen in blood group distribution among the three severity categories: 85% of the asymptomatic patients had blood group O, compared to 10% in the severe COVID-19 group, while 25% blood group B patients and 30% of AB group patients had severe disease. The significance of blood type and disease severity in the current study is consistent with the previous studies reporting a link between blood group and disease severity [16, 27 - 29]. This link

has been attributed to natural ABO system antibodies preventing the interaction of the SARS-CoV spike protein with angiotensin-converting enzyme-II [17]. However, a multi-center study showed that blood groups were not linked to the probability of developing severe disease needing intubation or leading to death, nor were they linked to higher peaks of inflammatory markers [15]. The frequency of Rh positivity among all the patients resembles previous findings in different regions of Libya [23 - 26]. Zietz and others [6] reported a protective relationship between Rh negativity and SARS-CoV-2 infection, intubation, and mortality rate. About ten patients died (5% of total patients) and their mean age was more than 60 years. Although it is found an association between vitamin D and the outcome of the disease, but no clear association with blood group, thus, these findings should be confirmed on a larger study sample.

Conclusion: The findings show that a low level of vitamin D might be one of the factors influencing COVID-19 severity. Low vitamin D levels may lead to lowered immunity. Thus, individuals with blood type A may be more susceptible to severe COVID-19 while positive Rh factor seems to be related to disease severity.

Acknowledgments: Authors would like to thank Souq Althalath Isolation Center for their help and collaboration to carry out the study.

Author contributions: AMM, NB, HE, AS and MA conceived and designed the study; AAM, HA and OE collected data; AMM and NB analyzed and interpreted the results; AMM and NB drafting the first form of the manuscript with support from AS, MA and HE. All authors critically reviewed the final form of the manuscript and approved its submission.

Conflict of interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data availability statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical issues: Including plagiarism, informed Consent, data fabrication or falsification and double publication or submission have completely been observed by authors.

Author declarations: We confirm all relevant ethical guidelines have been followed and any necessary IRB and/or ethics committee approvals have been obtained.

References

1. Jain A, Chaurasia R, Sengar NS, Singh M, Mahor S, Narain S (2020) Analysis of vitamin D level among asymptomatic and critically ill COVID-19 patients and its correlation with inflammatory markers. Scientific Reports - Nature. 10 (1): 1-8. doi:10.1038/s41598-020-77093-z.
2. Ellinghaus D, Bujanda L, Albillos A, Invernizzi P (2020) Genomewide association study of severe covid-19 with respiratory failure. The New England Journal of Medicine. 383 (16): 1522-1534. doi:10.1056/nejmoa2020283.
3. Maghbooli Z, Sahraian MA, Ebrahimi M, Pazoki M, Kafan S, Tabriz HM, Hadadi A, Montazari M, Nasiri M, Shirvani A, Holick MF (2020) Vitamin D sufficiency, a serum 25- hydroxyvitamin D at least 30 ng/mL reduced risk for adverse clinical outcomes in patients with COVID-19 infection. PLOS ONE. 15 (9): 1-13. doi:10.1371/journal.pone.0239799.
4. Bredan A, Bakoush O (2021) COVID-19 epidemic in Libya. Libyan Journal of Medicine. 16 (1): 1-3. doi:10.1080/19932820.2021.1871798.
5. Göker H, Aladağ-Karakulak E, Demiroğlu H, Ceylan CMA, Büyükaşik Y, Inkaya AC, Aksu S, Sayinalp N, Haznedaroğlu IC, Uzun O, Akova M, Ilhami Özcebe I, Ünal S (2020) The effects of blood group types on the risk of COVID-19 infection and its clinical outcome. Turkish Journal of Medical Sciences. 50 (4): 679-683. doi:10.3906/sag-2005-395.

6. Zietz M, Zucker J, Tatonetti NP (2020) Associations between blood type and COVID-19 infection, intubation, and death. Nature Communications. 11: 1-6. doi:10.1038/s41467-020-19623-x.
7. Yamshchikov AV, Desai NS, Blumberg HM, Ziegler TR, Tangpricha V (2009) Vitamin D for treatment and prevention of infectious diseases: A systematic review of randomized controlled trials. Endocrinology Practice. 15 (5): 438-449. doi:10.4158/EP09101.ORR.
8. Ye K, Tang F, Liao X, Shaw BA, Deng M, Huang G, Qin Z, Peng X, Xiao H Chen C, Liu X, Ning L, Wang B, Tang N, Min Li, Xu F, Lin S, Yang J (2020) Does serum vitamin D level affect COVID-19 infection and its severity? A case-control study. Journal of American College of Nutrition. 40 (8): 724-731. doi:10.1080/07315724.2020.1826005.
9. Murdaca G, Pioggia G, Negrini S (2020) Vitamin D and Covid-19: an update on evidence and potential therapeutic implications. Clinical and Molecular Allergy. 18 (1): 1-8. doi:10.1186/s12948-020-00139-0.
10. Siddiqui M, Manansala JS, Abdulrahman HA, Nasrallah GK, Smatti MK, Younes N, Althani AA, Yassine HM (2020) Immune modulatory effects of vitamin D on viral infections. Nutrients. 12 (9): 1-16. doi:10.3390/nu12092879.
11. Das P, Samad N, Ahinkorah BO, Peprah P, Mohammed A, Seidu AA (2020) Effect of vitamin D deficiency on COVID-19 status: A systematic review. medRxiv. 1-21. doi.org/10.1101/2020.12.01.20242313.
12. Ebadi M, Montano-Loza AJ (2020) Perspective: improving vitamin D status in the management of COVID-19. European Journal of Clinical Nutrition. 74 (6): 856-859. doi:10.1038/s41430-020-0661-0.
13. Laird E, Kenny RA (2020) Vitamin D deficiency in Ireland – implications for COVID-19. Results from the Irish longitudinal study on ageing (TILDA). The Irish logitudinal Study on Ageing. Trinity College Dublin. doi:10.38018/TildaRe.2020-05.
14. Hernández JL, Nan D, Fernandez-ayala M, et al. (2020) Vitamin D Status in Hospitalized Patients with SARS-CoV-2 Infection. Journal of Clinical Endocrinology and Metabolism. 106 (3): e1343–e1353. doi:10.1210/clinem/dgaa733.
15. Latz CA, DeCarlo C, Boitano L, Png CYM, Patell R, Conrad MF, Eagleton M, Dua A (2020) Blood type and outcomes in patients with COVID-19. Annals of Hematology. 99 (9): 2113-2118. doi:10.1007/s00277-020-04169-1.
16. Zhao J, Yang Y, Huang H, Li D, Gu D, Lu Z, Zhang Z, Liu L, Liu T, Liu Y, He Y, Sun B, Wei M, Yang G, Wang X, Zhang L, Zhou X, Xing M, Wang PG (2020) Relationship between the ABO Blood Group and the COVID-19 Susceptibility. medRxiv. 1-18. doi:10.1101/2020.03.11.20031096.
17. Guillon P, Clément M, Sébille V, Rivian JG, Chou CF, Clouet NR, Le Pendu J (2008) Inhibition of the interaction between the SARS-CoV Spike protein and its cellular receptor by anti-histo-blood group antibodies. Glycobiology. 18 (12): 1085-1093. doi:10.1093/glycob/cwn093.
18. Arac E, Solmaz I, Akkoc H, Donmezdil S, Karahan Z, Kaya Y, Mertsoy Y, Yilditim Ekin N, Arac S, Demir C (2020) Association between the Rh blood group and the Covid-19 susceptibility. International Journal of Hematology and Oncology. 30 (2): 81-86. doi:10.4999/uhod.204247.
19. Basaran N, Adas M, Gokden Y, Turgut N, Yildirmak T, Guntas G (2021) The relationship between vitamin D and the severity of COVID-19. Bratisl Medical Journal. 122 (3): 200-205. doi:10.4149/BLL_2021_034.
20. Grove A, Osokogu O, Al-Khudairy L, Mehrabian A, Zanganeh, Brown A, Court R, Phillips S, Uthman OA, Mc Carthy N, Kumer S, Clarke A (2021) Association between vitamin D supplementation or serum vitamin D level and susceptibility to SARS-CoV-2 infection or COVID-19 including clinical course, morbidity and mortality outcomes? A systematic review. British Medical Journal Open. 11 (5): 1-9. doi:10.1136/bmjopen-2020-043737.
21. Hastie CE, Mackay DF, Ho F, Morales CA, Katikireddi SV, Neidzwiedz L, Jani BD, Mair FS, Gray ST, O'Donnell C, Gill MR, Satter N, Pell JP (2020) Vitamin D concentrations and COVID-19 infection in UK Biobank. Diabetes and Metabolic Syndrome: Clinical Research and Reviews. 14 (4): 561-565. doi:10.1016/j.dsx.2020.04.050.
22. Butler-Laporte G, Nakanishi T, Mooser V, Morrison DR, Adeleye O, Mamlouk N, Kimchi N, Afrasaabi Z, Rezk N, Giliberili A, Chen Y, Richards JB (2021) Vitamin D and COVID-19 susceptibility and severity in the COVID-19 Host Genetics Initiative: A Mendelian randomization study. PLOS Medicine. 18 (6): e1003605. doi:10.1371/journal.pmed.1003605.
23. Salih K, Abdrhman OM, Irhuma AA, Elgadi B, Abd El Latef MH (2005) Anthropological studies among Libyans of Fazzan Province□: ABO and Rh Systems. Sebha Univeristy Journal of Medical Sciences. 4 (1): 64-69.
24. Saad KAO (2016) Distribution of ABO blood groups and resus factor (RH) in ALBIYDA/LIBYA. Journal of Medical and Dental Science Research. 3 (9): 28-31.

25. Ameigaal SD, Ageel AA (2019) A Cross sectional preliminary study on the prevalence of ABO and Rhesus blood groups in Bani Waleed city, Libya. Libyan International Medical University Journal. 4 (2): 56-61. doi:10.4103/LIUJ.LIUJ.
26. Matough FA, Alhoderi J, Abdullkader A, Abdullsalam J, Alwahaibi N (2019) The frequency of ABO and Rhesus blood groups phenotypes, genotypes from Sebha city of Libya. Journal of Pure and Appl Science. 1 (1): 17-22.
27. Dai X (2020) ABO blood group predisposes to COVID-19 severity and cardiovascular diseases. European Journal of Preventive Cardiology. 27 (13): 1436-1437. doi:10.1177/2047487320922370.
28. Al-Khikani FHO (2020) The role of boold group in COVID-19 infection: more information is needed. Journal of Nature and Science of Medicine. 3 (3): 225-226. doi:10.4103/JNSM.JNSM.
29. Yaylacı S, Dheir H, İşsever K, Issever K, Genc AB, Senocak D, Kocayrigt H, Guclu E, Suner K, Ekerbier H, Koroglu M (2020) The effect of abo and Rh blood group antigens on admission to intensive care unit and mortality in patients with COVID-19 infection. Revista de Associacao Medica Brasileira. 66 (2S): 86-90. doi:10.1590/1806-9282.66.S2.86.