Blood group A epitopes do not facilitate entry of SARS-CoV-2

Keypoint

The risk of contracting SARS-CoV-2 was slightly higher for individuals with blood group A versus O but did not differ between blood groups A_1 versus A_2. With much higher epitope density of blood group A_1, this suggests that the A epitope itself does not facilitate viral entry.

Information on the impact of ABO blood group (BG) on SARS-CoV-2 infections is conflicting [1–4]. To identify risk factors for severe COVID-19 courses, we performed a cross-sectional study in volunteers between 18 and 61 years of age registered with DKMS for stem cell donation approved by the institutional review board of the Technische Universität Dresden. All participants provided explicit consent that COVID-19-specific data were linked to genotype data in the donor registry file. Patient-reported data on swabs, risk factors, symptoms and treatment of COVID-19 were collected with a health questionnaire and linked to existing data on ABO and Rhesus [5]. *ABO* genotype data were grouped into ABO BG phenotypes by assuming dominant expression for A_1 over A_2 and BG A or B over BG O. Severe respiratory tract infections (RTIs) were defined by the combination of at least fever and cough, dyspnoea and cough, dyspnoea and fever, or dyspnoea and myalgia. This group included patients with respiratory hospitalization, defined by inpatient care with supplemental oxygen or mechanical ventilation or hospitalization for dyspnoea or cough. We fitted multivariable logistic regression models for the risk of contracting SARS-CoV-2, risk of severe respiratory infection and risk of hospitalization. All models were adjusted for age, sex, BMI, diabetes mellitus, arterial hypertension and smoking status. Age, BMI and month of positive test were modelled as categorical variables.

Amongst 125 125 participants tested for SARS-CoV-2 with ABO genotypes available (102 426 at allele-level resolution), 6257 tested virus-positive. A patient flow chart and characteristics are shown in Figure S1 and Table S1. Overall, 11.9% of SARS-CoV-2-positive participants reported asymptomatic courses, 59.5% reported mild/moderate symptoms, 25% reported severe respiratory tract infections, and 3.6% reported hospitalization for respiratory tract infections.

We found that BG A was a risk factor for contracting SARS-CoV-2 compared with BG O (adjusted OR 1.15; 95% CI 1.08–1.22, $P < 0.001$) (Figure S2, Panels A + C). Based on similar observations in previous studies, the hypothesis had been raised that A epitopes facilitate virus entry [2–4]. Individuals with BG A_1 have a higher glycosyltransferase activity and thus expose more than fourfold higher numbers of A epitopes compared with individuals with BG A_2 [6]. Therefore, we tested whether individuals with A_1 phenotype have a greater risk of infection compared with individuals with A_2 phenotype. Participants with A_1 and A_2 phenotypes, however, showed comparable rates of infections (adjusted OR 1.03; 95% CI 0.93–1.15, $P = 0.58$) (Figure S2). Our data therefore argue against the hypothesis that A epitopes facilitate SARS-CoV-2 entry into cells. Participants with BG AB (adjusted OR 1.19; 95% CI 1.06–1.35, $P = 0.004$) had significantly more infections as well, but no difference was found for participants with BG B phenotype compared with BG O. Exploratory analyses of *ABO* genotypes showed that participants who were homozygous for BG *B* had the lowest odds ratio and participants who were homozygous for A_2 had the highest odds ratio for positive tests (Table 1 and Table S2).

Genetic variance in *ABO* genes has been associated with the risk for venous thromboembolism, stroke, coronary artery disease and acute respiratory distress syndrome regardless of COVID-19 [7–9]. Glycosylation patterns may impact on the clearance of plasma proteins (e.g. of the von Willebrand factor) and thus impact on end-stage coagulation and thrombosis [10]. In our study, however, BG A did not show an impact on COVID-19 severity. Blood group B was associated with a higher risk of severe RTI (OR 1.24; 95% CI 1.01–1.53, $P = 0.038$) and respiratory hospitalizations (OR 1.78; 95% CI 1.18–2.68, $P = 0.006$) compared with BG O (Figure S2, Panels B + D). Exploratory analyses of the genotype compositions of BG B, however, did not reveal a pattern suggesting causality (Table 1), and

Table 1. *Impact of ABO genotypes and phenotypes*

| Genotype | Contracting SARS-CoV-2 | | | | Evaluable[a] infections | Severe respiratory tract infections | | | Respiratory hospitalizations | | |
	Tests (%)	Cases	OR (95% CI)	P	N	N	OR (95% CI)	P	N	OR (95% CI)	P
$O+O$	40 975 (40.0)	1916	1		1653	398	1		55	1	
$B+O$	10 997 (10.7)	533	1.05 (0.94–1.16)	0.392	443	138	1.45 (1.14–1.83)	0.002	30	2.16 (1.36–3.45)	0.001
$B+B$	869 (0.8)	37	0.95 (0.68–1.34)	0.784	33	6	0.71 (0.29–1.77)	0.467	1	0.79 (0.10–6.07)	0.817
$B+A_1$	4072 (4.0)	215	1.17 (1.01–1.36)	0.042	186	53	1.29 (0.92–1.83)	0.140	6	1.01 (0.42–2.39)	0.987
$B+A_2$	1298 (1.3)	70	1.29 (1.00–1.66)	0.052	59	17	1.30 (0.73–2.33)	0.377	0	-	-
A_1+O	27 251 (26.6)	1462	1.15 (1.07–1.23)	<.001	1229	316	1.09 (0.92–1.30)	0.311	36	0.89 (0.58–1.37)	0.589
A_1+A_1	4612 (4.5)	214	0.99 (0.85–1.15)	0.860	187	54	1.26 (0.90–1.77)	0.180	5	0.78 (0.31–1.99)	0.604
A_1+A_2	3031 (3.0)	169	1.22 (1.03–1.44)	0.023	150	35	0.90 (0.60–1.34)	0.611	5	0.99 (0.39–2.55)	0.990
A_2+O	8714 (8.5)	470	1.16 (1.04–1.29)	0.008	407	112	1.23 (0.96–1.58)	0.101	12	0.92 (0.48–1.74)	0.785
A_2+A_2	523 (0.5)	30	1.32 (0.90–1.95)	0.157	28	10	1.93 (0.87–4.27)	0.107	0	-	-

CI, confidence interval; N, number of cases; OR, odds ratio; P, P value.
Odds ratios were calculated in a multivariable logistic regression model containing information on age, sex, BMI, diabetes mellitus, arterial hypertension, smoking status and month of testing.
[a]Infections reported for the months January to July, excluding August and September.

BG B has not been described consistently as risk factor for severe COVID-19 courses [2,4]. Therefore, we interpret this association as incidental finding. Rhesus BG did not have an impact on any clinical end-point (Table S2).

In conclusion, we confirm that individuals with BG A have a greater risk of infection compared with individuals with BG O. The observation of comparable risks of contracting SARS-CoV-2 amongst individuals with A_1 versus A_2 together with the knowledge of a more than fourfold higher epitope density for A_1 versus A_2 suggests that the A epitope itself, for example by modifying the ACE protein, does not facilitate viral entry. This leaves alternative hypotheses of absorbing anti-A antibodies or genetic linkage as possible explanations for the higher risk of contracting SARS-CoV-2 for individuals with BG A compared with BG O. In line with others, we did not find a consistent impact of ABO BG on the severity of COVID-19.

Conflict of interest statement

All authors have completed the Unified Competing Interest form (available on request from the corresponding author) and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous three years and no other relationships or activities that could appear to have influenced the submitted work.

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Transparency declaration

The corresponding author (JS) declares that this manuscript is an honest, accurate and transparent account of the study being reported. No important aspects of the study have been omitted, and there were no discrepancies from the study as planned and registered.

Author contribution

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Data availability statement

De-identified analysis of data of this study may be shared under the following conditions. Applicants have to guarantee full compliance with the European General Data Protection Regulation. Researchers have to submit a study protocol, which has been approved by their local institutional review board together with a curriculum vitae. Project proposals will be reviewed formally for compliance, feasibility, scientific merit and potential clinical impact. Data will only be shared after a mutually agreed data transfer agreement had been signed.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Flow chart.

Figure S2. Rates of positive SARS-CoV-2 tests and severe respiratory tract infection by ABO blood group genotype and phenotype.

Table S1. Characteristics of SARS-CoV-2 positive and negative participants.

Table S2. Risk of infection, severe respiratory tract infection, and respiratory hospitalization by *ABO* genotype including rare variants and Rhesus genotype.