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ABO Histo-Blood Group and the von Willebrand Factor Axis in Severe COVID-19

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To the Editor:

The COVID-19 pandemic, resulting from SARS-CoV-2, has led to millions of deaths globally and substantial morbidity.[1] COVID-19 has heterogeneous severity, with symptoms ranging from mild fever and cough to ARDS, multisystem organ failure, and death. Genome-wide association studies have identified genetic variants that may explain some of this variability, including the variation that determines ABO histo-blood type.[2] The ABO gene encodes glycosyltransferases responsible for carbohydrate modifications on glycoproteins and has been linked to risk of several vascular diseases,[3] as well as plasma concentrations of coagulopathic proteins, particularly von Willebrand factor (vWF).[4] In ambulatory individuals, ABO blood type explains 30% of the variability of plasma vWF concentration. Excess release of vWF from injured endothelium and a relative deficiency of A disintegrin and metalloprotease with thrombospondin 1 repeats, number 13 (ADAMTS13), the enzyme responsible for cleaving vWF into less thrombogenic multimers, have been implicated in severe COVID-19.[5] ABO antigens are located on the vWF glycoprotein, and the A antigen interferes with ADAMTS13 binding, reducing vWF cleavage, possibly explaining the associations between ABO blood type, vWF, and COVID-19.[6]

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Clinically and genetically determined ABO blood type A previously was associated with increased vWF levels, ARDS risk, and disseminated intravascular coagulation risk in critically ill patients without COVID-19.[7] Significant hypercoagulability and endothelial dysfunction are frequent characteristics of severe COVID-19.[8] We therefore hypothesized that ABO blood type and the ratio of plasma vWF to ADAMTS13 concentrations would associate with COVID-19 outcomes and that measuring the three markers together could identify a population at high risk of poor outcomes for whom drugs targeting the vWF axis may be beneficial.

We conducted a prospective cohort study of 215 patients admitted to one of two affiliated hospitals with a primary diagnosis of COVID-19 and followed their clinical status through 28 days. Thirty-seven additional patients screened did not have ABO blood type measured nor plasma collected and were excluded. The study was approved by the institutional review board and informed consent was obtained. We collected plasma samples within 48 h of admission and analyzed them with the multiplex Olink Proximity Extension Assay, which included semiquantitative measurements for vWF and ADAMTS13 concentration. Concentrations were expressed as normalized protein expression values based on the relative concentration compared with pooled healthy control plasma. Normalized protein expression values are arbitrary units on the log2 scale, and therefore, a 1-point normalized protein expression difference corresponds to a doubling of protein concentration. Clinical data, including ABO blood type, were extracted from the medical record. The primary outcome was 28-day mortality, and the secondary outcome was a simplified World Health Organization COVID-19 ordinal severity score at 28 days. We tested the unadjusted associations of ABO blood type and vWF to ADAMTS13 ratio with mortality using the χ^2 test and rank-sum test, respectively, and the unadjusted associations with severity score using the nonparametric test for trend. We then constructed multivariable logistic regression models adjusting for age, sex, race, and active malignancy to determine the association of ABO blood type and vWF to ADAMTS13 ratio with mortality. We used these models to estimate standardized risks of death across values of the vWF to ADAMTS13 ratio by ABO blood type. Statistical analyses were conducted using STATA version 16.1 software (StataCorp).

Of 215 patients enrolled, the median age was 61 years (interquartile range, 49–71 years), 112 patients (52%) were male, 143 patients (67%) were Black, 61 patients (28%) were White, 10 patients (5%) were Asian, race was unknown for 1 patient (1%), and 14 patients (7%) were Hispanic. An active malignancy was present in 21 patients (10%). ABO blood type was available for 191 patients (89%), and plasma was assayed in 165 patients (78%). At 28 days, 29 patients (13%) had died. Mortality ranged from 10% among patients with blood type O to 22% in patients with blood type A ($P = 0.039$, unadjusted). Table 1 provides blood type, vWF levels, and ADAMTS13 levels by ordinal 28-day outcome. In multivariable models, blood type A was associated with a higher 28-day mortality relative to blood type O (OR, 3.25; 95% CI, 1.08–9.77; $P = .036$), and vWF to ADAMTS13 ratio also was associated with 28-day mortality (OR, 1.81; 95% CI, 1.08–3.04 per 1-SD increase; $P = .024$). We did not detect an interaction in the association of vWF to ADAMTS13 ratio and mortality by blood type. Figure 1 shows standardized risks of death across vWF to ADAMTS13 ratios

stratified by blood types A and O, demonstrating that mortality was higher as the ratio increased, but that blood type A shifted the curve toward higher mortality.

We identified associations among ABO blood type A, higher plasma vWF, and lower ADAMTS13 with higher 28-day mortality and worse outcome in a large population of patients with COVID-19.[9] Additionally, we measured these three markers in a single population and integrated the distinct measurements of vWF biological features to generate standardized mortality curves based on dysregulation of the vWF axis, a novel aspect of our findings. vWF is an essential component of vascular homeostasis. In the setting of severe inflammation and endothelial dysfunction, however, vWF can lead to excess coagulation, organ injury, and death. Our study further suggests that disruption of the relative plasma vWF to ADAMTS13 concentration may contribute to the pathogenesis of severe COVID-19, may be modified by ABO blood type, and may be an important therapeutic target.

Severe deficiencies of ADAMTS13 lead to the life-threatening disorder thrombotic thrombocytopenic purpura. Similar to our findings in COVID-19, more moderate ADAMTS13 deficiency and vWF excess are common in sepsis and are relevant to the coagulopathy of sepsis.[10] Recombinant ADAMTS13, a drug in development for thrombotic thrombocytopenic purpura, also may be a potential therapeutic for select patients with severe COVID-19 and sepsis of other infectious causes. In an exploratory study, incubation of plasma samples from patients with severe COVID-19 with recombinant ADAMTS13 substantially reduced abnormality high vWF clotting activity.[9] We hypothesize that three major pathways contribute to excess activation of the vWF axis in COVID-19: excess vWF release, plasma ADAMTS13 deficiency, and impaired cleavage of vWF multimers by ADAMTS13 resulting from the presence of A antigens. Future studies of therapeutics aimed at the vWF axis, such as recombinant ADAMTS13, should consider evaluatingfor heterogeneity of treatment effect by ABO blood type and plasma vWF to ADAMTS13 ratio early in severe COVID-19.

Our study has limitations including its small sample size at a two-hospital center, lack of differentiation between genetic blood type A subtypes, lack of measurements of enzymatic activity, and the semiquantitative nature of our measurements; however, we believe our study provides key preliminary data to support a potential role of the vWF to ADAMTS13 axis for prognostic and predictive enrichment for future clinical trials of targeted therapeutics.

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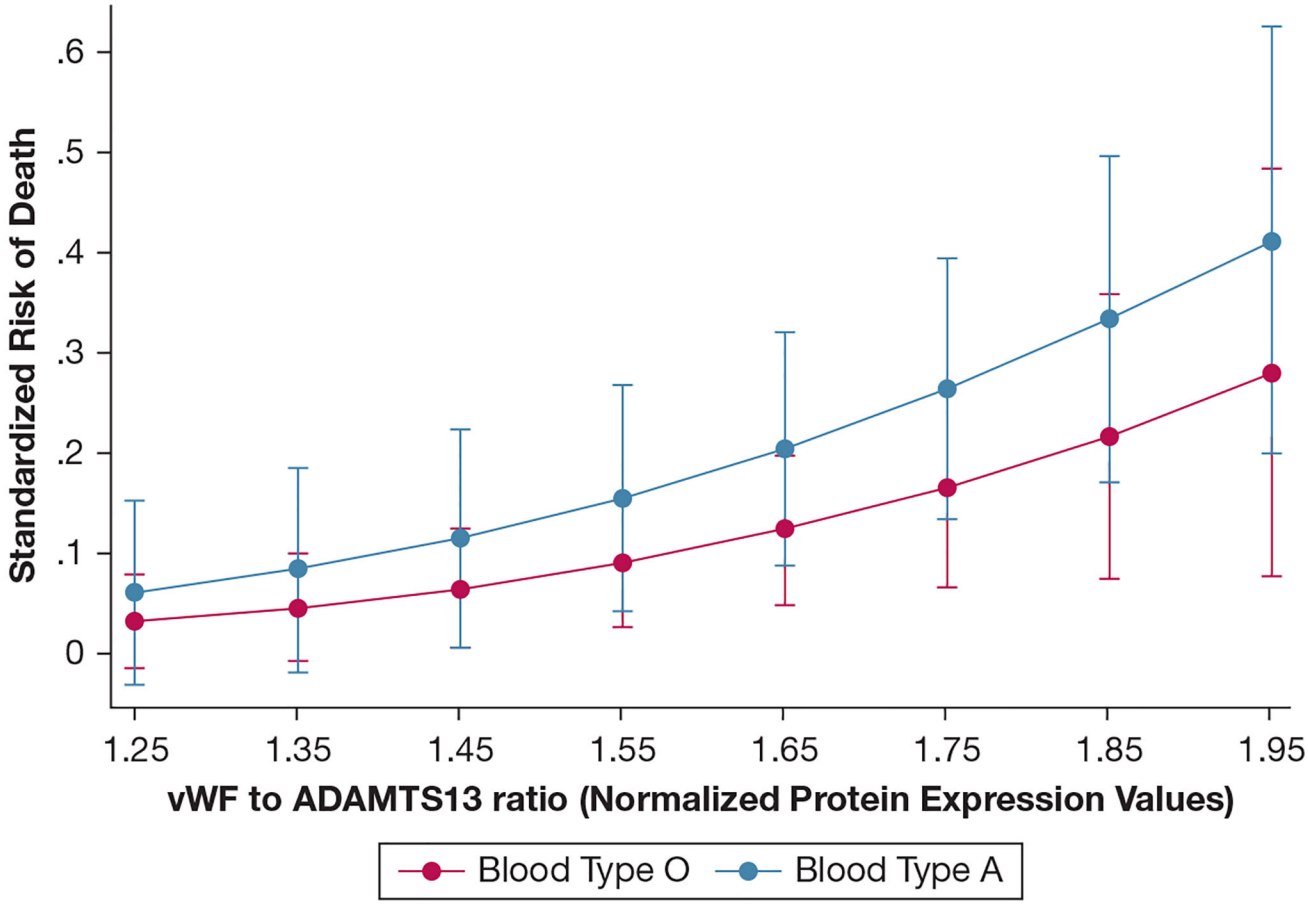

Figure 1 –.

Line graph showing standardized risk of 28-day mortality adjusting for age, sex, race, and active malignancy with 95% CIs by plasma vWF to ADAMTS13 ratio stratified by blood types A and O. ADAMTS13 = A disintegrin and metalloprotease with thrombospondin 1 repeats, number 13; vWF = von Willebrand factor.

TABLE 1]

Association of ABO Histo-Blood Type, Plasma vWF Levels, Plasma ADAMTS13 Levels, and Plasma vWF to ADAMTS13 Ratio With Outcome at 28 Days After Hospitalization With COVID-19

Ordinal Outcome	No.[a]	ABO Blood Type, %				Plasma Proteins[b]		
		A (n = 58)	O (n = 82)	B (n = 37)	AB (n = 14)	vWF	ADAMTS13	vWF to ADAMTS13 Ratio[c]
Death	29	22%	10%	11%	21%	10.0 (9.1–10.9)	5.82 (5.56–6.03)	1.67 (1.57–1.88)
Mechanically ventilated	21	16%	9%	11%	7%	10.8 (10.0–11.2)	5.82 (5.73–6.61)	1.72 (1.62–1.93)
Hospitalized, requiring oxygen	10	3%	5%	5%	14%	10.1 (9.9–11.4)	6.15 (5.86–6.38)	1.65 (1.58–1.90)
Discharged	155	59%	77%	73%	57%	9.7 (8.7–10.4)	5.97 (5.85–6.11)	1.57 (1.46–1.72)
P value	…	.010[d]				< .001[e]	.025[e]	< .001[e]

ADAMTS13 = A disintegrin and metalloprotease with thrombospondin 1 repeats, number 13; vWF = von Willebrand factor.

[a] In total, 215 patients with COVID-19 were enrolled and followed up to determine 28-day outcome. ABO blood type was available for 191 patients and was missing in 24 patients.

[b] Plasma proteins are expressed as median normalized protein expression value (interguartile range), arbitrary units expressed on the log2 scale, whereby a 1-point difference means a doubling of protein concentration.

[c] The vWF to ADAMTS13 ratio was calculated by dividing the raw vWF normalized protein expression value by the raw ADAMTS13 normalized protein expression values. These values are expressed on the log2 scale.

[d] Comparison of blood type A with type 0 using the nonparametric test for trend across the ordinal outcome categories.

[e] From the nonparametric test for trend across the ordinal outcome categories.