The scientific community is focused on the coronavirus disease-2019 (COVID-19) pandemic. The role of different factors in individual susceptibility to this infection and risk of severe illness is of great interest [1,2].

ABO blood group testing is cheap and can be performed at bedside, thus making it an accessible parameter to analyze in case-control studies. Differences in blood group antigen expression can increase or decrease host susceptibility to many infections, including severe acute respiratory syndrome coronavirus (SARS), which originated in China in 2002 [3]. Based on this evidence several research groups have assessed the association between ABO blood groups and both risk of COVID-19 infection and its severity. The speed at which science is moving has encouraged us to summarize recent findings on this subject.

What is the evidence base for the association of ABO groups with COVID-19? The most recent meta-analysis included seven studies through 15 July 2020 with a total of 7503 SARS-CoV-2 positive cases and 2,962,160 controls [4]. The results of this meta-analysis indicated that SARS-CoV-2 positive individuals are more likely to have blood group A (pooled odds ratio [OR 1.23], 95% confidence interval [95%CI] 1.09–1.40) and less likely to have blood group O (pooled OR 0.77, 95%CI 0.67–0.88) than controls. There are also more papers published after 15 July 2020 confirming that non-O blood group individuals have a higher risk of being infected [5-9]. However, some authors did not find an association between ABO blood groups and susceptibility to COVID-19 [10,11]. In a big study performed in the United States overrepresentation of the A group and underrepresentation of the O group among COVID-19 patients were confirmed for white non-Hispanic patients, while the observed and expected distributions of ABO phenotypes were similar in Black non-Hispanic and Hispanic patients [12].

The meta-analysis by Golinelli and colleagues [4] did not assess the association between ABO blood groups and severity of COVID-19. However, an assessment was conducted in a previous meta-analysis, which included four studies published before 20 April 2020. That report included data on the relationship between ABO blood type and clinical outcomes of COVID-19 [13]. The meta-analysis showed that the association between ABO blood group and severity or demise of COVID-19 lacked statistical significance. However, the odds of COVID-19 severity were higher in individuals with blood group AB (OR 2.424, 95%CI 0.934–6.294) and lower in individuals with blood group O (OR 0.748, 95%CI 0.556–1.007). Blood group AB were at increased risk of COVID-19 demise (OR 1.348, 95%CI 0.507–3.583) while blood group B were at decreased risk (OR 0.891, 95%CI 0.669–1.188). Such results indicated that further research was needed on this subject.

When comparing studies published after 20 April 2020, conflicting results were observed. Blood types A and AB were associated with critical COVID-19 and death in a Swedish cohort [14]. Hoiland and co-authors [15] showed that critically ill COVID-19 patients in Vancouver with blood group A or AB were at increased risk for requiring mechanical ventilation and prolonged intensive care unit admission compared with patients with blood group O or B [15]. Another study performed in Iraqi patients demonstrated that A and AB groups were associated with increased risk of death in deceased cases of COVID-19 [5]. According to the Spanish authors, blood group B had significantly higher rates of thrombotic complications and required more admissions in intensive care units [16]. At the same time other authors did not find an association between blood type and hospitalization or risk of intubation or death in patients with COVID-19 [6-8,10,12] or the results did not reach statistical significance [9].

One possible explanation for the discrepancy between results is that blood group could play an important role in the clinical outcome only for the specific groups of patients. For example, regarding COVID-19 hypertensive patients, non-O blood groups seemed to be an independent predictor of cardiac injury and death in this cohort. The authors revealed potential pathophysiological mechanisms under this association: non-OCOVID-19 hypertensive patients had significantly higher values of pro-thrombotic indexes compared with COVID-19.
hypertensive patients who had O blood group [17]. Since it was reported that anti-phospholipid antibodies can be frequently detected in patients with SARS-CoV-2 infection [18], it is of interest, whether non-O blood groups magnify the thrombogenic potential of anti-phospholipid antibodies.

In addition to comparing results of individual blood tests results, another approach has been considered. A group of scientists compared genome data from 1610 patients with severe COVID-19 and 2205 healthy blood donors (all from Italy and Spain) [19]. In that study gene variants in two regions of the genome were associated with severe COVID-19. While one of these regions carries several genes and a causative gene cannot be reliably identified, the association signal at the other locus coincided with the ABO blood group locus. The authors found that, compared with healthy controls, patients with severe COVID-19 were 1.45 times more likely to have type A blood, whereas the odds of having type O blood in these patients was 50% less than in controls.

Epidemiological studies, in addition to clinical investigations, have been performed on the subject. Padhi et al. [20] evaluated whether ABO blood group distribution in different territories of India was associated with COVID-19 confirmed cases and deaths. They found a significant inverse correlation for O blood group and a significant positive correlation for blood group B regarding the COVID-19 mortality rate. Severe Covid-19 GWAS Group, et al. [21] compared ABO allele frequencies and COVID-19 mortality from 54 countries of the Northern hemisphere. In this epidemiological study the B allele frequency was significant determinant for predicting COVID-19 mortality. Takagi et al. [22] demonstrated in a meta-regression multivariate analysis that COVID-19 fatality (but not prevalence) was lower in nations with higher blood group O prevalence. However, these authors did not find any association for the other blood groups.

We have evidence from different sources, the majority of which confirm that individuals with O blood group (at least in white non-Hispanic population), showing a lower risk of getting the infection than those with non-O blood group. At the same time, the data on the association of ABO blood groups with severity of COVID-19 remain controversial. This finding may be attributed to the fact that the disease progression also depends on other underlying factors, which mask the ABO effects on clinical outcomes of severity and mortality [23].

Finally, attention must be paid to the potential mechanisms underlying the reported associations. The most important two are:

• Neutralizing activity of natural anti-A antibodies against SARS-CoV spike protein, which was demonstrated in 2008. Spike proteins facilitate virus adhesion to ACE2-expressing cell lines and the receptor-binding domains of SARS-CoV and SARS-CoV-2 are structurally similar [4]

• Known impact of non-O blood groups on von Willebrand Factor levels, and therefore on the risk of both arterial and venous thrombosis as well as acute respiratory distress syndrome, following severe sepsis and major trauma [24]

From an immunological point of view, it is interesting that anti-A antibodies from O individuals but not from B individuals were shown to be protective against SARS-CoV-2 infection [23,25]. It was suggested that this difference is because B individuals produce mainly anti-A antibodies belonging to IgM class, whereas predominant class of anti-A antibodies in O individuals is IgG [23,25].

CONCLUSIONS
Further work is needed to confirm associations between ABO blood group and both risk of COVID-19 infection and its severity to better understand the molecular mechanisms underlying these associations.

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References
Coronavirus disease-2019 (COVID-19) is associated with diffuse lung damage. Glucocorticoids may modulate inflammation-mediated lung injury and thereby reduce progression to respiratory failure and death. In this controlled, open-label trial comparing a range of possible treatments in patients who were hospitalized with COVID-19, the RECOVERY Collaborative Group randomly assigned patients to receive oral or intravenous dexamethasone (at a dose of 6 mg once daily) for up to 10 days or to receive usual care alone. The primary outcome was 28-day mortality. A total of 2104 patients were assigned to receive dexamethasone and 4321 to receive usual care. Overall, 482 patients (22.9%) in the dexamethasone group and 1110 patients (25.7%) in the usual care group died within 28 days after randomization (age-adjusted rate ratio 0.83, 95% CI 0.75–0.93, P < 0.001). The proportional and absolute between-group differences in mortality varied considerably according to the level of respiratory support that the patients were receiving at the time of randomization. In the dexamethasone group, the incidence of death was lower than in the usual care group among patients receiving invasive mechanical ventilation (29.3% vs. 41.4%, rate ratio 0.64, 95% CI 0.51–0.81) and among those receiving oxygen without invasive mechanical ventilation (23.3% vs. 26.2%, rate ratio 0.82, 95% CI 0.72–0.94) but not among those who received no respiratory support at randomization (17.8% vs. 14.0%, rate ratio 1.19, 95% CI 0.92–1.55). In patients hospitalized with COVID-19, the use of dexamethasone resulted in lower 28-day mortality among those who received either invasive mechanical ventilation or oxygen alone at randomization but not among those who received no respiratory support.

Tumor hypoxia represses γδ T cell-mediated antitumor immunity against brain tumors

The anatomic location and immunologic characteristics of brain tumors result in strong lymphocyte suppression. Consequently, conventional immunotherapies targeting CD8 T cells are ineffective against brain tumors. Tumor cells escape immunosurveillance by various mechanisms and tumor cell metabolism can affect the metabolic states and functions of tumor-infiltrating lymphocytes. Park et al. discovered that brain tumor cells had a particularly high demand for oxygen, which affected γδ T cell-mediated antitumor immune responses but not those of conventional T cells. Specifically, tumor hypoxia activated the γδ T cell protein kinase A pathway at a transcriptional level, resulting in repression of the activatory receptor NKG2D. Alleviating tumor hypoxia reinvigorated NKG2D expression and the antitumor function of γδ T cells. These results reveal a hypoxia-mediated mechanism through which brain tumors and γδ T cells interact and emphasize the importance of γδ T cells for antitumor immunity against brain tumors.

Dexamethasone in hospitalized patients with COVID-19

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