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Brief report

Association of blood group A with hospital comorbidity in patients infected by SARS-CoV-2☆

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ABSTRACT

Background and objectives: In the pandemic caused by SARS-CoV-2, identifying which risk factors are associated with the most serious forms of the disease is important. Blood group A has been presented in various studies as a poor prognostic factor. The objective of this study was to evaluate whether patients with blood group A were associated with more important comorbidities, measured by the Charlson Index, which may explain their worse clinical evolution.
Patients and methods: A prospective and consecutive study examined 100 patients diagnosed with COVID-19 and admitted in March 2020. A multivariate linear regression model was used to evaluate the association of blood group A with the Charlson Index.
Results: Patients in group A had a higher Charlson Index (P=.037), rate of lymphopenia (P=.039) and thrombopenia (P=.014), and hospital mortality (P=.044). Blood group A was an independent factor associated with the Charlson Index (B 0.582, 95% CI 0.02–1.14, P=.041).
Conclusions: Group A was independently associated with greater comorbidity, associated with an increase of 0.582 points in the Charlson Index compared to other blood groups. It was also associated with lower hospital mortality.

Asociación del grupo sanguíneo A con mayor comorbilidad hospitalaria en pacientes infectados por SARS-CoV-2

Palabras clave:
Grupos sanguíneos
COVID-19
Índice de Charlson
Mortalidad

RESUMEN

Fundamento y objetivos: En la pandemia provocada por SARS-CoV-2, es importante identificar qué factores de riesgo se asocian a las formas más graves de la enfermedad. El grupo sanguíneo A se ha presentado en diversos estudios como factor de mal pronóstico. El objetivo de este estudio radica en evaluar si los pacientes de grupo sanguíneo O asocian comorbilidades más importantes, medido por el Índice de Charlson, que puedan justificar también su peor evolución clínica.
Pacientes y método: Estudio prospectivo y consecutivo con 100 pacientes diagnosticados de COVID-19 ingresados en marzo de 2020. Se empleó un modelo de regresión lineal multivariante para evaluar la asociación del grupo sanguíneo A con el Índice de Charlson.
Resultados: Los pacientes del grupo A presentaron mayor Índice de Charlson (P=.037), linfopenia (P=.039), trombopenia (P=.014) y mortalidad hospitalaria (P=.044).
El grupo sanguíneo A demostró ser un factor independiente asociado a dicho índice [B 0.582, IC 95% (0.02–1.14), P=.041].

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Conclusiones: El grupo A se asocia de forma independiente a mayor comorbilidad, asociando un incremento de 0.582 puntos en el índice de Charlson con respecto al resto de grupos sanguíneos. Además, asocia una tendencia de menor mortalidad hospitalaria.

Rationale and objectives

A new strain of coronavirus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), appeared in Wuhan (China) in December 2019.[1] Numerous studies have been carried out ever since to understand the epidemiological and pathophysiological characteristics of the disease caused by it. We know that at least half of patients who become infected by this virus experience mild or no symptoms after an average incubation period of five days. The remainder develop a moderate or severe respiratory disease, with around 20% manifesting a severe disease with high fever and pneumonia[2] that lead to acute respiratory distress syndrome.

Broadly speaking, at a pathophysiological level the virus causes a rapid activation of the innate immune cells. In addition, risk profiles have been developed with biomarkers linked to a moderate or severe infection, such as absolute lymphopenia, increased serum Creactive protein levels, hypoalbuminemia, or increased levels of liver enzymes, lactate dehydrogenase, ferritin, or D-dimer,[3] but these markers are not definitive and, as can be seen in the literature, cannot explain or predict many cases.

The association between a person's blood group and their susceptibility to suffer from infectious diseases, such as *Helicobacter pylori, Plasmodium falciparum*, or other viruses, including noroviruses,[4] the hepatitis B virus,[5] the severe acute respiratory syndrome coronavirus (SARS-CoV),[6] and the Middle East respiratory syndrome-related coronavirus (MERS-CoV)[7] is well known, and, more recently, its relationship with the SARS-CoV-2 is starting to become evident. Given this previous knowledge in relation to multiple viral infections, several studies have been conducted to explore the influence of blood groups on the clinical evolution and severity of the 2019 coronavirus disease (COVID-2019),[8] observing an increased susceptibility among subjects with blood group A.[9]

Hence, the aim of this study is to demonstrate this worse evolution of the disease among subjects with blood group A and to determine whether these COVID-19 patients have increased comorbidities, as measured by Charlson's comorbidity index, that could explain their worse in-hospital clinical evolution.

Patients and method

Study design

This was a prospective, sequential study including 100 adult patients diagnosed with COVID-19 who were admitted to the Clinical University Hospital of Valladolid (Spain) between the 23rd and 27th of March 2020 to receive treatment. All of them had manual blood typing performed on samples of blood collected routinely in hematology testing blood tubes with ethylenediaminetetraacetic acid (EDTA) on their admission to the hospital. All patients had a positive diagnosis for a SARS-CoV-2 infection detected by means of a specific polymerase chain reaction (PCR) test performed on a nasopharyngeal swab sample. Clinical and epidemiological data, in addition to analytical variables, were collected. Patients with an active infection or under palliative treatment were excluded from the study. Their blood group was determined using an autoanalyzer (Erytra automated system). Our study was approved by the hospital's clinical ethics committee (CEC) (code: PI 20-1717). We applied the code of ethics of the World Medical Association (Helsinki Declaration) and the STROBE declaration for the conduct and completion of the study.

Statistical analysis

The main study variable was Charlson's comorbidity index, a quantitative variable in the form of a scale established with a set of clinical variables. Differences between continuous variables were determined through the Mann-Whitney *U* test Categorical clinical and demographic variables were analyzed with the chi-square test. A multivariate linear regression analysis was carried out using the automatic forward stepwise method to evaluate the association between blood group A and Charlson's comorbidity index. Potential confounding factors with a *P*-value <.1 were included in the model as adjustment variables. There were no missing values for any of the variables included in the analysis. The statistical analysis was carried out with IBM SPSS software version 24.

Results

Both study arms were similar in terms of age and sex. As for comorbidities, a greater number of patients with blood group A had a history of cancer ($P = .038$). The treatment history of both study arms was also similar. The arm including patients with blood group A had a higher number of comorbidities, as determined by Charlson's comorbidity index ($P = .037$), as well as a higher percentage of non-survivors ($P = .044$) compared with the arm including patients with other blood groups. Patients with this blood group also had a lower platelet ($P = .014$) and lymphocyte ($P = .039$) count compared with those of the other study arm (Table 1).

The multivariate linear regression analysis showed that blood group A is a factor independently associated with the presence of comorbidities. In fact, this blood group was linked to a 0.582-point increase in Charlson's comorbidity index (B 0.582; 95% confidence interval [CI] 0.02–1.14; $P = .041$) (Table 2).

Both the calculation of frequencies and the chi-square test demonstrate that blood group A is linked to a higher in-hospital mortality ($P = .044$) compared with the others.

Discussion

The results of our study show that patients with blood group A have an increased rate of comorbidities associated with COVID-19, as they had a 0.582-point higher score in Charlson's comorbidity index compared with patients with other blood groups. Thus, these findings could indicate that a person's ABO blood group correlates with their susceptibility to developing a SARS-CoV-2 infection.

The ABO blood group system mostly involves the A and B antigens and their corresponding antibodies. Hence, according to this system, there are four genetic phenotypes (groups A, B, O, and AB).

Differences in antigen expression have been related to a person's susceptibility to develop infections,[10] as several antigens can modify the innate immune system. This theory has been validated in certain studies, such as that performed by Cooling,[10] whose findings demonstrated that antigens from blood groups are valid receptors for some infectious microorganisms. In fact, it has been described for several widely known viral infections, such as the West Nile virus infection or rotaviral gastroenteritis.

In the case of SARS-CoV-2, prior knowledge about SARS-CoV, which has a similar nucleic acid sequence and angiotensin-converting enzyme 2 combination to that of SARS-CoV-2, might explain the reason why some people with blood group A could be

Table 1
Patients' clinical characteristics.

	Blood group A (n = 55)	Other blood groups (n = 45)	*P* value
[0.1-4] *Characteristics*			
Age, years, median (IQR)	70 (15)	66 (16)	.376
Sex, % (n)	55.6 (30)	59.1 (26)	.765
[0.1-4]*Comorbidities, % (n)*			
Heart disease	20 (11)	13.3 (6)	.472
COPD	10.9 (6)	4.4 (2)	.356
Asthma	3.6 (2)	0 (0)	.542
HBP	54.5 (30)	37.8 (17)	.298
Chronic kidney failure	3.6 (2)	2.2 (1)	.671
Chronic liver disease	3.6 (2)	0 (0)	.193
Stroke	1.8 (1)	0 (0)	.360
Diabetes mellitus	0 (0)	2.2 (1)	.755
Obesity	12.7 (7)	11.1 (5)	.720
Cancer	9.1 (5)	0 (0)	**.038**
Autoimmune disease	1.8 (1)	0 (0)	.360
[0.1-4] *Prior treatments, % (n)*			
Oral glucocorticosteroids	3.6 (2)	4.4 (2)	.671
Thyroid hormones	12.7 (7)	13.3 (6)	.513
Prior treatment with statins	43.6 (24)	31.1 (14)	.123
Beta-blockers	14.5 (8)	6.7 (3)	.785
Immunosuppressants	9.1 (5)	2.2 (1)	.243
ACEIs	18.2 (10)	13.3 (6)	.219
ARAs II	18.2 (10)	13.3 (6)	.879
[0.1-4] *Severity*			
Charlson's comorbidity index, median (IQR)	3 (2)	2 (2)	**.037**
Admission to the Resuscitation Unit, % (n)	45.5 (25)	33.3 (15)	.089
Mechanical ventilation, % (n)	38.2 (21)	24.4 (11)	.056
In-hospital mortality, % (n)	27.3 (15)	11.1 (5)	**.044**
[0.1-4] *Measures taken at diagnosis, median (IQR)*			
CRP (mg/L)	97 (113)	63 (158)	.819
Procalcitonin (ng/mL)	0.15 (0.38)	0.09 (0.20)	.993
D-dimer (ng/mL)	983 (1,700)	907 (1,250.25)	.233
LDH (IU/L)	321.50 (159.25)	300 (147)	.234
CPK (IU/L)	87.50 (112)	87 (106.25)	.801
Platelets (cells/mm^3)	191,000 (84,500)	237,000 (139,500)	**.014**
Leukocytes (cells/mm^3)	7,270 (5,750)	7,390 (3,965)	.897
Lymphocytes (cells/mm^3)	735 (735)	940 (601)	**.039**
Neutrophils (cells/mm^3)	5,665 (5,172.50)	5,250 (3,965)	.894

ACEIs: angiotensin-converting enzyme inhibitors; ARAs II: angiotensin II receptor antagonists; COPD: chronic obstructive pulmonary disease; CPK: creatine phosphokinase; CRP: C-reactive protein; IQR: interquartile range; HBP: high blood pressure; LDH: lactate dehydrogenase.
Continuous variables were represented as a median (IQR).
Categorical variables were represented as a % (n).
Values in bold are those that reached statistical significance.

Table 2
Multivariate analysis to evaluate the association between blood group A and Charlson's comorbidity index.

	[0.2-6] Multivariate analysis for Charlson's index				
	B	Error	[0.4-5] [95% CI]		*P*
Prior treatment with statins	1.386	0.288	0.81	1.96	<.001
Thyroid hormones	0.937	0.411	0.12	1.75	.025
Blood group A	0.582	0.281	0.02	1.14	.041

more susceptible to developing an infection by this virus. Guillon et al. described how anti-A antibodies could block the interaction between SARS-CoV and its receptor, therefore offering protection against the infection.[6] Thus, adhesion of cells expressing the SARS-CoV-2 protein could be specifically inhibited by anti-A antibodies.

Another important factor to be considered is the higher proportion of patients with blood group A who were hospitalized in our cohort (55%) compared with that observed in the general Spanish population (43%). Likewise, a decreased rate of admissions among patients with blood group O was also observed. This would corroborate the hypothesis of the existence of a greater susceptibility to develop an infection by this virus among patients with blood group A,[8] who, as a result of having a greater morbidity, mortality, and severity, have to be hospitalized more frequently and, as seen in our study, are even linked to greater in-hospital mortality rates.

Our study had certain limitations, including, on the one hand, our reduced sample size of 100 COVID-19 patients and a hypothesis testing power of 52%, which could result in a certain degree of bias in our results. On the other hand, we did not include a control arm of patients without COVID-19, although the variations detected in our sample of patients with a SARS-CoV-2 infection have not been evidenced in the general healthy population. Considering the above, new studies with a larger sample size analyzing the association between susceptibility to the infection and the relationship with numerous comorbidities should be carried out, in addition to molecular studies that would allow to explain these facts.

Conclusion

In the context of a SARS-CoV-2 infection, blood group A was found to be independently related to Charlson's comorbidity index

using a multivariate model with specified adjustment variables. In addition, we identified a relationship between the presence of this blood group and greater in-hospital mortality.

It would be necessary to confirm these findings with new analyses including other predictor variables and to define susceptibility to this infection by describing its mechanism at a molecular level.

Conflicts of interest

The authors of this paper declare no conflicts of interest.

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