Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Short Communication

ABO blood groups, COVID-19 infection and mortality☆,☆☆

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ABSTRACT

Background: A recent study showed that the ABO gene, chr 9q34.2, which determines blood type, may affect COVID-19 disease severity, although this result has not been reproducible. A UK study of 2200 COVID-19 patients found no relationship of ABO blood type to disease severity. A Danish study identified ABO blood group as a risk factor for SARS-CoV-2 infection but not for hospitalization or death from COVID-19.
Aim: In the current study, we wished to analyze the relationship of ABO blood group and the ABO genetic locus to COVID-19 test positivity and mortality in subjects from the UK Biobank (UKB).
Methods: ABO blood type is from UKB data field 23165. Blood type was imputed for genotyped UK Biobank participants using three SNPs (rs505922, rs8176719, and rs8176746) in the ABO gene on chromosome 9q34.2. We analyzed the chromosome 9 snp rs657152 to assess the relationship of the ABO locus to COVID-19 test positivity and mortality.
Results: COVID-19 test results (negative or positive) were not related to blood group in males ($p = 0.977$, two tailed Fisher exact test) or females ($p = 0.548$). COVID-19 outcomes (alive or died) were not related to blood group in males ($p = 0.102$, two tailed Fisher exact test) or females ($p = 0.226$). We found no significant relationship of rs657152 to COVID-19 test positivity or mortality.
Conclusion: We were not able to confirm that ABO blood group influences risk of COVID-19 infection or outcome.

1. Introduction

Most people infected by SARS-CoV-2 never become ill, whereas some die within days. Age and preexisting conditions, such as obesity, account for some of the disparity. But genetics plays a role.

Genome-wide association studies have found multiple genes and loci that increase risk of respiratory failure in COVID-19. Analyzing the SNP rs657152, located in the intron area of ABO, one study found that the ABO gene, chr 9q34.2, which determines blood type, may affect disease severity [1], although this result has not been reproducible. A UK study of 2200 COVID-19 patients found no relationship of ABO blood type to disease severity [2]. A Danish study identified ABO blood group as a risk factor for SARS-CoV-2 infection but not for hospitalization or death from COVID-19 [3].

In the current study, we analyzed the relationship of ABO blood types and rs657152, which has been associated with cancer and cardiocerebrovascular disease risk [4], to COVID-19 test positivity and mortality.

2. Methods

We utilized UK Biobank (UKB) data. The UKB consists of more than 500,000 community volunteers aged 40–70 years at baseline (2006–2010), living close to 22 assessment centers in England, Scotland, and Wales. Baseline assessments include demographics, lifestyle, and disease history, with linkages to electronic medical records. Our UK Biobank application was approved as UKB project 57,245 (S.L., P.H.R.). Electronic linkage between UKB records and National Health Service COVID-19 laboratory test results in England are available from March 16 to April 26, 2020, including the peak of daily COVID-19 laboratory-confirmed cases in the current outbreak. During this period, testing of

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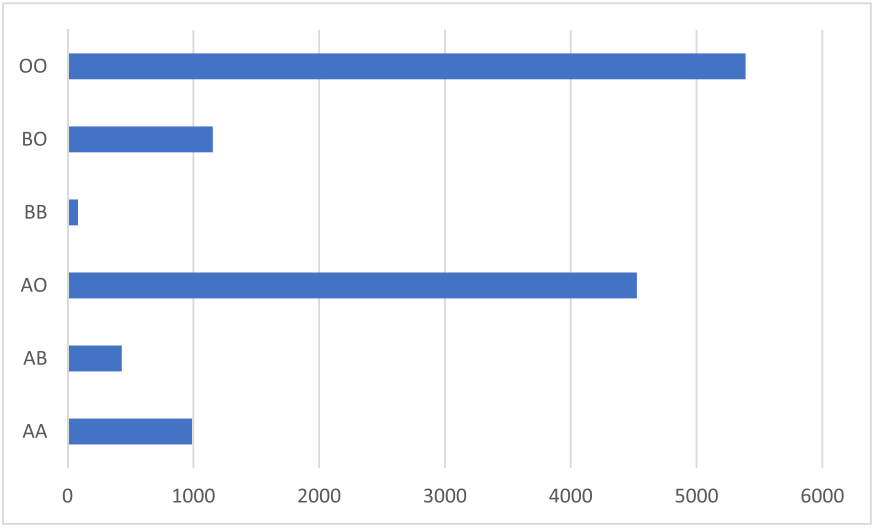

Fig. 1. Blood group versus number of cases, 12,575 subjects in this analysis.

Table 1
COVID-19 test results (negative or positive) versus blood group by gender. The results for males ($p = 0.977$, two tailed Fisher exact test) and females ($p = 0.548$) were not significant.

Gender	Blood group		Result		Total	*p* value
			Negative	Positive		
Female	AA	Count	483	31	514	0.548
		% within females	94.00%	6.00%	100.00%	
	AB	Count	217	10	227	
		% within females	95.60%	4.40%	100.00%	
	AO	Count	2254	132	2386	
		% within females	94.50%	5.50%	100.00%	
	BB	Count	39	0	39	
		% within females	100.00%	0.00%	100.00%	
	BO	Count	572	26	598	
		% within females	95.70%	4.30%	100.00%	
	OO	Count	2646	152	2798	
		% within females	94.60%	5.40%	100.00%	
Total	Total	Count	6211	351	6562	
		% within males	94.70%	5.30%	100.00%	
Male	AA	Count	449	27	476	0.977
		% within males	94.30%	5.70%	100.00%	
	AB	Count	191	13	204	
		% within males	93.60%	6.40%	100.00%	
	AO	Count	2007	133	2140	
		% within males	93.80%	6.20%	100.00%	
	BB	Count	41	3	44	
		% within males	93.20%	6.80%	100.00%	
	BO	Count	520	37	557	
		% within males	93.40%	6.60%	100.00%	
	OO	Count	2436	156	2592	
		% within males	94.00%	6.00%	100.00%	
Total	Total	Count	5644	369	6013	
		% within both	93.90%	6.10%	100.00%	

Table 2
COVID-19 outcome (alive or died) versus blood group by gender. The results for males (p = 0.102, two tailed Fisher exact test) and females (p = 0.226) were not significant.

Gender	Blood group		Alive	Died		p value
Females	AA	Count	25	6	31	
		% within females	80.60%	19.40%	100.00%	0.226
	AB	Count	10	0	10	
		% within females	100.00%	0.00%	100.00%	
	AO	Count	114	18	132	
		% within females	86.40%	13.60%	100.00%	
	BO	Count	23	3	26	
		% within females	88.50%	11.50%	100.00%	
	OO	Count	140	12	152	
		% within females	92.10%	7.90%	100.00%	
Total		Count	312	39	351	
		% within females	88.90%	11.10%	100.00%	
Males	AA	Count	23	4	27	0.102
		% within males	85.20%	14.80%	100.00%	
	AB	Count	9	4	13	
		% within males	69.20%	30.80%	100.00%	
	AO	Count	111	22	133	
		% within males	83.50%	16.50%	100.00%	
	BB	Count	3	0	3	
		% within males	100.00%	0.00%	100.00%	
	BO	Count	33	4	37	
		% within males	89.20%	10.80%	100.00%	
	OO	Count	114	42	156	
		% within males	73.10%	26.90%	100.00%	
Total		Count	293	76	369	
		% within males	79.40%	20.60%	100.00%	

older groups was largely restricted to hospital inpatients with clinical signs of infection, so test positivity is considered a good marker of severe COVID-19 [5].

Table 3
COVID-19 test results (negative or positive) versus rs657152 genotype by gender. The results for males (p = 0.707, two tailed Fisher exact test) and females (p = 0.875) were not significant.

Gender	rs657152		COVID-19		Total	p value
			Negative	Positive		
Female	AA	Count	763	45	808	0.875
		% within females	94.40%	5.60%	100.00%	
	AC	Count	2833	155	2988	
		% within females	94.80%	5.20%	100.00%	
	CC	Count	2593	148	2741	
		% within females	94.60%	5.40%	100.00%	
Total		Count	6189	348	6537	
		% within females	94.70%	5.30%	100.00%	
Male	AA	Count	690	47	737	0.707
		% within males	93.60%	6.40%	100.00%	
	AC	Count	2526	172	2698	
		% within males	93.60%	6.40%	100.00%	
	CC	Count	2410	150	2560	
		% within males	94.10%	5.90%	100.00%	
Total		Count	5626	369	5995	
		% within males	93.80%	6.20%	100.00%	

Table 4
COVID-19 outcome (alive or died) versus rs657152 genotype by gender. The result for males (p = 0.046, two tailed Fisher exact test) was of borderline significance, females (p = 0.144) not significant.

Gender	rs657152		Alive	Died	Total	p value
Female	AA	Count	39	6	45	0.144
		% within females	86.70%	13.30%	100.00%	
	AC	Count	133	22	155	
		% within females	85.80%	14.20%	100.00%	
	CC	Count	137	11	148	
		% within females	92.60%	7.40%	100.00%	
Total		Count	309	39	348	
		% within females	88.80%	11.20%	100.00%	
Male	AA	Count	36	11	47	0.046
		% within males	76.60%	23.40%	100.00%	
	AC	Count	146	26	172	
		% within males	84.90%	15.10%	100.00%	
	CC	Count	111	39	150	
		% within males	74.00%	26.00%	100.00%	
Total		Count	293	76	369	
		% within males	79.40%	20.60%	100.00%	

ABO blood type is from UKB data field 23165. Blood type was imputed for genotyped UK Biobank participants using three SNPs (rs505922, rs8176719, and rs8176746) in the ABO gene on chromosome 9q34.2. rs8176719 deletion was taken as indicative of haplotype O; for participants with no result for rs8176719, rs505922 of T was used to indicate type O. Type B was indicated by T at rs8176746 [6–9].

Data processing was performed on Minerva, a Linux mainframe with Centos 7.6, at the Icahn School of Medicine at Mount Sinai. We used PLINK, a whole-genome association analysis toolset, to process the UKB chromosome 9 files; and the UK Biobank Data Parser (ukbb parser), a python-based package that allows easy interfacing with the large UK Biobank dataset [10].

3. Results

We analyzed data from 12,575 subjects. The mean age was 58 ± 8 (mean ± SD). 52% were female, 48% were male. 98% were white British. 5.7% were positive for COVID-19. Overall mortality of COVID-19 test-positive subjects was 16%.

Blood group versus number of cases is shown in Fig. 1. Type OO was most frequent.

COVID-19 test results (negative or positive) were not related to blood group in males ($p = 0.977$, two tailed Fisher exact test) or females ($p = 0.548$, Table 1). COVID-19 outcomes (alive or died) were not related to blood group in males ($p = 0.102$, two tailed Fisher exact test) or females ($p = 0.226$, Table 2).

COVID-19 test results (negative or positive) were not related to rs657152 genotype for males ($p = 0.707$, two tailed Fisher exact test) or females ($p = 0.875$, Table 3). COVID-19 outcomes (alive or died) were marginally related to rs657152 genotype in males ($p = 0.046$, two tailed Fisher exact test); the result was insignificant when the Bonferroni correction for multiple comparisons was applied [11]. For females there was no relationship between COVID-19 outcome and rs657152 genotype ($p = 0.144$, Table 4).

4. Discussion

Studies of blood type have reported that type O blood protects against COVID-19, whereas type A blood makes an individual more vulnerable [12]. In addition, O blood is said to provide modest protection against severe illness, whereas group A is detrimental [13,14]. Type O individuals are less prone to thrombosis and vascular dysfunction than non-O individuals and therefore could be at lesser risk in case of severe lung dysfunction [15]. We are not able to confirm these observations with UKB data. Others, as well, are skeptical of any significant role ABO blood groups might play in COVID-19 [2].

A 3p21.31 6 gene cluster is a genetic susceptibility locus in patients with Covid-19 and respiratory failure [1]. This locus came from Neanderthals through interbreeding with *Homo sapiens* tens of thousands of years ago [16]. It appears in 16% of Europeans and 50% of south Asians but is absent from most people of African descent. UKB did not have the SNPS that were used to associate this locus with COVID-19.

Other Covid-19 susceptibility genes have been identified, for example, IFNAR2, which codes for a cell receptor for interferon. A variant of IFNAR2 found in one in four Europeans raises the risk of severe COVID-19 by 30%. The gene DPP9 codes for an enzyme active in lung disease. Another, gene, TYK2, encodes a signaling protein involved in inflammation. Drugs that target DPP9 and TYK2 proteins are already in use: inhibitors of DPP9 for diabetes, and baricitinib, which blocks TYK2, for arthritis. Baricitinib is in early clinical testing for COVID-19 [2].

One weakness in our study is immortal time bias [17]. During the period of observation, an interval exists during which the outcome event cannot occur. The research participants are immortal because they must survive long enough for the outcome event being evaluated. In the current study the outcome events would be COVID-19 test positivity and death. The possibility exists that we have not been able to substantiate the role of the ABO locus 9q34.2 and ABO blood groups in COVID-19 due to immortal time bias.

The impact of genetic risk factors on COVID-19 seems modest at best. The massive vaccination campaign now underway, combined with increasing population immunity, will no doubt end the current epidemic.

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CRediT authorship contribution statement

Dr. Lehrer and Dr. Rheinstein contributed equally to the conception, writing, and data analysis of this study.

Declaration of competing interest

None.

References

[1] Group SCG, D. Ellinghaus, F. Degenhardt, L. Bujanda, M. Buti, A. Albillos, P. Invernizzi, J. Fernandez, D. Prati, G. Baselli, R. Asselta, M.M. Grimsrud, C. Milani, F. Aziz, J. Kassens, S. May, M. Wendorff, L. Wienbrandt, F. Uellendahl-Werth, T. Zheng, X. Yi, R. de Pablo, A.G. Chercoles, A. Palom, A.E. Garcia-Fernandez, F. Rodriguez-Frias, A. Zanella, A. Bandera, A. Protti, A. Aghemo, A. Lleo, A. Biondi, A. Caballero-Garralda, A. Gori, A. Tanck, A. Carreras Nolla, A. Latiano, A.L. Fracanzani, A. Peschuck, A. Julia, A. Pesenti, A. Voza, D. Jimenez, B. Mateos, B. Nafria Jimenez, C. Quereda, C. Paccapelo, C. Gassner, C. Angelini, C. Cea, A. Solier, D. Pestana, E. Muniz-Diaz, E. Sandoval, E.M. Paraboschi, E. Navas, F. Garcia Sanchez, F. Ceriotti, F. Martinelli-Boneschi, F. Peyvandi, F. Blasi, L. Tellez, A. Blanco-Grau, G. Hemmrich-Stanisak, G. Grasselli, G. Costantino, G. Cardamone, G. Foti, S. Aneli, H. Kurihara, H. ElAbd, I. My, I. Galvan-Femenia, J. Martin, J. Erdmann, J. Ferrusquia-Acosta, K. Garcia-Etxebarria, L. Izquierdo-Sanchez, L.R. Bettini, L. Sumoy, L. Terranova, L. Moreira, L. Santoro, L. Scudeller, F. Mesonero, L. Roade, M.C. Ruhlemann, M. Schaefer, M. Carrabba, M. Riveiro-Barciela, M.E. Figuera Basso, M.G. Valsecchi, M. Hernandez-Tejero, M. Acosta-Herrera, M. D'Angio, M. Baldini, M. Cazzaniga, M. Schulzky, M. Cecconi, M. Wittig, M. Ciccarelli, M. Rodriguez-Gandia, M. Bocciolone, M. Miozzo, N. Montano, N. Braun, N. Sacchi, N. Martinez, O. Ozer, O. Palmieri, P. Faverio, P. Preatoni, P. Bonfanti, P. Omodei, P. Tentorio, P. Castro, P.M. Rodrigues, A. Blandino Ortiz, R. de Cid, R. Ferrer, R. Gualtierotti, R. Nieto, S. Goerg, S. Badalamenti, S. Marsal, G. Matullo, S. Pelusi, S. Juzenas, S. Aliberti, V. Monzani, V. Moreno, T. Wesse, T.L. Lenz, T. Pumarola, V. Rimoldi, S. Bosari, W. Albrecht, W. Peter, M. Romero-Gomez, M. D'Amato, S. Duga, J.M. Banales, J. R. Hov, T. Folseraas, L. Valenti, A. Franke, T.H. Karlsen, Genomewide association study of severe covid-19 with respiratory failure, N. Engl. J. Med. 383 (2020) 1522–1534.

[2] J. Kaiser, Found: genes that sway the course of the coronavirus, Science 370 (2020) 275–276.

[3] M.B. Barnkob, A. Pottegård, H. Støvring, T.M. Haunstrup, K. Homburg, R. Larsen, M.B. Hansen, K. Titlestad, B. Aagaard, B.K. Møller, T. Barington, Reduced prevalence of SARS-CoV-2 infection in ABO blood group O, Blood Adv. 4 (2020) 4990–4993.

[4] Y. Li, L. Liu, Y. Huang, H. Zheng, L. Li, Association of ABO polymorphisms and pancreatic cancer/cardiocerebrovascular disease: a meta-analysis, BMC Med. Genet. 21 (2020) 1–10.

[5] J.L. Atkins, J.A. Masoli, J. Delgado, L.C. Pilling, C.-L. Kuo, G.A. Kuchel, D. Melzer, Preexisting comorbidities predicting COVID-19 and mortality in the UK Biobank community cohort, J. Gerontol. A Biol. Sci. Med. Sci. (2020), https://doi.org/10.1093/gerona/glaa183.

[6] D. Melzer, J.R. Perry, D. Hernandez, A.-M. Corsi, K. Stevens, I. Rafferty, F. Lauretani, A. Murray, J.R. Gibbs, G. Paolisso, A genome-wide association study identifies protein quantitative trait loci (pQTLs), PLoS Genet. 4 (2008), e1000072.

[7] G. Paré, D.I. Chasman, M. Kellogg, R.Y. Zee, N. Rifai, S. Badola, J.P. Miletich, P. M. Ridker, Novel association of ABO histo-blood group antigen with soluble ICAM-1: results of a genome-wide association study of 6,578 women, PLoS Genet. 4 (2008), e1000118.

[8] B.M. Wolpin, P. Kraft, M. Gross, K. Helzlsouer, H.B. Bueno-de-Mesquita, E. Steplowski, R.Z. Stolzenberg-Solomon, A.A. Arslan, E.J. Jacobs, A. LaCroix, Pancreatic cancer risk and ABO blood group alleles: results from the pancreatic cancer cohort consortium, Cancer Res. 70 (2010) 1015–1023.

[9] H.E. Groot, L.E. Villegas Sierra, M.A. Said, E. Lipsic, J.C. Karper, P. van der Harst, Genetically determined ABO blood group and its associations with health and disease, Arterioscler. Thromb. Vasc. Biol. 40 (2020) 830–838.

[10] A. Zhu, L.E. Salminen, P.M. Thompson, N. Jahanshad, The UK Biobank Data Parser: A Tool With Built in and Customizable Filters for Brain Studies, Organization for Human Brain Mapping, Rome, Italy, 2019 (June 9–13, 2019).

[11] E.W. Weisstein, Bonferroni Correction. https://mathworld.wolfram.com/, 2004.

[12] J. Zhao, Y. Yang, H. Huang, D. Li, D. Gu, X. Lu, Z. Zhang, L. Liu, T. Liu, Y. Liu, Relationship between the ABO blood group and the COVID-19 susceptibility, Clin. Infect. Dis. (2020), https://doi.org/10.1093/cid/ciaa1150.

[13] X. Dai, ABO blood group predisposes to COVID-19 severity and cardiovascular diseases, Eur. J. Prev. Cardiol. 27 (2020) 1436–1437.

[14] E. Muñiz-Diaz, J. Llopis, R. Parra, I. Roig, G. Ferrer, J. Grifols, A. Millán, G. Ene, L. Ramiro, L. Maglio, Relationship between the ABO blood group and COVID-19 susceptibility, severity and mortality in two cohorts of patients, Blood Transfus. 19 (2021) 54.

[15] J.L. Pendu, A. Breiman, J. Rocher, M. Dion, N. Ruvoen-Clouet, ABO blood types and COVID-19: spurious, anecdotal, or truly important relationships? A reasoned review of available data, Viruses 13 (2021).

[16] H. Zeberg, S. Pääbo, The major genetic risk factor for severe COVID-19 is inherited from Neanderthals, Nature 587 (2020) 610–612.

[17] K. Yadav, R.J. Lewis, Immortal time bias in observational studies, JAMA 325 (2021) 686–687.