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Short communication

ABO blood group system is associated with COVID-19 mortality: An epidemiological investigation in the Indian population

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ABSTRACT

Background. – Novel coronavirus disease-19 (COVID-19) has spread worldwide, and to date presence of the virus has been recorded in 215 countries contributing 0.43 million of death. The role of blood groups in susceptibility/resistance to various infectious diseases has been reported. However, the association of blood groups with susceptibility to COVID-19 infections or related death are limited. In the present report, we performed an epidemiological investigation in the Indian population to decipher the importance of blood groups concerning susceptibility or mortality in COVID-19 infection.
Materials and methods. – Data on COVID-19 infection and mortality was obtained from the website of the Government of India. Prevalence of ABO blood groups in different states and union territories of India were searched using different databases such as PubMed and Google Scholar. Relevant articles were downloaded, and data were extracted. Spearman's rank coefficient analysis was employed to study the correlation between blood group frequencies and COVID-19 infection or mortality rate.
Results. – A significant inverse correlation was observed between the frequency of O blood group and the COVID-19 mortality rate (Spearman $r = -0.36$, $P = 0.03$), indicating a possible protective role of O blood group against COVID-19 related death. In contrast, the prevalence of blood group B was positively correlated with COVID-19 death/million (Spearman $r = 0.67$, $P < 0.0001$), suggesting B blood type as a deleterious factor in COVID-19 infection.
Conclusions. – ABO blood group system is associated with poor prognosis of COVID-19 infection. Blood group O may protects, and subjects with blood type B could be susceptible to COVID-19 mortality. However, further studies on COVID-19 infected patients in different population are required to validate our findings.

1. Introduction

Novel coronavirus disease 2019 (COVID-19) was reported for the first time in Wuhan, China in December 2019, broke out worldwide, and to date reported over 215 countries and responsible for 0.43 million death (https://www.worldometers.info/coronavirus/ accessed on 14/06/2020). In comparison to other populations, the United States of America reported the maximum number of COVID-19 infected cases (2.1 million) and related death (0.11 million) (https://www.worldometers.info/coronavirus/accessed on 14/06/2020). The COVID-19 infection rate and mortality frequency vary among countries. The exact reason for differential COVID-19 infection and mortality rates in the different populations is unclear so far. Several factors, such as age profile, gender, comorbidity factors, economic condition, doctor density, and genetic makeup of the subject, could be attributed to the disparity in susceptibility to COVID-19 disease or poor prognosis. Some recent reports highlighted a significant association of glutathione S-transferase T1 [1] and angiotensin-converting 1 enzyme [2] genetic variants with COVID-19 infection and mortality.

The ABO gene is located on the long arm of the 9th chromosome (34.1-34.2), consist of 7 exons and codes for glycosyltransferases. The enzyme glycosyltransferases transfer specific sugar residues to H substance, and responsible for the formation of antigens in blood group A and/or B. The enzyme encoded by the A allele use the donor uridine-diphosphate-n-acetyl galactosamine (UDP-GalNAc)

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and convert H into antigen A. Similarly, glycosyltransferase coded by allele B, transfer the donor uridine-diphosphate-galactose (UDP-galactose) to the acceptor H lead to the formation of antigen B. In contrast, allele O produces non - functional enzyme owing to deletion at 261st nucleotide leading to a pre-termination of the translational process [3]. Antigen-A-bearing individuals have anti-B in their serum, and antibody- B bearing subjects express have antigen-A on the red blood cells. Blood group O has both antibodies A and B in their serum. Blood group antibodies are produced after birth, as a response to similar environmental carbohydrates, reach peak levels between the ages of 5 to 10, and decline after the age of 50 [4]. Previous reports have demonstrated the association of ABO blood group system with susceptibility to a wide range of virus infections such as Severe Acute Respiratory Syndrome [5], symptomatic West Nile Virus[6], Human Immunodeficiency Virus [7], Hepatitis B [8] and Norwalk virus [9]. Some recent reports highlighted a possible association between ABO blood groups system and COVID-19 infections and mortality in the Chinese [10], American [11], Spanish and Italian populations [12]. O blood group has been associated with protection from COVID-19 infection and clinical severity [10–12]. In contrast, blood group A has demonstrated as a risk factor for COVID-19 [10–12]. In the present epidemiological investigation, we explored the possible association of blood groups with COVID-19 infection and mortality in the Indian population.

2. Materials and methods

2.1. ABO blood group data

India is comprising of twenty-eight states and eight union territories (UTs). Data on the prevalence of different blood groups in various states and UTs were screened through PubMed, Google Scholar. A recent report highlighted the enrolment of appropriate controls for the association study between the ABO blood group system and the COVID-19 infection or mortality [13]. The present study included publications on the frequency of ABO blood group system in healthy controls. Various data such as names of the states or UTs, the total number of healthy controls, and the frequency of different blood groups were extracted.

2.2. COVID-19 data

COVID-19 related information was obtained from the official website of the Ministry of Health and Family Welfare, Government of India (https://www.mohfw.gov.in, assessed on 12/06/2020). The number of confirmed cases and patients who died due to COVID-19 infections were noted down. The total population of each state and UTs were acquired from data of census-2011 (https://censusindia.gov.in/2011-common/censusdata2011.html), and COVID-19 cases per million and death rate/million were calculated.

2.3. Statistical analysis

The prevalence of blood groups in different states and UTs of India, along with the infection, and the rate of mortality due to COVID-19 per million of the population were calculated. All statistical analysis was performed by Graphpad Prism 8.3.0. Correlation between different blood groups and COVID-19 infections/death rate per million was investigated by Spearman rank coefficient analysis, where a P-value < 0.05 was considered significant.

3. Results and discussion

On 30th January 2020, India reported the first case of COVID-19 in a student who returned from Wuhan University China in Thrissur district of Kerala state (https://www.cnbc.com/2020/01/30/india-confirms-first-case-of-the-coronavirus.html). As of 12/06/2020, about 0.27 million COVID-19 infected cases have been reported from India, and 8102 number of deaths has been encountered. Delhi and Maharashtra contributed the maximum number of infected cases and posed high mortality rates per million of the population (Table 1).

Prevalence of the ABO blood group in the subjects of different state and UTs of India were obtained from various databases. Out of twenty-eight states and eight UTs, the frequency of the ABO blood group was not available for Goa, Chandigarh, and Lakshadweep, leading to the exclusion of these states and UTs from the present analysis. Spearman correlation analysis revealed a marginal inverse association between blood group O and COVID-19 death per million ($r = -0.370$, $P = 0.033$) (Table 2). However, the correlation between blood type O and the COVID-19 infection rate was not significant ($r = -0.225$, $P = 0.206$). A recent report in the Chinese population demonstrated an association of blood type O with a lower risk of COVID-19 infection and mortality [10]. However, patients enrolled from Renmin Hospital of Wuhan University, and Shenzhen Third Peoples's Hospital failed to demonstrate such association of blood group O with COVID-19 infection or mortality [10]. Besides, a hospital-based investigation in New York, USA, revealed a lower risk of COVID-19 infection in the subject harboring O type blood [11]. A recent genome-wide association study in Spanish and Italian COVID-19 infected patients revealed the protection of blood group O from severe respiratory failure [12].

A significant association of blood type A with susceptibility to COVID-19 infection and mortality has been reported in Chinese patients enrolled in Wuhan Jinyintan Hospital [10]. Such a relationship was not withstood in patients included from the Renmin Hospital of Wuhan University and Shenzhen Third People's Hospital of China [10]. Furthermore, the association of blood type A has been documented with susceptibility to COVID-19 infection in New York, USA [11], and increased risk of respiratory failure in Spanish and Italian patients [12]. In contrast, we observed a positive correlation of blood group B with COVID-19 infection ($r = 0.364$, $P = 0.037$) and mortality rate ($r = 0.687$, $P < 0.0001$) (Table 2). These conflicting observations on the association of blood group A or B with COVID-19 infection and related death could be attributed to the discrepancies in investigated ethnic populations and different strains of SARS-CoV2 with varying pathogenicity. Earlier reports have elegantly demonstrated a population-specific link between blood groups A, B, or AB with severe *Plasmodium falciparum* malaria and death [14].

The mechanism of how B blood type is associated with susceptibility to COVID-19 infections and mortality is not known. The spike protein of COVID-19 requires angiotensin-converting enzyme-2 (ACE-2) receptor to infect a cell [15]. The interaction between spike protein of SARS-CoV and ACE-2 receptor is hampered in the presence of anti-blood type A [16], which could be an explanation for the protection of blood group O against COVID-19 infection and mortality. However, the role of ABO antibodies on altering the interaction between the spike protein of SARS-CoV-2 and ACE-2 receptor is still unknown. On multiplication of SARS-CoV-2 in the host cell and their subsequent release to infect other hosts, the spike protein of virions possibly carries A, B, or AB glycan antigen depend on the blood group of the carriers. Since subject with blood group O carries both antibodies A and B, the infection rate of SARS-CoV-2 loaded with A, B, or AB antigens would be reduced [17]. Furthermore, the degree of protection against SARS-CoV-2 infection maybe

Table 1
Prevalence of ABO blood group and COVID-19 cases in different states and union territories of India.

State/Union territories	Population (Census 2011)	Number of COVID-19 infected cases	Infected cases per million of population	Number of death due to COVID-19	Death rate per million of population	Blood group-O number (%)	Blood group-A number (%)	Blood group- B number (%)	Blood group-AB number (%)	Total number of healthy subjects	Total number of reports included	References
Andaman and Nicobar	380581	34	89.337	0	0	35 (23.489)	56 (37.583)	40 (26.845)	18 (12.080)	149	1	(B.V, Patel et al., 2016)
Andhra Pradesh	49386799	5269	106.688	78	1.579	30052 (38.926)	18784 (24.330)	23971 (31.049)	4395 (5.692)	77205	3	(Rao, Reddy et al., 2003; C, R et al., 2016; R, K et al., 2018)
Arunachal Pradesh	1383727	57	41.193	0	0	2155 (30.772)	2335 (33.342)	1851 (26.431)	662 (9.453)	7003	1	(Nath, Singh et al., 2000)
Assam	31205576	3092	99.084	4	0.128	7589 (37.077)	5102 (24.926)	6341 (30.980)	1436 (7.015)	20468	4	(Sengupta and Das, 2002; Baishya, Saharia et al., 2015; Deori and De, 2016; Kumbhakar, 2016)
Bihar	104099452	5710	54.851	33	0.317	767 (28.737)	842 (31.547)	871 (32.633)	189 (7.081)	2669	1	(Sinha, Singh et al., 1999)
Chandigarh	1055450	327	309.820	5	4.737	—	—	—	—		DNA	
Chhattisgarh	25545198	1262	49.402	6	0.234	19579 (33.019)	13819 (23.305)	20364 (34.342)	5534 (9.332)	59296	2	(Shrivastava, Gahine et al., 2015; Badge, Ovhal et al., 2017)
Dadra and Nagar Haveli, Daman and Diu	586956	28	47.703	0	0	98 (49)	38 (19)	59 (29.5)	5 (2.5)	200	1	(Meitei and Kshatriya, 2009)
Delhi	16787941	32810	1954.379	984	58.613	19603 (29.205)	14543 (21.666)	26080 (38.854)	6896 (10.273)	67122	3	(Agarwal, Thapliyal et al., 2013; Arora, Kaushik et al., 2015; Kaur, Doda et al., 2016)
Goa	1458545	387	265.332	0	0	—	—	—	—		DNA	
Gujarat	60439692	21521	356.073	1347	22.286	18428 (32.131)	13602 (23.717)	20270 (35.343)	5051 (8.807)	57351	3	(Gupte, Patel et al., 2012; Patel, Patel et al., 2012; Raja, Dobariya et al., 2016)
Haryana	25351462	5579	220.066	52	2.051	1769 (29.851)	1335 (22.527)	2269 (38.288)	553 (9.331)	5926	2	(Singh, Sharma et al., 2015; Puri and Kochhar, 2016)
Himachal Pradesh	6864602	451	65.699	6	0.874	1230 (25.802)	1175 (24.648)	1707 (35.808)	655 (13.740)	4767	3	(Nishi, Gupta et al., 2012; Jain, Devaraj et al., 2017; Singh and Arora, 2018)
Jammu and Kashmir	12267013	4507	367.408	51	4.157	2816 (34.170)	1928 (23.395)	2830 (34.340)	667 (8.093)	8241	2	(Calcutti, Lone et al., 2003; Handoo and Bala, 2014)
Jharkhand	32988134	1489	45.137	8	0.242	7197 (34.463)	4646 (22.247)	7363 (35.258)	1677 (8.030)	20883	2	(Sarkar, 1949; Singh, Srivastava et al., 2016)

Table 1 (*Continued*)

State/Union territories	Population (Census 2011)	Number of COVID-19 infected cases	Infected cases per million of population	Number of death due to COVID-19	Death rate per million of population	Blood group-O number (%)	Blood group-A number (%)	Blood group- B number (%)	Blood group-AB number (%)	Total number of healthy subjects	Total number of reports included	References
Karnataka	61095297	6041	98.878	69	1.129	25235 (39.956)	15523 (24.578)	18715 (29.632)	3683 (5.831)	63156	4	(Bijanzadeh, Ramachandra et al., 2009; Gadwalkar, Sunil et al., 2013; Rao and Shetty, 2014; CN, R et al., 2017)
Kerala	33406061	2161	64.688	18	0.538	13489 (37.983)	9306 (26.204)	10313 (29.040)	2405 (6.772)	35513	2	(John, 2017; Shashidhar, Hana et al., 2017)
Ladakh	274289	115	419.265	1	3.645	47 (16.785)	106 (37.857)	86 (30.714)	41 (14.642)	280	2	(Bansal, 1967; Fatima and Dolma, 2019)
Lakshadweep	64473	0	0	0	0	—	—	—	—		DNA	
Madhya Pradesh	72626809	10049	138.364	427	5.879	7262 (31.167)	5489 (23.557)	8528 (36.600)	2021 (8.673)	23300	5	(Koley, 2008; Chaurasia, Sharma et al., 2015; Saluja and Sharma, 2015; Anjulika and Mehta, 2016; Kumar, Ajmani et al., 2017)
Maharashtra	112374333	94041	836.854	3438	30.594	4427 (31.499)	3963 (28.198)	4470 (31.805)	1194 (8.495)	14054	4	(Warghat, Sharma et al., 2010; Giri, Yadav et al., 2011; Purandare and Prasad, 2012)
Manipur	2855794	311	108.901	0	0	417 (43.848)	221 (23.238)	188 (19.768)	125 (13.144)	951	2	(Panmei, Yumnam et al., 2014; Soram, Panmei et al., 2014)
Meghalaya	2966889	44	14.830	1	0.337	233 (33.190)	175 (24.928)	220 (31.339)	74 (10.541)	702	2	(Haloi, 2011; Sahu, Sadhukhan et al., 2013)
Mizoram	1097206	93	84.760	0	0	41 (37.272)	41 (37.272)	21 (19.090)	7 (6.363)	110	1	(Ghosh, Limbu et al., 2010)
Nagaland	1978502	128	64.695	0	0	173 (42.610)	126 (31.034)	87 (21.428)	20 (4.926)	406	2	(Pojar, 2018; Kiewhuo, Yanthan et al., 2019)
Odisha	41974218	3250	77.428	9	0.214	124 (43.661)	56 (19.718)	74 (26.056)	30 (10.563)	284	2	(Panda, Panda et al., 2011; Rout, Dhangadamajhi et al., 2012)
Puducherry	1247953	127	101.766	0	0	218 (37.328)	135 (23.116)	201 (34.417)	30 (5.136)	584	2	(Srividya and Pani, 1993; Subhashini, 2007)
Punjab	27743338	2805	101.105	55	1.982	5411 (34.085)	2904 (18.292)	6038 (38.034)	1522 (9.587)	15875	2	(Sidhu, 2003; Kaur, Khanna et al., 2013)
Rajasthan	68548437	11600	169.223	259	3.778	5260 (33.889)	3479 (22.414)	5575 (35.919)	1207 (7.776)	15521	3	(Shekhar, Kaur et al., 2014; Taibanganba and Sachdev, 2017; Jain, P. et al., 2018)
Sikkim	610577	13	21.291	0	0	1884 (35.149)	1862 (34.738)	1195 (22.294)	419 (7.817)	5360	2	(Mathur and Lamichaney, 2017; Rai and Singh, 2017)

Table 1 (*Continued*)

State/Union territories	Population (Census 2011)	Number of COVID-19 infected cases	Infected cases per million of population	Number of death due to COVID-19	Death rate per million of population	Blood group-O number (%)	Blood group-A number (%)	Blood group- B number (%)	Blood group-AB number (%)	Total number of healthy subjects	Total number of reports included	References
Tamil Nadu	72147030	36841	510.637	326	4.518	5925 (33.234)	3528 (19.789)	6489 (36.397)	1886 (10.578)	17828	2	(Anumanthan, Muddegowda et al., 2015; Manikandan, Devishamani et al., 2019)
Telengana	35193978	4111	116.809	156	4.432	9525 (41.582)	4368 (19.069)	7704 (33.633)	1309 (5.714)	22906	3	(Koram, Sadula et al., 2014; Sukumaran, Padma et al., 2016; Reddy, Kumar et al., 2019)
Tripura	3673917	895	243.609	1	0.272	331 (30.876)	288 (26.865)	329 (30.690)	124 (11.567)	1072	2	(Gupta, 1958; Choudhuy, Chakrabarti et al., 2016)
Uttar Pradesh	199812341	11610	58.104	321	1.606	41489 (29.328)	30246 (21.380)	56430 (39.889)	13300 (9.401)	141465	3	(Rai, Verma et al., 2009; Chandra and Gupta, 2012; Verma, Singh et al., 2013)
Uttarakhand	10086292	1562	154.863	15	1.487	6239 (27.625)	6648 (29.436)	7204 (31.898)	2493 (11.038)	22584	2	(Garg, Upadhyay et al., 2014; Kumar, Modak et al., 2018)
West Bengal	91276115	9328	102.195	432	4.732	120 (28.846)	114 (27.403)	139 (33.413)	43 (10.336)	416	2	(Chaudhuri, Ghosh et al., 1964; Ganguly, Sarkar et al., 2016)

Note: Data are number (%) of subjects unless otherwise specified, DNA: data not available, references are provided in supplementary file.

Table 2
Correlation of different blood groups with COVID-19 infection and death rate in India.

Correlation between blood group vs. COVID-19 infection/death rate per million	Spearman r	Two tailed *P* value
O vs. infection rate	−0.225	0.206
O vs. death rate	−0.370	0.033
A vs. infection rate	−0.135	0.452
A vs. death rate	−0.270	0.128
B vs. infection rate	0.364	0.037
B vs. death rate	0.687	< 0.0001
AB vs. infection rate	0.239	0.179
AB vs. death rate	0.173	0.333

Note: Data from 33 states and union territories were analyzed for possible correlation of different blood groups with COVID–19 cases or death per million of population.

depends on ABO antibodies titer, which is inversely correlated with the extent of industrialization [18].

Plasmodium falciparum malaria has been a major selective force on the human genome and beneficial genotype selected out in the endemic population. India and Africa contribute most malaria infections and death worldwide. In earlier reports, in malarial-endemic areas, we have demonstrated an association of blood group O with reduced risk and blood type B with an increased possibility of malarial death [14,19]. Thus, blood type O remains highly prevalent in malaria-endemic areas compared to other blood groups [14,19]. Possibly higher occurrence of O blood type in malaria-endemic regions is lowering the incidence of COVID-19 mortality. The higher prevalence of blood group O in malaria-endemic areas such as Odisha, Bihar, Jharkhand could be a possible reason for lower COVID-19 mortality rate in those geographical areas.

Although the present epidemiological report highlighted a possible role of blood groups with COVID-19 infection and mortality rate, it has some limitations. First, the association study was not performed in COVID-19 patients. Blood group frequency and COVID-19 infection status were obtained from the online database and reports. Second, due to the unavailability of data, Rh factors were not considered for analysis. Third, confounding factors such as age, gender, comorbidity status, the economic condition of states and UTs, doctors, and nursing staff density were not included in the present analysis. Further studies in COVID-19 patients from other geographical areas are required to validate our findings.

Disclosure of interest

The authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tracli.2020.08.009.

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