breath and was treated with oxygen to maintain oxygen saturation >90%. Her hypoxia was attributed to COVID-19. At the time of her admission, there were no COVID-19-specific trials active at our institution, and she received no specific COVID intervention.

Hb had fallen to 6.7 g/dL and she was transfused with 2 units of leukoreduced, fully cross-matched red blood cells (RBCs), but without a resulting increase in Hb level. Post hydration volume redistribution and hyperhemolysis were considered as potential causes of this lack of response. No alloantibodies were detected at the time of transfusion.

Treatment with erythrocytapheresis which requires nurse and technician presence for 4 to 5 hours was contemplated for this patient. However, the patient did not meet the criteria for acute chest syndrome; she had improved hemodynamically, and in an effort to avoid additional transfusions and the associated health care provider exposure risks during a period of limited personal protective equipment, we elected to administer voxelotor 1500 mg orally daily. Voxelotor is a HbS polymerization inhibitor that increases hemoglobin in individuals with SCD, thus improving oxygen carrying capacity.4,5 Within 2 days of starting voxelotor, her Hb had risen to 8.0 g/dL (Table 1). She remained clinically stable and was discharged home off supplemental oxygen (room air O2 sat 98%). By day 10, her Hb was 10.3 g/dL. To our knowledge, this is the first report of voxelotor being used acutely in the setting of COVID-19 pneumonia in an individual with SCD and respiratory distress in lieu of transfusion. In this case, the patient’s Hb and overall status improved quickly upon treatment, thereby avoiding exchange transfusion, decreasing hospital staff exposure to coronavirus and sparing RBC units; important during this pandemic era of limited blood supply.

CONFLICT OF INTEREST
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Association of ABO blood group and secretor phenotype with severe COVID-19

To the Editor

We read with interest the letter by Dzik and colleagues,1 who compared the ABO blood group distribution between 957 COVID-19 patients admitted in the Boston area during the 2020 pandemic for whom ABO typing was available and 5840 historical controls from the same period of 2019 and found no significant difference. The investigation was prompted by evidence from previous studies conducted in Asia and Mediterranean Europe highlighting a higher risk of severe SARS-CoV-2
infection in individuals carrying the A blood group, and relative protection in those carrying the O group, although evidence is still controversial. By examining Italian and Spanish cohorts, we detected a cross-replicating association between rs657152 at the ABO locus with severe COVID-19 with respiratory failure that was significant at genomewide level. The analysis was restricted to unrelated individuals of European descent and was independent of age, sex and the genetic background. A blood group–specific analysis showed a higher risk of severe COVID-19 in blood group A (odds ratio [OR], 1.45 95% confidence interval [95% CI], 1.20-1.75; P = .028) and a protective effect in blood group O compared with other blood groups (OR, 0.65; 95% CI, 0.53-0.79; P = .004). By analyzing a local control group of 14,658 first-time Italian blood donors from Milan, it was shown that the association was not driven by a selection bias in the controls due to selective retention of blood group O individuals in the blood donation program.

Several factors may account for the discrepant results obtained by Dzik et al. Indeed, the Boston cohort included a different range of COVID-19 severity (including mild infections), and the analysis was not adjusted for confounders; in particular, it did not account for genetic background differences between cases and controls. On the other side, previous studies could not discriminate whether the association between ABO and COVID-19 was explained by an increased risk of infection by SARS-CoV-2 or by an increased risk of progression toward the development of more severe symptoms.

Supporting the association between ABO and the risk of severe COVID-19, we now provide data on the ABO

### TABLE 1 Frequency distribution of ABO blood groups between unrelated European patients with COVID-19 admitted at the Fondazione IRCCS Ca Granda during March and April 2019 and two different control groups

| Blood group       | GWAS case–control study | Expanded case–control study |
|-------------------|-------------------------|-----------------------------|
|                   | Severe COVID-19 (n = 505) | Transfused 2019 (n = 18,097) |
| O                 | 190 (37.6)               | 7831 (43.3)                 |
| A                 | 225 (44.6)               | 7291 (40.3)                 |
| B                 | 53 (10.5)                | 2174 (12.0)                 |
| AB                | 37 (7.3)                 | 801 (4.4)                   |
| OR                | REF                     | REF                         |
| 95% CI            | 1.43                    | 1.24                        |
| P valuea          | 0.028                   | 0.032                       |
|                   | Blood donors (n = 890)   |                             |
| O                 | 416 (46.7)               |                             |
| A                 | 339 (38.1)               |                             |
| B                 | 106 (11.9)               |                             |
| AB                | 29 (3.3)                 |                             |
| OR                | REF                     |                             |
| 95% CI            | 1.04-1.96               | 1.02-1.52                   |
| P valuea          | 0.83                    | 0.80                        |
|                   | Severe COVID-19 patients |                             |
| ICU               | 32 (33.0)                |                             |
| Medicine          | 158 (38.7)               |                             |
| OR                | REF                     |                             |
| 95% CI            | 0.71-2.00                |                             |
| P valuec          | 0.51                    |                             |
|                   | ICU                      |                             |
| ICU               | 32 (33.0)                |                             |
| Medicine          | 158 (38.7)               |                             |
| OR                | REF                     |                             |
| 95% CI            | 0.71-2.00                |                             |
| P valuec          | 0.51                    |                             |

Note: Unrelated European healthy blood donors evaluated at the Fondazione during the same period (top panel) and patients evaluated at the Fondazione Blood Bank during 2019 for blood transfusion (middle panel). The impact of ABO blood groups on the risk of admission to the ICU is reported in the bottom panel.

Abbreviations: GWAS, Genomewide association study; ICU, intensive care unit; REF, reference.

aOR of severe COVID-19 with respiratory failure; at logistic regression analysis adjusted for age, sex, smoking status, arterial hypertension, and carriage of rs11385942, the top COVID-19 risk variant at the Chromosome 3 gene cluster.
bOR of severe COVID-19 with respiratory failure; at logistic regression analysis adjusted for age and sex.
cOR of admission to ICU due to requirement of mechanical ventilation in COVID-19 with respiratory failure; at logistic regression analysis adjusted for age, sex, smoking status, arterial hypertension, and carriage of rs11385942, the top COVID-19 risk variant at the Chromosome 3 gene cluster.
blood frequency among patients admitted at the Fondazione IRCCS Ca’ Granda Milan during the outbreak. In Table 1 (top panel), we report the impact of ABO group on the risk of severe COVID-19 with respiratory failure in a case–control study conducted in unrelated European individuals for whom genetic typing is available.\(^2\) We confirmed the findings in the overall cohort (shown in Table 1, middle panel) that carriage of group A was associated with higher risk of severe COVID-19 than group O independently of founders (OR, 1.43; 95% CI, 1.04-1.96; \(P = .032\)), while group B was not.\(^2\) We also observed a marked increase in the risk of severe disease in carriers of the AB group (OR, 2.78; 95% CI, 1.38-5.58; \(P = .005\)). To further validate the association, as suggested by Dzik et al.,\(^1\) we next examined the impact of ABO on severe COVID-19 by comparing the same patients to a further control group of European patients evaluated at the Milan blood bank during 2019, where ABO blood group could not be biased by inclusion in a blood donation program (Table 1, middle panel). The overall ABO distribution in this control group was similar than that of Milan blood donors. We confirmed a higher risk of severe COVID-19 in carriers of group A (OR, 1.24; 95% CI, 1.02-1.52) and AB (OR, 1.72; 95% CI, 1.18-2.51) compared to group O, although the effect size was smaller than in the previous analysis. When we evaluated the impact of ABO on disease severity (admission to intensive care unit due to the requirement of mechanical ventilation) within the severe COVID-19 cohort of patients with respiratory failure, we observed a non-significant trend for a higher risk in carriers of type B blood (\(P = .051\)), while group A did not further increase the risk (Table 1, bottom panel).

Potential biologic mechanisms underlying the epidemiologic association encompass the neutralizing activity of natural anti-A against SARS-CoV spike protein\(^6\) and/or the known impact of non-O blood groups on von Willebrand factor levels, which predisposes to thrombotic disorders.\(^7\) Consistently with the latter hypothesis, carriage of blood group A was previously associated with development of acute respiratory distress syndrome after severe sepsis and major trauma.\(^9\) The secretor ABO phenotype has also been robustly linked to protection against other RNA virus infections affecting mucous membranes, namely, rotaviruses and enteroviruses.\(^10\) Therefore, secretion of A/B antigens may promote COVID-19 progression, but further studies will be necessary to confirm the protective effect of nonsecretor phenotype.

These data are consistent with the hypothesis that carriage of non-O blood groups predisposes to severe
COVID-19 with respiratory failure in European individuals and that the secretor phenotype may moderate disease progression. However, we definitively agree with Dzik and colleagues that additional studies, taking into account genetic and acquired cofactors, are required to confirm the association of ABO blood group and the secretor phenotype with the risk of COVID-19 worldwide and to investigate the underlying mechanisms and the possible translational implications.

CONFLICT OF INTEREST
The authors declare no potential conflict of interest.

PLASMIC score: Not intended to replace but rather to prompt the ADAMTS13 testing

We read with interest the paper by Moosavi et al.1 who reported findings from a validation study of the PLASMIC score. The investigative scenario was thrombotic microangiopathy and differential diagnosis of thrombotic thrombocytopenic purpura (TTP). The sensitivity and specificity of the PLASMIC score, calculated on data of 46 patients, were 78% and 63%, respectively. On the basis of these findings, the authors conclude that routine use of the PLASMIC score should be discouraged, whereas they suggest that testing ADAMTS13 is the only strategy to identify patients with TTP, especially when turnaround time for testing ADAMTS13 is particularly short.

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