I read with interest the recent article by Li et al., detailing the risk for COVID-19 pneumonia and for the different ABO blood groups.

After demonstrating that group O healthcare workers were less likely to become infected with SARS-CoV-2, a research group proved that anti-A blood group natural isoagglutinins inhibit SARS-CoV-2 entry into competent cells and could opsonize viral particles leading to complement-mediated neutralization. Since SARS-CoV-2 uses the same receptor as SARS-CoV, anti-A isoagglutinins are expected to have similar effects against SARS-CoV-2, accordingly, clusters of glycosylation sites exist proximal to the receptor-binding motif of the SARS-CoV and SARS-CoV-2 S protein.

Several recent publications from China, the USA, Turkey, Spain and Italy have shown that the odd ratio for acquiring COVID-19 is higher in blood group A than in blood group O when compared to healthy controls (Table I), while no statistically significant difference was found for groups B and AB. Most importantly, the Italian–Spanish genome-wide association study identified the rs657152 polymorphism in the ABO locus on chromosome 9q34 (and only one other polymorphism in chromosome 3p21-31) as the only susceptibility locus for respiratory failure in COVID-19, suggesting that, in addition to disease acquisition, ABO blood group could also affect disease severity.

Blood group A and ABO polymorphisms (rs495828, gene promoter, and rs8176746, exon 7) predispose to COVID-19 severity via increased ACE activity and cardiovascular disorders. In a multivariate regression analysis for predicting COVID-19 prevalence, C3 and ACE1 polymorphisms were more important confounders in the spread and outcome of COVID-19 in comparison with the A allele. But an alternative explanation should be considered.

Enveloped viruses show ABO antigens on the virion’s surface and isoagglutinins act as neutralizing antibodies. Under this model, transmission from group O individuals and between individuals of the same group will always be maximal. High titre isoagglutinins can prevent transmission, while low-titre isoagglutinin could lead to milder disease presentations.
COVID-19 has more severe clinical presentations and outcome in elderly and in males: intriguingly, elderly males are known to experience greater reductions in isoagglutinin titres than females. Studies are hence ongoing to evaluate correlations between isoagglutinin titres and outcome in blood group O and B patients.

Since the phenomenon apparently does not benefit group B patients, I suggest that only anti-A IgG (which is more prevalent than IgM in group O patients, and occurs at titres >1:16 in about 70%), but not anti-A IgM (which is more prevalent than IgG in group B patients), could confer benefit. Apart from specificity, steric hindrance could affect receptor saturation from different antibody isotypes, making IgM less ideal for masking. Since the A1 subgroup accounts for more than 80% of group A, investigations should specifically focus on anti-A1 IgG.

It is known that passively acquired maternal isoagglutinins are rare in infants after the first month of life, but levels of anti-A isoagglutinins are already about 25% of the adult levels at month 3 and reach 90% of the adult level at three years, peaking at age 5–10, with individuals of 80 years of age and over showing reduced levels similar to those seen in 6- to 12-month-old infants. So the isoagglutinin titre hypothesis does not explain why infants are generally spared by severe COVID-19. A lot of additional co-factors could also explain the association, such as cross-protection from childhood vaccinations, lack of antibody-dependent enhancement (ADE) due to missing original antigenic sin (OAS) for other betacoronaviruses, or stable Fc fucosylation.

If confirmed, this hypothesis will have implications for convalescent plasma therapy, since anti-A1 IgG could confer additional benefit over anti-SARS-CoV-2 neutralizing antibodies: in fact, while preserving ABO match compatibility, it could be wiser to prefer blood group O donors for convalescent plasma (CP) in COVID-19. In the mean time, it seems wiser to titre anti-A isoagglutinins in group O CP donations (or to preserve frozen plasma aliquots for later investigation), and to preferentially choose group O units. In view of the growing worldwide trend to manufacture hyperimmune serum from CP, it should also be considered that hyperimmune serum, arising from pooled diverse ABO groups, contains a far lower anti-A isoagglutinin titre than an average O group convalescent donation.

### Conflict of interest

I declare that I have no conflict of interest related to this manuscript.

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### References

1. Li J, Wang X, Chen J, Cai Y, Deng A, Yang M. Association between ABO blood groups and risk of SARS-CoV-2 pneumonia. Br J Haematol. 2020.
2. Cheng Y, Cheng G, Chui CH, Lau FY, Chan PKS, Ng MHL, et al. ABO blood group and susceptibility to severe acute respiratory syndrome. JAMA. 2005;293(12):1447–51.
3. Guillou P, Clément M, Sébille V, Rivain J-G, Chou C-F, Ruvoën-Clouet N, et al. Inhibition of the interaction between the SARS-CoV Spike protein and its cellular receptor by anti-histo-blood group antibodies. Glycobiology. 2008;18(12):1085–93.
4. Neil SJ, McKnight A, Gustafsson K, Weiss RA. HIV-1 incorporates ABO histo-blood group antigens that sensitize virions to complement-mediated inactivation. Blood. 2005;105(12):4693–9.
Amelioration of COVID-19-related cytokine storm syndrome: parallels to chimeric antigen receptor-T cell cytokine release syndrome

Case series
Coronavirus disease 2019 (COVID-19) severity appears to parallel the host immune response, with a subset of patients developing COVID-19 cytokine storm syndrome (CSS). Serum inflammatory cytokines are elevated in COVID-19 and interleukin 6 (IL-6) appears to play a central role in COVID-19-related CSS. Based on the success of IL-6-receptor blockade for chimeric antigen receptor T-cell therapy associated cytokine release syndrome (CAR-T cell CRS), similar strategies using tocilizumab are being investigated in COVID-19. However, early reports described only modest elevations of IL-6 of approximately 50 pg/ml (reference range <7 pg/ml) in severe COVID-19 compared to IL-6 levels often >10 000 pg/l in CAR-T cell CRS, leading authors to conclude that COVID-19 pathophysiology is attributable to alternate mechanisms apart from CSS.

Two central mechanistic considerations may help resolve this controversy. First, determining if COVID-19 is associated with markedly elevated IL-6, in the range seen in CAR-T cell CRS, is crucial. Second, current trials are focussing on mortality and ventilation endpoints, but data pertaining to the effect of IL-receptor blockade on inflammatory cytokine levels and cardiorespiratory outcomes are needed to establish biological efficacy. We therefore conducted a preliminary evaluation of tocilizumab on inflammatory cytokines including IL-1β, IL-6, IL-10 and tumour necrosis factor alpha (TNF-α), and physiological parameters in five consecutive patients with severe COVID-19 CSS. Study approval was obtained from the institutional research ethics board. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection was confirmed by real-time reverse transcription polymerase chain reaction from a tracheal aspirate. All patients underwent invasive mechanical ventilation and were diagnosed with acute respiratory distress syndrome (ARDS). Two patients required veno-venous extracorporeal membrane oxygenation (VV-ECMO) for refractory hypoxaemia. Tocilizumab was administered (single 400 mg dose).