Down the Rabbit-Hole of blood groups and COVID-19

I read with great interest the recently published article by Li et al.[1] which suggests that a risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection may be significantly higher in subjects with blood group A and significantly lower in those with blood group O. This case-control study compared the ABO blood-group distribution in 265 cases with coronavirus disease 2019 (COVID-19) at the Central Hospital of Wuhan with that in 3 694 healthy controls.[1] To verify the clinical findings by Li et al.[1] I herein would like to epidemiologically analyze the relationship between blood-group distribution (i.e. proportion of subjects with blood-group O, and A, B, and AB) and SARS-CoV-2 infection (i.e. COVID-19 prevalence) in nations around the world.

Blood-group distribution in 101 different nations was available on Rhesus Negative (http://www.rhesusnegative.net/themission/bloodtypefrequencies/). For these nations, I extracted total confirmed COVID-19 cases and deaths on 25 June 2020 from the website of the World Health Organization (WHO) (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/); total population, total pure-alcohol consumption, life expectancy at birth, medical-doctor and nursing/midwifery personnel density, hypertension and obesity prevalence, and annual PM2.5 [particulate matter 2.5] concentrations from WHO (https://www.who.int/gho/publications/world_health_statistics/2020/en/); population ages 0–14 and ≥65, GDP (Gross Domestic Product) and GNI (Gross National Income) per capita, PPP (Purchasing Power Parity), and diabetes prevalence from World Bank (https://data.worldbank.org/indicator/); and daily-ambient UV (ultraviolet) radiation from WHO (https://apps.who.int/gho/data/view.main.35300) (Table SI). Random-effects meta-regression (i.e. inverse variance-weighted regression), dealing with a nation as a study (in a meta-analysis), was performed using OpenMetaAnalyst (http://www.cebm.brown.edu/openmeta/index.html). No comparable data regarding COVID-testing regimens, death timing (post a positive test), and imposed-lockdown timing/extent/duration were available. All the above-mentioned covariates were together entered in the multivariate model. A meta-regression graph depicted the COVID-19 prevalence/fatality (plotted as the logarithm-transformed prevalence/fatality on the *y*-axis) as a function of a given covariate (plotted on the *x*-axis). Because of relatively low proportions of subjects with blood-group Rh(−), only blood-group Rh(+) was investigated.

The present analysis included a total of 8·9-million COVID-19 cases and 465 000 deaths on a total of 6·8-billion populations. Results of the univariate and multivariate meta-regression were summarized in Table I. The univariate model for COVID-19 prevalence indicated a significant association of higher blood-group B-Rh(+) (coefficient, −0·089; P <0·001; Fig 1A) with lower prevalence and no correlation of O-Rh(+), A-Rh(+), and AB-Rh(+) to prevalence. In the multivariate regression, however, there was no association of B-Rh(+) with prevalence. The univariate model for COVID-19 fatality indicated

Table I. Meta-regression summary.

	COVID-19 prevalence					COVID-19 fatality				
Covariate	Coefficient	Lower limit of 95% CI	Upper limit of 95% CI	*P* value	Figure	Coefficient	Lower limit of 95% CI	Upper limit of 95% CI	*P* value	Figure
Univariate model										
Blood-group O-Rh(+) (%)	−0·008	−0·041	0·024	0·615		−0·030	−0·047	−0·014	**<0·001**	Fig 1B
Blood-group A-Rh(+) (%)	0·032	−0·022	0·086	0·247		0·073	0·047	0·099	**<0·001**	Fig 1D
Blood-group B-Rh(+) (%)	−0·089	−0·134	−0·043	**<·001**	Fig 1A	−0·037	−0·063	−0·012	**0·004**	Fig 1C
Blood-group AB-Rh(+) (%)	−0·096	−0·254	0·062	0·233		−0·003	−0·088	0·082	0·945	
Multivariate model*										
Blood-group O-Rh(+) (%)	Not performed					−0·024	−0·044	−0·003	**0·022**	
Blood-group A-Rh(+) (%)	Not performed					0·028	−0·003	0·059	0·081	
Blood-group B-Rh(+) (%)	−0·573	−1·439	0·293	0·195		−0·001	−0·035	0·034	0·970	
Blood-group AB-Rh(+) (%)	Not performed					Not performed				

CI, confidence interval.

*Adjusted for population ages 0–14/≥65, hypertension, obesity, diabetes, tobacco-use, life expectancy at birth, medical-doctor/nursing/midwifery personnel density, GDP (Gross Domestic Product)/GNI (Gross National Income) per capita–PPP (Purchasing Power Parity), annual PM2·5 (particulate matter 2·5) concentration, and daily ambient UV (ultraviolet) radiation. Bold values mean statically significant.

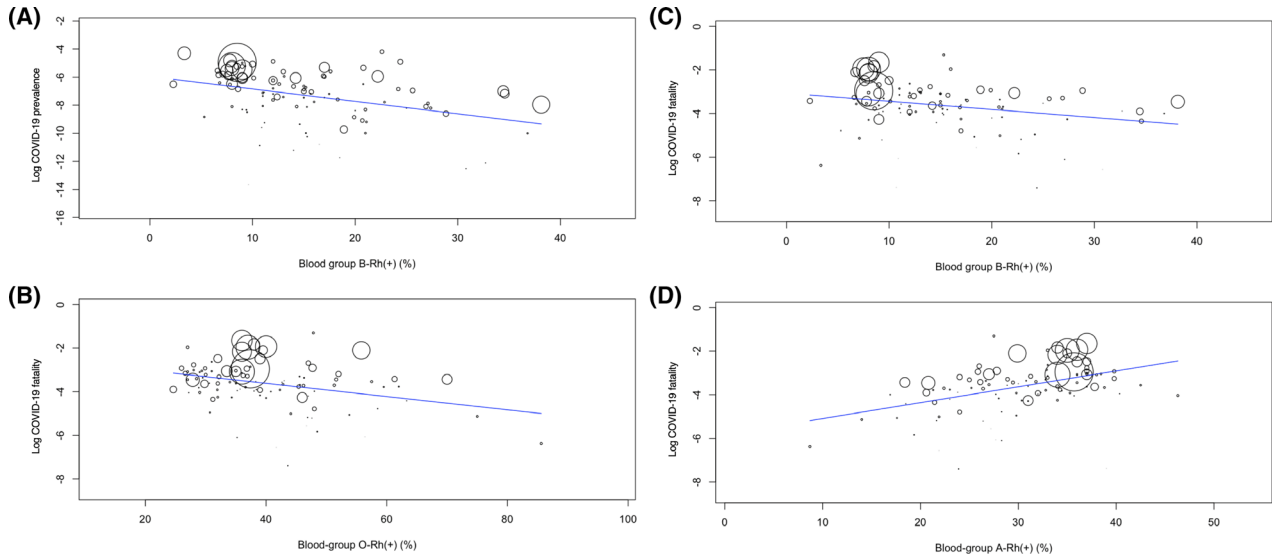

Fig 1. Metaregression graphs depicting the COVID-19 prevalence/fatality (plotted as the logarithm-transformed prevalence/fatality on the *y*-axis) as a function of a given covariate (plotted on the *x*-axis). Logarithm-transformed prevalence on blood group B-Rh(+) (A) and logarithm-transformed fatality on O-Rh(+) (B), B-Rh(+) (C), and A-Rh(+) (D).

significant correlations of higher O-Rh(+) (coefficient, −0·030; $P < 0·001$; Fig 1B) and B-Rh(+) (coefficient, −0·037; $P = 0·004$; Fig 1C) to lower fatality, a significant association of higher A-Rh(+) (coefficient, 0·073; $P = 0·001$; Fig 1D) with higher fatality, and no correlation of AB-Rh(+) to fatality. In the multivariate regression, there was no association of A-Rh(+) and B-Rh(+) with fatality but a significant correlation of higher O-Rh(+) (coefficient, −0·024; $P = 0·022$) to lower fatality.

In summary, although blood groups may not be associated with SARS-CoV-2 infection (i.e. COVID-19 prevalence), O-Rh(+) may be independently and protectively correlated to COVID-19 fatality. The present findings do not mean directly that COVID-19 patients with blood group O-Rh(+) are at lower risk of death, which should be heeded. The present results denote simply that COVID-19 fatality was lower in nations with higher blood group O-Rh(+) prevalence because not patients' but populations' blood groups were analyzed. It should be also mentioned that COVID-testing regimens, death timing (post a positive test), and imposed-lockdown timing/extent/duration were not considered as covariates in the present multivariate regression, which may have brought about inconsistence of COVID prevalence and fatality. The absence of an association of blood groups with SARS-CoV-2 infection suggested in the present analysis does not correspond with the findings by Li et al.[1] which may be explained by the following. First, the present analysis applied meta-regression (i.e. inverse variance-weighted regression) with the multivariable model adjusting for 14 potential confounders, whereas Li et al.[1] simply compared the COVID-19 cases and the healthy controls. Second, sample size of the study by Li et al.[1] was only 3 959 (265 cases and 3 694 controls), which is far smaller than the total of 6·8-billion people (including a total of 8·9-million cases) in the present analysis. Several previous findings,[2-4] however, may strengthen the results of the study by *Li* et al.[1] Furthermore, the Severe Covid-19 GWAS [genome-wide association study] Group[5] recently found, in their meta-analysis adjusting for age and sex, a higher and lower risk for respiratory failure due to COVID-19, respectively, in blood groups A and O than in other blood groups. Because of the nation-level epidemiological design, the present results should be confirmed by further experimental and clinical investigations.

Conflict of interest

The author declares no competing interests.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table SI. Data from 101 nations across the world.

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Thrombolysis restores perfusion in COVID-19 hypoxia

Thrombolysis with tissue plasminogen activator (tPA) is an established treatment strategy for patients with intermediate and high-risk pulmonary embolism (PE) and signs of haemodynamic instability. The use of tPA in coronavirus disease 2019 (COVID-19) patients with PE and acute respiratory distress syndrome (ARDS) may be of benefit due to the unusually high incidence of pulmonary embolism and pulmonary thrombosis, particularly microvascular thrombosis, which are thought to contribute significantly to hypoxaemia.[1] It may also ameliorate the effects of extravascular and intra-alveolar fibrin deposition described in ARDS.[2] Inhaled delivery of tPA and two doses of tPA against placebo[3] are currently under trial. Small case series have reported transient improvements in oxygenation without significant bleeding from systemic fibrinolytic therapy in patients with ARDS and COVID-19.[4] Here, we describe the largest cohort to date of patients with COVID-19 treated with alteplase for severe hypoxia. This retrospective observational study was approved by the institutional review board as a service evaluation project and no further ethical approval was required.

All alteplase prescriptions from 17 April 2020 to 25 May 2020 were retrieved from pharmacy electronic records and those used for COVID-19 were identified. Clinical and laboratory parameters were extracted from patient electronic records. Statistical analyses were performed using GraphPad Prism v8·4 (GraphPad Software, San Diego, CA, USA). Descriptive statistics were used to summarize the data; results are reported as medians and ranges or means and standard deviations, as appropriate. Categorical variables were summarized as counts and percentages. Pre- and post-thrombolysis parameters were compared using a paired *t*-test. A two-sided P value $< 0{\cdot}05$ was considered statistically significant.

During the study period, 12 patients received thrombolysis with alteplase for profound hypoxia on mechanical ventilation (except patient 5 on continuous positive airway pressure) and failed proning, with or without evidence of pulmonary thrombosis on computed tomography pulmonary angiography (CTPA). Baseline demographic features, clinical history, CTPA and echocardiographic findings prior to thrombolysis, dose of alteplase with infusion time and days since admission to thrombolysis are summarized in Table I. Only one patient[4] was on antithrombotic therapy (warfarin) and aspirin prior to admission due to a previous history of left apical mural thrombus. None of the patients had previous malignancy or autoimmune disease. Median (range) age of the group was 61·5 (51–75) years and 7/12 patients were male. Median duration from admission to thrombolysis was nine days (range 2–22). All patients received therapeutic heparin pre and post thrombolysis. Five of the 12 patients had multiorgan failure (defined as failure of two or more organ supports) and required renal replacement therapy. All except one (patient 5 on continuous positive airway pressure) were retained on mechanical ventilation following thrombolysis. The decision to use thrombolysis was made due to moderate to severe hypoxia with ratios of arterial pressure to inspired oxygen (PaO_2/FiO_2, PF ratio) <200 mm Hg on mechanical ventilation and failing all other interventions including proning and nitrates.

PF ratios pre and 24 h post thrombolysis are shown in Fig 1, which showed a significant improvement in all patients ($P = 0{\cdot}002$). Only three patients had a follow-up CTPA and echocardiogram. These showed marked improvement in thrombotic occlusions and right ventricular strain (patients 5, 11 and 12). Seven patients survived to hospital discharge whilst others died from 2 to 11 days following thrombolysis due to multiorgan failure (patient 2, 3 4, 6 and 9). Overall mortality was 41·67%.

Twenty-four hours after thrombolysis, median fibrinogen level fell from 7·0 (range 4·95–8·9) g/l to 3·40 (2·50–6·30) g/l ($P = 0{\cdot}03$) and median D-dimer level increased from 3502 (range 862–9929) ng/ml to 19450 (11495–>20000) ($P = 0{\cdot}002$). There were no differences in haemoglobin, platelet count, C-reactive protein, prothrombin time, activated partial thromboplastin time, renal or liver function tests pre and 24 h post thrombolysis.

There were no major or clinically significant minor bleeding complications of thrombolysis. However, one patient had intracranial bleeding 17 days after thrombolysis whilst on unfractionated heparin.