AUTHOR CONTRIBUTIONS

R.L.C., C.V. and A.G. designed the research; D.T., A.G., J.A., B.R., H.J.L., and R.L.C. collected data; A.G., H.J.L. and R.L.C. analyzed and interpreted the results; R.L.C., A.G. and N.S.S. designed the figures; A.G., and R.L.C wrote the manuscript. All authors critically reviewed the final draft prior to submission.

DATA AVAILABILITY STATEMENT

Data are not publicly archived.

Amandeep Godara[1,2], Denis Toskic[1], Jack Albanese[1], Benjamin Rosenthal[1], Nauman S. Siddiqui[2], Adin Kugelmass[1], Ping Zhou[1], Teresa Fogaren[1,2], Cindy Varga[1,2], Heather J Landau[3], Raymond L Comenzo[1,2]

[1]*John Conant Davis Myeloma and Amyloid Program, Tufts Medical Center, Boston, Massachusetts*
[2]*Division of Hematology-Oncology, Department of Medicine, Tufts Medical Center, Boston, Massachusetts*
[3]*Division of Hematologic Oncology, Memorial Sloan-Kettering Cancer Center, New York, New York*

Correspondence
Raymond L Comenzo, Director, John C. Davis Myeloma and Amyloid Program, Professor, Tufts University School of Medicine, Tufts Medical Center, 800 Washington Street, Box 826, Boston, MA 02111.
Email: rcomenzo@tuftsmedicalcenter.org

ORCID

Amandeep Godara https://orcid.org/0000-0003-1943-4442
Denis Toskic https://orcid.org/0000-0002-3340-762X

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SUPPORTING INFORMATION

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Association of ABO/Rh with SARS-CoV-2 positivity: The role of race and ethnicity in a female cohort

To the Editor:

Previous reports have documented an association between ABO blood group and risk for infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of the coronavirus disease 2019 (Covid-19) pandemic.[1-3] Associations between race/ethnicity and SARS-CoV-2 positivity have also been reported.[4,5] Here we describe the first large-scale observational study investigating the associations between ABO group/Rh types with SARS-CoV-2 positivity, by major race/ethnicity.

In this retrospective, observational study, test results from a national reference clinical laboratory were assessed to determine the influence of race/ethnicity on the associations of ABO/Rh with SARS-CoV-2 RNA positivity. Results from SARS-CoV-2 RNA nucleic acid amplification tests (NAAT) performed March through July 2020 were matched with ABO/Rh test results obtained for the same individual since January 2010. Only one SARS-CoV-2 result per patient was considered; a patient was considered to have a positive result if any SARS-CoV-2 test result was positive. The ABO/Rh testing is generally performed as part of maternal screening; males were excluded. The influence of race/ethnicity on the associations of ABO type/Rh group with SARS CoV-2 positivity was assessed in a subset of females with available race/ethnicity data.

The SARS-CoV-2 RNA NAAT was performed using one of four US Food and Drug Administration (FDA) Emergency Use Authorized

tests (Quest Diagnostics SARS-CoV-2 RNA [Covid-19], Qualitative NAAT; Hologic Panther Fusion SARS-CoV-2 assay; Roche Diagnostics cobas SARS-CoV-2 test; or Hologic Aptima SARS-CoV-2 assay). The ABO/Rh typing was performed using solid-phase technology (Immucor NEO).

Differences in proportions were analyzed using the chi-square test (with results presented as nominal *P* values). For multivariable logistic regression models, race/ethnicity was grouped into the following categories: Black non-Hispanic, Hispanic, white non-Hispanic, and "other" race/ethnicity ("other" included females of multiple race/ethnicities). Analyses were performed using SAS Studio 3.6 on SAS 9.4 (SAS Institute). This Quest Diagnostics Health Trends study was deemed exempt by the Western Institutional Review Board (Puyallup, Washington).

The study cohort comprised 276 536 females with matched SARS-CoV-2 and ABO-Rh results from all 50 American states and the District of Columbia. There were 34 178 females who were SARS-CoV-2 positive (12.4%, 95% CI 12.2%-12.5%).The median patient age at the time of SARS-CoV-2 testing was 34.4 (IQR 29.2-40.0) years. The SARS-CoV-2 positivity rate was higher in both females under 30 years of age (15.1%, 95% CI 14.9%-15.4%) and those 30-39 years (11.9%, 95% CI 11.7%-12.0%) than in females age 40 years or over (10.1%, 95% CI 9.9%-10.4%) (*P* < .001 for both comparisons). The most common blood type was O+ (123 642; 44.7%), followed by A+ (83 219; 30.1%); B+ (32 961; 11.9%); O- (12 871; 4.7%); A- (10 531; 3.8%); AB+ (9048; 3.3%); B- (3179; 1.2%); and AB- (1085; 0.4%).

The SARS-CoV-2 positivity rate was 38% higher in Rh+ patients (12.7%, 95% CI 12.6%-12.8%) than in Rh- patients (9.2%, 95% CI 8.9%-9.5%) (*P* < .001). The SARS-CoV-2 positivity rate was also significantly higher among type O patients (13.0%, 95% CI 12.8%-13.2%) than among type A (11.8%, 95% CI 11.6%-12.0%), type B (11.9%, 95% CI 11.5%-12.2%), or type AB (11.4%, 95% CI 10.7%-12.0%) patients (*P* < .001 for all comparisons). No statistically significant differences in SARS-CoV-2 positivity between females with type A and B (*P* = .66), type A and AB (*P* = .21), or type B and AB (*P* = .16) were observed. In stratified analyses, the relationship between SARS-CoV-2 positivity and Rh type remained significant across ABO blood groups (Figure S1).

Among the 88 975 females with available race/ethnicity data, the distributions of ABO groups/Rh types were remarkably similar to findings from a large study of blood donors conducted by the American Red Cross.[6] In this study SARS-CoV-2 positivity rates, as well as ABO/Rh distributions, differed significantly between race/ethnicity groups (Table S1). Hispanic females were significantly more likely to have type O blood (58.3%) than were black non-Hispanic (49.5%), white-non-Hispanic (45.2%), and "other" race/ethnicity females (*P* < .001 for all comparisons). White non-Hispanic females were more than twice as likely to be Rh- (15.1%) compared to other groups, including "other" race/ethnicity (6.6%), Hispanic (6.4%), and black non-Hispanic (6.1%) groups (*P* < .001 for all comparisons). Hispanic females had the highest SARS-CoV-2 positivity rate (21.4%, 95% CI 20.9%-21.9%), followed by black non-Hispanic (16.3%, 95% CI 15.7%-16.9%), "other" race/ethnicity (12.8%, 95% CI 12.3%-13.4%), and white non-Hispanic (7.2%, 95% CI 6.9%-7.4%) females.

Unadjusted logistic regression analyses demonstrated similar associations between ABO/Rh variables and SARS-CoV-2 positivity in the subset of females with race/ethnicity data as in the overall cohort (Figure 1). However, when race/ethnicity groups were included in an adjusted model, there were two important changes. First, the increased risk of SARS-CoV-2 positivity in Rh+ patients fell from 1.44 (95% CI 1.34-1.54) in the unadjusted model to 1.15 (95% CI 1.06-1.23) in the adjusted model. Second, the association between type O and SARS-CoV-2 positivity changed from being significantly predictive in the unadjusted model (OR 1.07, 95% CI 1.03-1.11), to

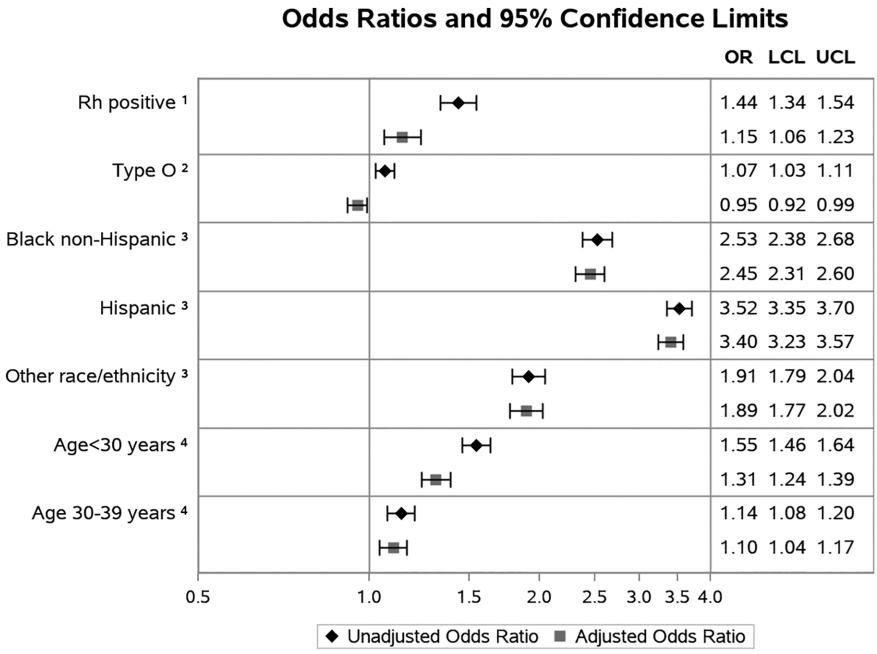

FIGURE 1 Logistic regression models, associations with SARS-CoV-2 positivity. Reference Groups: 1, Rh negative; 2, Blood types A, B, and AB; 3, White non-Hispanic; 4, Age > =40 years. "LCL", lower confidence limit; "OR", odds ratio; "UCL", upper confidence limit. The bars represent the 95% Wald Confidence Limits. Multivariable adjusted model n = 88 970 of 88 975 females with race/ethnicity data (five were missing age)

significantly protective in the adjusted model (OR 0.95, 95% CI 0.92-0.99).

This is the largest reported study to date assessing SARS-CoV-2 positivity rates by ABO/Rh and race/ethnicity. In line with prior studies,[2,3] our findings demonstrated that Rh positivity, independent of ABO blood group and race/ethnicity, was a statistically significant risk factor for SARS-CoV-2 positivity. In contrast to findings from smaller studies,[1] our unadjusted analysis showed a significantly higher SARS-CoV-2 positivity rate among individuals with type O blood than in those with other blood types. However, after adjusting for race/ethnicity, the relationship between type O and SARS-CoV-2 reversed from predictive to protective. Type O and Rh + blood is more prevalent in Hispanics and black non-Hispanics, two groups in our study with the highest proportions of positive SARS-CoV-2 tests. Thus we conclude, in concordance with findings from other studies,[1] that type O blood is slightly protective against SARS-CoV-2 positivity once race/ethnicity has been considered. The multivariable model also demonstrated that the influence of Rh+ blood type was attenuated when adjusted for race/ethnicity, suggesting that the association between ABO/Rh and SARS-CoV-2 positivity is strongly influenced by race/ethnicity.

Much attention has been paid to the disproportionate rates of SARS-CoV-2 infection in Hispanic and black non-Hispanic populations in the United States.[4,5] The reasons for this relationship are not fully understood. Theories include increased exposure to the virus among Hispanic and black non-Hispanic populations owing to employment, economic hardship, dense living conditions, and other general disparities.[4,5] Here, we demonstrated additional racial/ethnic influences on relationship between ABO group/Rh type and SARS-CoV-2 positivity.

One explanation for variations among studies is differences in the underlying distributions of blood groups/types by race/ethnicity in the populations studied. The race/ethnicity distribution for the subset of females with available data in this study was remarkably similar to estimates for the total U.S. population.[6] ABO blood types are known to influence susceptibility to other infectious agents, including the severe acute respiratory syndrome-associated coronavirus-1 (SARS-CoV-1), where similar associations with blood group have been described.[1,2] The ABO antigens are carbohydrate-enriched epitopes present on erythrocytes, endothelial cells, and other specialized tissues and secreted within certain body fluids of some individuals. These antigens induce a potent immune response, triggering isoagglutinin antibodies against non-expressed ABO antigens. The spike proteins of SARS viruses also express carbohydrate-rich moieties, as well as ABO antigens borrowed from the infected host. In this way, type O individuals, whose blood naturally contains both anti-A and anti-B isoagglutinin antibodies, are thought to have an inherent immune advantage against SARS viral infections.[1,2]

The Rh blood type consists of more than 50 protein antigens, the most clinically relevant of which are D, C, c, E, and e. The RH locus encodes two genes *RHD* and *RHCE*. An individual's Rh type is largely determined by the presence or absence of the D antigen on erythrocytes, Rh+ or Rh-, respectively. The Rh antigens complex with associated glycoproteins on the red blood cell surface, but physiologic roles of RhD and RhE have yet to be elucidated. The association between Rh + blood and SARS-CoV-2 positivity merits further investigation.

This study was limited by several factors. The majority of those studied were likely pregnant at the time of ABO/Rh testing, but not necessarily pregnant at the time of SARS-CoV-2 testing. It is unclear how pregnancy and its associated immunotolerance affect SARS-CoV-2 positivity rates. People with symptoms, or high exposure risk, for example, healthcare workers, are theoretically more likely to be tested for SARS-CoV-2. In addition, race/ethnicity data were reported by the ordering clinician and were only available for 32.2% of the study cohort. However, the group of females with race/ethnicity available (n = 88 975) still represents one of the largest known studies to date comparing the association between ABO/Rh and SARS-CoV-2 positivity. No clinical information was available to corroborate test results, correlate outcome, or assess clinical course.

In summary, an association between ABO/Rh and SARS-CoV-2 positivity was confirmed but greatly attenuated after factoring in race/ethnicity. Future studies to evaluate the influence of race/ethnicity on COVID-19 risk and clinical course are necessary for comprehensive assessment of the impact of blood group/Rh type on infection and disease.

CONFLICT OF INTEREST

J.K.N., H.E.K., J.S.D., and H.W.K. are employees of Quest Diagnostics; J.S.D. and H.W.K. own stock in Quest Diagnostics.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Justin K. Niles, Hope E. Karnes, Jeffrey S. Dlott, Harvey W. Kaufman

Quest Diagnostics, Secaucus, New Jersey

Correspondence
Harvey W. Kaufman, Quest Diagnostics, 500 Plaza Drive, Secaucus, NJ 07094.
Email: harvey.w.kaufman@questdiagnostics.com

ORCID

Justin K. Niles https://orcid.org/0000-0002-3150-2463
Harvey W. Kaufman https://orcid.org/0000-0003-2850-9047

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Efficacy of subcutaneous preemptive rituximab in immune-mediated thrombotic thrombocytopenic purpura: Experience from the first 12 cases

To the Editor:

Immune-mediated thrombotic thrombocytopenic purpura (iTTP) is a potentially fatal disease in the absence of treatment, which consists of daily therapeutic plasma exchange (TPE), in association with corticosteroids and increasingly rituximab and caplacizumab, an inhibitor of von Willebrand factor-platelet interaction.[1] Thus iTTP is characterized by the occurrence of several relapses of unpredictable severity, exposing patients to death and treatment-related complications. Consequently, the prevention of relapses represents an important goal to be achieved.[1,2] In this perspective, it has been shown that a persistently undetectable activity of the von Willebrand factor-cleaving protease ADAMTS13 in patients otherwise in remission represents a reliable early predictor of full clinical relapse.[1,2] Patients with a decreased ADAMTS13 activity following an iTTP episode may also experience more frequently ischemic strokes,[3] providing further evidence for the need to improve ADAMTS13 deficiency during clinical remission. Rituximab is a chimeric monoclonal antibody targeting CD20+ B lymphocytes that has demonstrated efficacy in acute iTTP, allowing a shortening of TPE duration and delaying relapses.[1,2] Rituximab is also used as a preemptive therapy in patients in clinical remission who experience a persistent severe ADAMTS13 deficiency during follow-up.[2] Preemptive rituximab (consisting in 1 single infusion to 4-weekly IV infusions) reduces the incidence of iTTP relapse by diminishing the production of anti-ADAMTS13 antibodies and restoring ADAMTS13 activity, which parallels peripheral B cell depletion.[2,4] In France, rituximab obtained a temporary recommendation of use for patients with iTTP as a frontline treatment and as a preemptive treatment (Table S1). Rituximab is relatively non-toxic, but IV infusions typically last for 3-4 hours, making it resource intensive for the healthcare system and time consuming for patients. A subcutaneous (SC) formulation of rituximab has recently been approved as an alternative to the IV infusion in both indolent lymphomas and diffuse large B-cell lymphoma.[5] Clinical studies have shown that SC rituximab administration resulted in non-inferior levels of product in the blood and comparable clinical efficacy outcomes when compared to the IV administration, with a comparable safety profile.[5-7] The subcutaneous administration results in a highly concentrated fixed dose of rituximab, reducing treatment times and nursing workload.[5-7] Additionally, preference and satisfaction improved in patients with the SC formulation, due to time saving, less emotional distress and a more comfortable administration.[8] These results, enabling a substantial decrease in the burden of care, are particularly relevant for iTTP patients as a majority may require a preemptive treatment following the acute episode with retreatment typically every 1 to 2 years to maintain ADAMTS13 within detectable values.[2,4] The aim of our study was to address the efficacy and tolerance of SC preemptive rituximab treatment in patients in clinical remission of iTTP displaying severe ADAMTS13 deficiency during follow-up.

We included non-pregnant patients (age ≥ 18 years) with a previous iTTP episode and managed in our center.[1] All patients displayed a severe ADAMTS13 deficiency, either persisting after clinical remission or occurring after an initial partial or complete enzyme recovery. During follow-up, SC rituximab was proposed to patients instead of the IV formulation when a preemptive treatment was needed. Informed consent was obtained from all patients. This study was approved by our institutional review board in accordance with the Declaration of Helsinki.

Preemptive treatment with SC rituximab consisted of a single administration of rituximab (Mabthera; Roche, Paris, France) 1400 mg (supplemental method). After receiving SC preemptive rituximab, patients were followed-up at 1 month, and then every 3 months during at least 24 months.[2] Clinical relapse, adverse events, ADAMTS13 activity and peripheral blood CD19+ B lymphocytes count were registered at each follow-up visit.[2] During follow-up, we considered <20 IU/dL as ADAMTS13 activity threshold for the need of preemptive rituximab treatment.[2] Patients who experienced further decreases in ADAMTS13 activity during follow-up were retreated with SC rituximab. We assessed the time between two SC preemptive rituximab administrations, defined as time to next treatment before each administration. Patients were interviewed about self-experience