ORIGINAL ARTICLE

Individuals with a Rh-positive but not Rh-negative blood group are more vulnerable to SARS-CoV-2 infection: demographics and trend study on COVID-19 cases in Sudan

S. A. H. Taha[1], M. E. M. Osman[2], E. A. A. Abdoelkarim[3], M. A. I. Holie[4], M. M. Elbasheir[5], N. M. K. Abuzeid[6], S. A. Al-Thobaiti[7], S. B. Fadul[8] and E. H. E. Konozy[9]

1) *Department of Clinical Chemistry, Faculty of Medical Laboratory Sciences, Alzaeim Alazhari University,* 2) *Zoology Department, Faculty of Sciences, Khartoum University,* 3) *Department of Microbiology, National Ribat University, Khartoum,* 4) *Department of Microbiology and Immunology, Faculty of Medical Laboratory Sciences, Alzaeim Alazhari University,* 5) *Department of Parasitology and Medical Entomology, Faculty of Medical Laboratory Sciences, Alzaiem Alazhari University,* 6) *Department Medical Microbiology, Omdurman Islamic University, Khartoum, Sudan,* 7) *Department of Biology, University College Turabah, Taif University, Saudi Arabia,* 8) *Africa City of Technology and* 9) *Biotechnology Department, Africa City of Technology, Khartoum, Sudan*

Abstract

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In Sudan, several haematological studies were conducted to study the ABO blood group distribution among the population, in which the O blood group was dominant followed by the A blood group. However, there is no systematic study into any correlation between COVID-19 and the population's blood group types, therefore we have intended to study the possible effect of blood group on the acquisition of SARS-CoV-2 infection. A questionnaire-based case–control study was carried out on 557 individuals with COVID-19 in Sudan; factors such as age, blood group, previous malaria infection, history of ailments such as diabetes, hypertension and symptoms suffered were also considered and analysed. More women were infected than men, and individuals between 25 and 35 years were the most affected age group. O Rhesus-positive (O+) blood group was the least affected by the disease while A Rhesus-positive (A+) individuals were the most vulnerable. Fatigue, fever and loss of smell were the major symptoms among the patients, but 13% of SARS-COV-2-positive individuals remained asymptomatic. As the Sudan population is largely constituted of O Rhesus-positive inhabitants (approximately 50%) these results might explain the relatively lower COVID-19 incidence in the country.

Keywords: Blood group A, blood group O, coronavirus disease 2019, questionnaire, Sudan, susceptibility
Original Submission: 26 August 2020; **Revised Submission:** 8 September 2020; **Accepted:** 14 September 2020
Article published online: 22 September 2020

Corresponding author: E.H.E. Konozy, Biotechnology Department, Africa City of Technology, Khartoum, Sudan.
E-mail: ehkonozy@yahoo.com

Introduction

Coronavirus disease 2019 (COVID-19) is a highly transmittable disease caused by the recently emerged severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was first detected and identified in December 2019 in Wuhan, China [1]. From there, it spread worldwide and has devastated the economy and growth of many countries in the developed and developing world and has caused a death toll of more than 500 000 [2]. The virus was first named 2019-nCoV by the WHO, but was later renamed as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the coronavirus study group of the International Committee on Taxonomy of Viruses [3]. The rapid spread and rise of the disease in all continents of the world sent an alert to scientists to screen for the characteristics that might make some individuals more susceptible to the virus, as well as risk factors that would increase the severity and progression of the disease. High SARS-CoV-2 infection rate is associated with old age, diabetes,

https://doi.org/10.1016/j.nmni.2020.100763

hypertension, chronic respiratory disease and cardiovascular disease [4]. An association of human ABO blood group types with many diseases has been known since the 1950s [5] and was recently reviewed by Liumbruno and Franchini [6]. For example, individuals with non-O blood groups were more prone to develop coronary heart disease and venous thromboembolism compared with individuals with O blood type [7]. Another Malaysian group conducted a study to correlate between ABO blood group types and the probability of developing diabetes mellitus; the study concluded that people with A and O blood groups had the lowest chances of having diabetes [8]. ABO blood groups and susceptibilities to different types of cancers have also been studied. Individuals with B blood groups were found to have the least risk of gastrointestinal, colorectal, stomach and bladder cancer [9]. Several studies have also reported close associations between ABO blood types and susceptibility to malaria. Individuals with blood group A are highly susceptible to *Plasmodium falciparum* infection, whereas blood group O provides protection against severe malaria; the mechanism of this protection is based on the rosette formation phenomenon [10]. The same noticeable selectivity of the malaria parasite with the ABO blood group system is proved to apply to SARS-CoV-2; individuals with O blood group had the lowest susceptibility to virus infection whereas the A blood type had the highest risk [11,12]. In Sudan, several haematological studies were conducted in different states to find the blood group dissemination pattern among populations, in which the O blood type was the dominant, followed by A, then B, and finally AB with slight differences among these studies [13,14]. So far, there is no systematic study that has been done in Sudan to correlate between COVID-19 and the population's blood group types, so in this study, we have investigated the possible correlation between blood groups and the acquisition of COVID-19. In addition, factors such as previous infection with malaria, sex, age, diseases such as diabetes and hypertension, as well as the number of symptoms suffered, were also studied. To the best of our knowledge, this is the first study in Sudan specifically, and Africa in general, to correlate between the ABO blood system and contracting COVID-19.

Methods

Study design and setting

This case–control study based on an online survey administered through a web browser was conducted on 557 individuals with confirmed COVID-19. Information about gender, age, blood group, COVID-19 symptoms, previous history of infection with malaria and chronic disease were collected through the questionnaire. Data from 1000 healthy volunteers were extracted from the medical registry of Omdurman Maternity Hospital, Omdurman, Sudan.

COVID-19 confirmation

SARS-COV-2 infection was confirmed at medical centres and hospitals certified by the Ministry of Health, using AccuPower® COVID-19 Real-Time RT-PCR Kit (Bioneer Corporation, Daejeon, South Korea) according to the manufacturer's instructions.

Statistical analysis

Data were statistically analysed using SPSS Version-20 (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp, USA). The significance of the results was investigated using one-tailed z-test at significance level p 0.001, and two-tailed binary logistic regression. One-way analysis of variance was used for the analysis of variance.

Ethical consideration

All patients who participated in this questionnaire were informed about the aim and objectives of the study and they agreed to participate. Ethical approval for the individuals who participated as controls was obtained from the ethics committee of Omdurman Maternity Hospital.

Results

Among the 557 participants with COVID-19, 234 (42%) were male and 323 (58%) were female; with female participants more likely to get COVID-19 than male (OR 0.739, 95% CI 0.6–0.911, p 0.005). A large age group range was used from <18 years to 55 years, in which the majority of COVID-19 patients among participants were between 26 and 35 years (41.8%), followed by 36–45 years (22.6%) and finally 19–25 years (21.6%). Seventy patients were reported to be from 46 to 56 years of age (12.6%) and only eight patients (1.4%) were <18 years old. Women with COVID-19 presented a healthier status than male patients with only 4% and 8% suffering from diabetes and hypertension, respectively (Fig. 1).

Distribution of blood group types among the patients is shown in Table 1; 241 (43%) of the total study population were of O blood group (O Rhesus positive (+ve) 39%, O Rhesus-negative (–ve) 4.5%); 180 patients (32%) were of A blood group (A +ve 30.9%, A –ve 1.4%); 102 patients (18.3%) had B blood group (B +ve 16.5%, B –ve 1.8%), and finally 34 (6.1%)

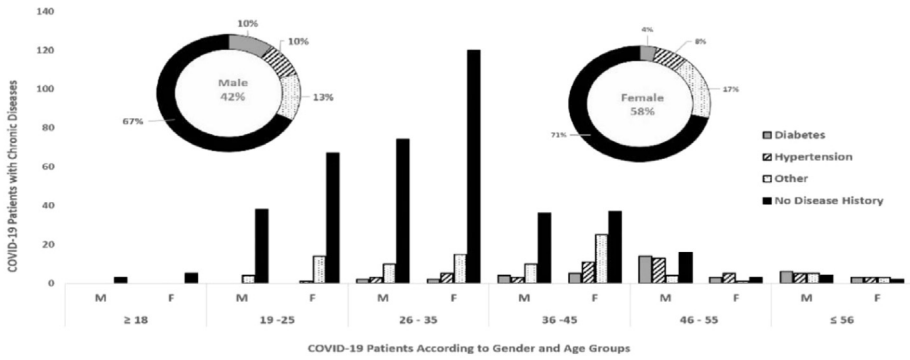

FIG. 1. Distribution of individuals with COVID-19 according to age and gender.

TABLE 1. z-test and logistic regression statistical analysis for blood group susceptibility towards infection with COVID-19

	COVID-19	Control	z value			
	n (%)	*n* (%)	$p_{0.001}$	$p_{0.05}$	OR	95% CI
A +ve	172 (30.9)	251 (25.1)	0.0008	0.008	1.316	0.782–2.215
A −ve	8 (1.4)	21 (2.1)	0.12	0.517	0.731	0.284–1.886
B +ve	92 (16.5)	173 (17.3)	0.33	0.940	1.021	0.592–1.762
B −ve	10 (1.8)	18 (1.8)	0.5	0.890	1.067	0.429–2.655
AB +ve	31 (5.6)	32 (3.8)	0.0006	0.078	1.860	0.932–3.712
AB −ve	3 (0.5)	2 (0.2)	0.06	0.263	2.880	0.451–18.378
O +ve	216 (38.8)	455 (45.5)	0.0006	0.722	0.911	0.547–1.518
O −ve	25 (4.5)	48 (4.8)	0.37	—[a]	—	—
Total	557	1000				

[a]This parameter is set to zero because it is redundant.

had AB blood group (AB +ve 5.6%, AB −ve 0.5%). The susceptibility to SARS-CoV-2 infection was correlated to A +ve blood group (OR 1.316, 95% CI 0.782–2.215, p 0.008).

A total of 406 patients (72.9%) did not have any chronic disease, while 52 (9.7%) had diabetes and hypertension; 446 patients (80.1%) had experienced a previous malaria infection, of whom 20% had been infected within the previous 3 years. The other individuals with COVID-19 had no previous history of malaria infection (Fig. 2).

Of the individuals with COVID-19, 87% presented with different combinations of symptoms. The major symptoms experienced by patients were as follows: fatigue (64%), headache (54.4%), fever (51%), anosmia (47.8%), sore throat (42.5%), ageusia (38.1%), anorexia (37.3%), cough (36.4%), diarrhoea (32.9%) and finally shortness of breath (25.7%). Seventy-three (13%) of those who were clinically confirmed SARS-COV-2-positive remained asymptomatic throughout their isolation period (Fig. 3). Of these asymptomatic patients, 18.2% had O +ve blood whereas 14.6% had A +ve blood. However, there was no significant difference in blood distribution between symptomatic and asymptomatic COVID-19 patients (OR 0.880, 95% CI 0.512–1.511, $\chi^2_{\alpha\ 0.05}$ 0.827). The one-way analysis of variance showed no variation between the ages and blood groups (α = 0.05). The relations between the blood groups and demography, major COVID-19 symptoms and common chronic diseases (diabetes and hypertension) are shown in Fig. 4.

Discussion

To assess the current pandemic trend of SARS-CoV-2 infection in Sudan, the current study was planned and executed in the period from May to August 2020. In total, 565 questionnaires were filled online and submitted, of which eight were improperly filled and therefore excluded from the study.

Demographic studies

The gender ratio in the Sudan population is almost 1:1 males to females; however, based on the current study the susceptibility to SARS-CoV-2 infection appears to be more towards females than males (1.4:1). In 125 countries, areas and territories surveyed, UNWOMEN reported that men (54%) were more vulnerable to COVID-19 infection than women (46%) [15]. The current study's results also contradict a study performed in India, in which incidence of male patients (76%) was significantly higher than that of females (24%) [16], whereas in

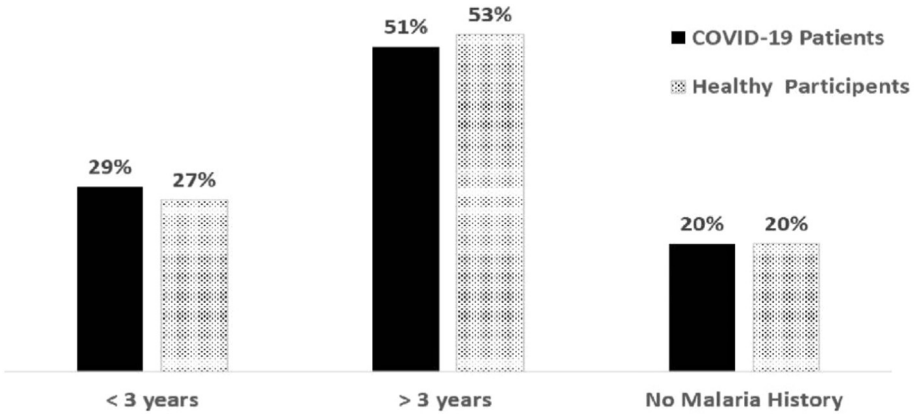

FIG. 2. Individuals with COVID-19 and their back history of malaria infection.

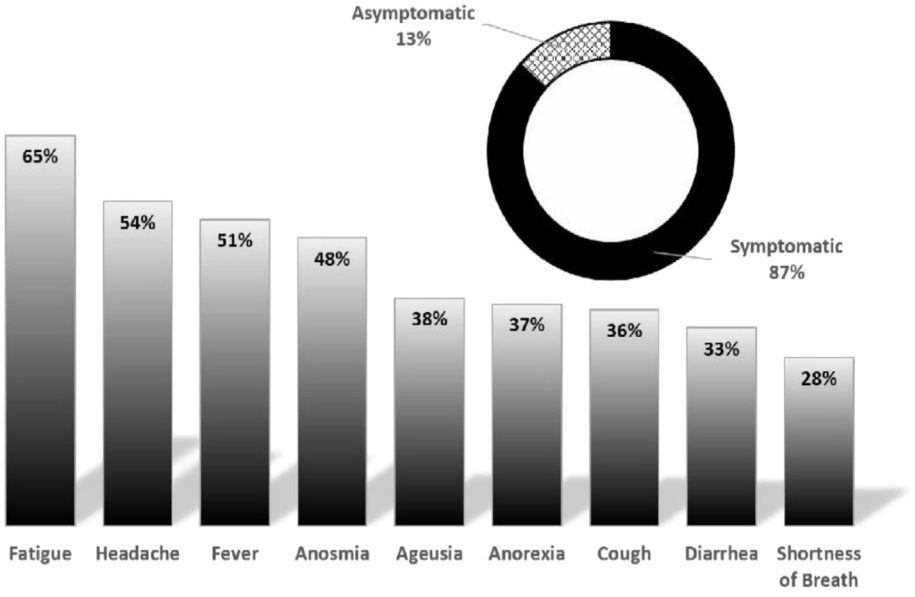

FIG. 3. Percentage of major symptoms suffered by individuals with COVID-19.

China, the prevalence between genders was equal, but the mortality rate was higher in men than women [17,18]. As this study was meant to explore the prevalence, no data about the mortality rate among genders were collected. Analysis of the demographic data of the 557 COVID-19 patients reported in this article revealed that around 86% of patients were between the ages of 19 and 45 years, which indicates that most of those who became infected with SARS-CoV-2 were of working age. Of the 557 patients who filled the questionnaire, only 22 (4%) were older than 56 years. These results are similar to those from India [16]. Another study conducted in Italy revealed that older age groups are more susceptible to SARS-COV-2 infection [19]. As the only available continuous variable within the data set is age, we performed one-way analysis of variance test to correlate between age and blood group, which produced an insignificant correlation between these two factors (mean sample age 32.7 years, $\alpha = 0.05$).

It should be noted that this study was conducted online, but older individuals in a country like Sudan are least exposed to smartphone technologies, so these results might not truly reflect a correct estimate for older individuals who contracted the disease.

Correlation between COVID-19, malaria and ABO blood system

The region falls within the zones where malaria is endemic; it is known that these zones have lower COVID-19 incidence compared with countries that fall outside this zone [20–22]. Zones of malaria endemicity remain a matter of scientific debate in justification of this limited spread [20]. In Sudan, the first case

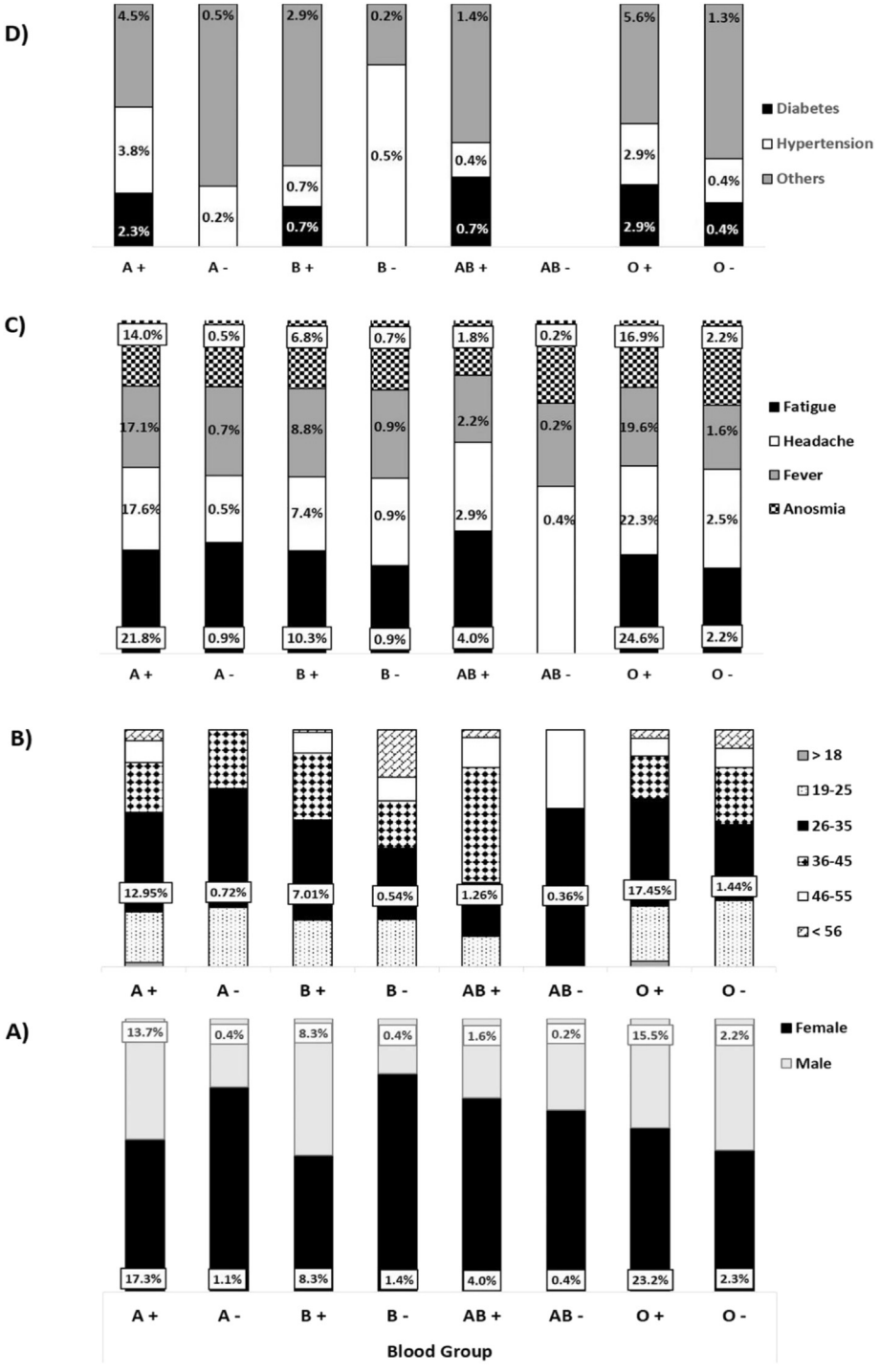

FIG. 4. Blood group relationship of individuals with COVID-19 with (a) gender, (b) age group, (c) major symptoms and (d) chronic diseases.

of SARS-CoV-2 infection was reported in mid-February 2020, although the population does not follow the strict social distancing instructed by medical regulations [23], only around 12 500 cases of COVID-19 were officially recorded after 6 months of the onset of the disease in Sudan. Reports that correlate the low incidences of COVID-19 in this zone with malaria infections are accumulating. Some hypotheses have already been put forward to explain the reduced rate of COVID-19 rates in the zones of malaria endemicity. Weather, environmental factors and previous exposure to malaria drugs like hydroxychloroquine were discussed [20,21,24]. This relation was further supported by several characteristics in common

between the two diseases. First, both malaria and COVID-19 are observed to be interlinked with the ABO blood group system, in which individuals with the O blood group are protected against severe progression of the diseases, whereas individuals with blood group A are highly susceptible to infections. Second, antimalarial drugs like chloroquine, hydroxychloroquine, mefloquine and recently artemisinin have been potential choices for COVID-19 treatment [25]. Third, the finding that besides its use of the angiotensin-converting enzyme 2 receptor, SARS-CoV-2 could also invade cells through interaction of the spike protein with the CD147 receptor, a receptor that is used by *P. falciparum* to cause malaria. Moreover, the nano-lipid Metadichol which inhibits SARS-CoV-2 could equally suppress the *P. falciparum* from entering erythrocytes [26,27]. The interaction between the virus glycoprotein (spike) and the host receptor is mediated by the virus's spike protein segment S1A of the domain S1, which is a sialic acid-binding lectin that recognizes the sialic acid receptor on the host cell surface [28]. Silva-Filho et al. have hypothesized that the sialic acid-containing host receptors angiotensin-converting enzyme-2 and CD147 are targets for the spike agglutinin [29]. Another hypothesis alleged some possible shared epitope conservation between SARS-CoV-2 and *P. falciparum* that would trigger related immune responses (personal communication). In our study, though the correlation between contracting COVID-19 and previous malaria infections gave a statistically insignificant relation. However, as we primarily dealt with recovered COVID-19 patients, a similar study on the malaria infection back history of those who died from COVID-19 would have been of more relevance for such a correlation. The fatality of malaria is attributed in part to the invasion of the *Plasmodium* to the erythrocytes, a process mediated by the *P. falciparum* reticulocyte-binding protein homologue 5 RH5-basigin/CD147 interactions. Interesting recent findings indicated infection of the host cell by SARS-CoV-2 through spike protein-basigin/CD147 interaction [30]. Blood groups have routinely been related to many ailments such as coronary heart disease, cancer and diabetes [8,31]. A few articles have already been published testing for a relation between COVID-19 and the ABO blood group system [32,33]. Studies have observed the susceptibility of A blood group individuals to SARS-CoV-2 infection, whereas individuals with O blood group are protected against severe progression of the disease. The current study did not deviate from this concept, however, interestingly our study indicates that individuals with A +ve blood group—but not those who are A −ve—are more prone to contract the disease compared with controls (p 0.0008), the same applies to AB +ve individuals, but not AB −ve individuals. On the other hand, O +ve, but not O −ve, are shown to have a statistically significantly reduced number of infections compared with control individuals (p 0.0006). No blood group effect was noticed for B blood group individuals. Testing the possible relation with blood type in the asymptomatic patients gave insignificant results (not shown), which indicates that the susceptibility to SARS-CoV-2 infection is only associated with the blood group rather than the symptoms [12].

Conclusion

This study provided for the first time the demographic features and trends of SARS-CoV-2 infection and symptoms among patients in Sudan. The study also furnished clear data on the association of the ABO blood system among the population with COVID-19. Furthermore, the study corroborated that individuals with A +ve, but not A −ve are more vulnerable to contracting the disease, whereas O +ve rather than O −ve individuals are least exposed to severe symptoms of the pandemic. Though some of the data presented in this article replicate the Chinese findings, it remains unique with respect to the Rhesus factor, the variability of symptoms and the gender infection profile. Moreover, the Sudanese population is dominated by the O +ve blood group, which might justify the low COVID-19 spreading rate in the country found in this study. Individuals with blood group A should observe maximum precaution to protect themselves against acquiring SARS-CoV-2 infection, but this study's results should not be considered by O blood carriers as a guarantee that would shield them from the disease, they must still be cautious to avoid increasing risk of infection.

Acknowledgements

The authors would like to thank Dr Sushma Sabharwal, Department of Chemistry, Division of Biochemistry, University of Pune, India for revising the manuscript.

Conflicts of interest

None to declare.

Authors' contributions

SAHT contributed to the investigation, formal analysis, writing the original draft, visualization and data curation. MEMO contributed to witing the original draft, to formal analysis and data curation. EAAAcontributed to conceptualization and data curation. MAIH supervised the study; MME contributed to the methodology; NMKA and SBF contributed to the formal

analysis; and SAAT contributed to resources and to writing the original draft. EHEK contributed to conceptualization, methodology, resources, writing the original draft, reviewing and editing the final article and to project administration.

References

[1] Singhal T. A review of coronavirus disease-2019 (COVID-19). Ind J Pediatrics 2020;87:281–6.

[2] Shereen MA, Khan S, Kazmi A, Bashir N, Siddique R. COVID-19 infection: origin, transmission, and characteristics of human coronaviruses. J Adv Res 2020;24:91–8.

[3] Wu Y, Ho W, Huang Y, Jin D-Y, Li S, Liu S-L, et al. SARS-CoV-2 is an appropriate name for the new coronavirus. Lancet 2020;395:949–50.

[4] Vishnevetsky A, Levy M. Rethinking high-risk groups in COVID-19. MS Relat Disord 2020;42:102139.

[5] Buckwalter JA. Disease associations of the ABO blood group. Acta Genet Stat Med 1956;57:561–3.

[6] Liumbruno GM, Franchini M. Beyond immunohaematology: the role of the ABO blood group in human diseases. Blood Transf 2013;11:491–9.

[7] Dentali F, Sironi AP, Ageno W, Turato S, Bonfanti C, Frattini F, et al. Non-O blood type is the commonest genetic risk factor for VTE: results from a meta-analysis of the literature. Semin Thromb Hemostas 2012;38:535–48.

[8] Kamil M, Al-Jamal HA, Yusoff NM. Association of ABO blood groups with diabetes mellitus. Libyan J Med 2010;5.

[9] Huang JY, Wang R, Gao YT, Yuan JM. ABO blood type and the risk of cancer—findings from the Shanghai Cohort Study. PLoS One 2017;12:e0184295.

[10] Rowe JA, Handel IG, Thera MA, Deans AM, Lyke KE, Koné A, et al. Blood group O protects against severe Plasmodium falciparum malaria through the mechanism of reduced rosetting. Proc Natl Acad Sci USA 2007;104:17471–6.

[11] Li J, Wang X, Chen J, Cai Y, Deng A. Association between ABO blood groups and risk of SARS-CoV-2 pneumonia. Br J Hematol 2020;190:24–7.

[12] Zietz M, Tatonetti NP. Testing the association between blood type and COVID-19 infection, intubation, and death. medRxiv : The Preprint Server Health Sci 2020. 2020.04.08.20058073.

[13] Shahata WM, Khalil HB, Abass A, Adam I, Hussien SM. Blood group and Rhesus antigens among blood donors attending the central blood bank, Sudan. Sudan J Med Sci 2012;7:245–8.

[14] Hassan FM. Frequency of ABO, subgroup ABO and Rh(D) blood groups in major sudanese ethnic groups. Pak J Med Res 2010;49:21–3.

[15] Azcona G, Bhatt A, Davies SE, Harman S, Smith J, C W. Spotlight on gender, COVID-19 and the SDGs: will the pandemic derail hard-won progress on gender equality? UNWOMEN 2020:1–34.

[16] Mahajan P, Kaushal J. Epidemic trend of COVID-19 transmission in India during lockdown-1 phase. J Commun Health 2020. https://doi.org/10.1007/s10900-020-00863-3.

[17] Jin JM, Bai P, He W, Wu F, Liu XF, Han DM, et al. Gender differences in patients with COVID-19: focus on severity and mortality. Front Public Health 2020;8:152.

[18] Gao Q, Hu Y, Dai Z, Xiao F, Wang J, Wu J. The epidemiological characteristics of 2019 novel coronavirus diseases (COVID-19) in Jingmen, Hubei, China. Medicine (Balt) 2020;99:e20605.

[19] Abbatecola AM, Antonelli-Incalzi R. Editorial: COVID-19 spiraling of frailty in older Italian patients. J Nutr Health Aging 2020;24:453–5.

[20] Muneer A, Kumari K, Tripathi M, Srivastava R, Mohmmed A, Rathore S. Comparative analyses revealed reduced spread of COVID-19 in malaria endemic countries. medRxiv 2020. 2020.05.11.20097923.

[21] Ahmed AE. Incidence of coronavirus disease (COVID-19) and countries affected by malarial infections. Travel Med Infect Dis 2020:101693.

[22] Sargin G, Yavaşoğlu Sİ, Yavasoglu I. Is coronavirus disease 2019 (COVID-19) seen less in countries more exposed to malaria? Med Hypoth 2020;140:109756.

[23] Altayb HN, Eldeen Altayeb NM, Hamadalnil Y, Elsayid M, Mahmoud NE. The current situation of COVID-19 in Sudan. N Microb N Infect 2020:100746.

[24] Arshad S, Kilgore P, Chaudhry ZS, Jacobsen G, Wang DD, Huitsing K, et al. Treatment with hydroxychloroquine, azithromycin, and combination in patients hospitalized with COVID-19. Int J Infect Dis 2020;97:396–403.

[25] Gendrot M, Duflot I, Boxberger M, Delandre O, Jardot P, Le Bideau M, et al. Antimalarial artemisinin-based combination therapies (ACT) and COVID-19 in Africa: in vitro inhibition of SARS-CoV-2 replication by mefloquine-artesunate. Int J Infect Dis 2020. https://doi.org/10.1016/j.ijid.2020.08.032.

[26] Raghavan P. Metadichol, a novel nano lipid formulation that inhibits SARS-COV-2 and a multitude of pathologicalviruses in vitro. Res Square 2020:1–31.

[27] Ulrich H, Pillat MM. CD147 as a target for COVID-19 treatment: suggested effects of azithromycin and stem cell engagement. Stem Cell Rev Rep 2020;16:434–40.

[28] Tortorici MA, Walls AC, Lang Y, Wang C, Li Z, Koerhuis D, et al. Structural basis for human coronavirus attachment to sialic acid receptors. Nat Struct Mol Biol 2019;26:481–9.

[29] Silva-Filho JC, de Melo CGF, de Oliveira JL. The influence of ABO blood groups on COVID-19 susceptibility and severity: a molecular hypothesis based on carbohydrate–carbohydrate interactions. Med Hypoth 2020;144:110155.

[30] Wang K, Chen W, Zhou Y-S, Lian J-Q, Zhang Z, Du P, et al. SARS-CoV-2 invades host cells via a novel route: CD147-spike protein. bioRxiv 2020. https://doi.org/10.1101/2020.03.14.988345.

[31] Cozzi GD, Levinson RT, Toole H, Snyder M-R, Deng A, Crispens MA, et al. Blood type, ABO genetic variants, and ovarian cancer survival. PLoS One 2017;12:e0175119.

[32] Fan Q, Zhang W, Li B, Li D-J, Zhang J, Zhao F. Association between ABO blood group system and COVID-19 susceptibility in Wuhan. Front Cell Infect Microbiol 2020;10.

[33] Latz CA, DeCarlo C, Boitano L, Png CM, Patell R, Conrad MF, et al. Blood type and outcomes in patients with COVID-19. Ann Hematol 2020;99:211318.