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Short Communication

Non-ABO red cell antibodies and risk of COVID-19

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ABSTRACT

It is not known whether non-ABO antibodies confer any protective effect against SARS-CoV-2 infection or COVID-19 severe illness alone or in conjunction with O blood group. This cohort study included 413 576 persons in Ontario, Canada with known ABO blood group and non-ABO antibody screen status, who subsequently underwent SARS-CoV-2 viral RNA polymerase chain reaction testing between January and November 2020. The risk of SARS-CoV-2 infection or COVID-19 severe illness was not associated with the presence of non-ABO antibodies, even among persons with O blood group.

Background

Persons with blood group O may be at lower risk of SARS-CoV-2 infection and COVID-19-related severe illness (Ray et al., 2021). The SARS-COV-2 spike (S) glycoprotein is responsible for its attachment and entry across the host cell membrane. Since A or B epitopes may be present on the viral S glycoprotein, the anti-A and anti-B antibodies of persons with O blood group may neutralize the virus by binding to corresponding antigens on the viral envelope (Pendu et al., 2021). A and B antigens are synthesized by epithelial cells of the respiratory and digestive tract, where COVID-19 tissue injury can occur (Pendu et al., 2021).

There also exist hundreds of non-ABO blood group antibodies, typically arising following sensitization with red cell transfusion or pregnancy (Gehrie and Tormey, 2014). Non-ABO antibodies are routinely tested at a patient's blood group and screen and include Rhesus, Kell, Lewis, Lutheran, Duffy, Kidd and P antigens (Gehrie and Tormey, 2014). It is not known whether non-ABO antibodies confer any protective effect against SARS-CoV-2 infection or COVID-19 severe illness alone or in conjunction with O blood group.

Methods

A population-based retrospective cohort study was performed across Ontario, Canada. Patient-level datasets, including all hospitalizations, emergency department visits and laboratory tests for SARS-CoV-2 were linked using unique encoded identifiers and analyzed at ICES (Ray et al., 2021).

Patients were included if they had ABO testing and non-ABO antibody screening (group and screen) between January 2007 and December 2019, and subsequently, SARS-CoV-2 viral RNA polymerase chain reaction (PCR) testing between January 15 and November 16, 2020.

Study outcomes included SARS-CoV-2 infection and COVID-19 severe illness or death (Ray et al., 2021), the latter including venous thromboembolism. Relative risks (RR) were calculated in relation to the presence vs absence of non-ABO antibodies, including in conjunction with O and non-O blood groups. RRs were adjusted for demographic characteristics and comorbidities. An additional analysis was restricted to those who tested positive for SARS-CoV-2 infection.

Statistical analyses were performed using SAS version 9.4 for UNIX (SAS Institute Inc., Cary, NC).

Results

Among 2 659 328 individuals who had an ABO blood group test from January 2007 to December 2019, 413 576 had a subsequent SARS-CoV-2 test and were included in the cohort. Altogether, 18.6% were aged ≥70 years. Patients with a non-ABO antibody (N = 5652

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[1.4%]) were older, more likely to be female and affected by more comorbidities than those without an antibody (Table 1).

The risk of SARS-CoV-2 infection was not associated with the presence of non-ABO antibodies, including among those who were O blood group (Figure 1, upper). While the unadjusted risk was significantly higher in persons with both non-O blood group and non-ABO antibodies (RR 1.86, 95% CI 1.06–2.78), this was not so in the adjusted model (RR 1.28, 95% CI 0.73–1.86), or in the other groups (Figure 1, middle). Restricting to those who tested positive for SARS-CoV-2 virus showed a similar pattern (Figure 1, lower).

Discussion

The risk of SARS-CoV-2 infection or COVID-19 severe illness was not associated with the presence of non-ABO antibodies, even among persons with O blood group.

We did not possess details about which specific non-ABO antibodies were detected in our study sample—only that they were present—yet, since hundreds exist (Gehrie and Tormey, 2014), any related analysis would be challenging. Non-A, non-B antigens are more prevalent in persons with a hemoglobinopathy, inflammatory disease and in certain ethnic groups (Wu et al., 2008), yet none of these other factors were accounted for herein.

As a study strength, it was required that blood group and non-ABO antibody status preceded SARS-CoV-2 testing, which was widely available under Ontario's universal health plan. The rate of non-ABO antibodies herein (1.4%) was consistent with that described by others (Gehrie and Tormey, 2014).

Blood group O may be somewhat protective against SARS-CoV-2 by neutralization of viral particles by the anti-A and anti-B antibodies (Pendu et al., 2021). In terms of non-ABO antibodies, exposure to an inflammatory RNA molecule heightens the immune response of rodents to a model blood group antigen, leading to alloantigen-specific immunity, as might occur in a viral infection like coronavirus (Gehrie and Tormey, 2014). Many non-A, non-B antigens serve structural and physiologic functions for red cell homeostasis (Gehrie and Tormey, 2014), yet it is unknown if any can confer protection against a viral infection like SARS-CoV-2. The current preliminary findings suggest that they might not.

O blood group is associated with a lower risk of both arterial and venous thrombosis (Wu et al., 2008), as well as SARS-CoV-2 (Ray et al., 2021). Since persons with COVID-19 illness have a high burden of thrombosis (Wichmann et al., 2020), a future study might assess whether non-ABO antibodies can modulate the risk of thrombosis in the presence of SARS-CoV-2 infection.

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Table 1
Characteristics of 413 577 individuals in Ontario, Canada with known ABO blood group and non-ABO antibody screen status, who subsequently underwent SARS-CoV-2 viral RNA polymerase chain reaction testing between January 15 and November 16, 2020. All data are presented as a number (%) unless otherwise indicated.

Characteristic		ABO blood group; non-ABO antibody (Ab) status			
		Non-O blood group; non-ABO Ab –VE (N = 227,898)	Non-O blood group; non-ABO Ab + VE (N = 3206)	O blood group; non-ABO Ab –VE (N = 180,027)	O blood group; non-ABO Ab + VE (N = 2446)
At the SARS-CoV-2 specimen collection date					
Mean (SD) age, years		48.4 (19.1)	56.6 (21.5)	48.4 (19.2)	57.3 (21.6)
Male		48,955 (21.5)	570 (17.8)	38,668 (21.5)	437 (17.9)
Area income quintile (Q)	*Q1 (lowest) or missing*[a]	43,948 (19.3)	719 (22.4)	36,658 (20.4)	542 (22.2)
	Q2	43,791 (19.2)	626 (19.5)	34,543 (19.2)	491 (20.1)
	Q3	45,673 (20.0)	628 (19.6)	35,913 (19.9)	455 (18.6)
	Q4	47,789 (21.0)	635 (19.8)	36,794 (20.4)	500 (20.4)
	Q5 (highest)	46,697 (20.5)	598 (18.7)	36,119 (20.1)	458 (18.7)
Rural residence or missing[b]		21,788 (9.6)	380 (11.9)	19,277 (10.7)	348 (14.2)
Pregnant		3223 (1.4)	24 (0.7)	2585 (1.4)	20 (0.8)
≤5 years before the SARS-CoV-2 specimen collection date					
Stroke or transient ischemic attack		5630 (2.5)	137 (4.3)	4410 (2.4)	126 (5.2)
Cardiac ischemia or arrhythmia		22,336 (9.8)	579 (18.1)	17,216 (9.6)	423 (17.3)
Chronic kidney disease		16,252 (7.1)	405 (12.6)	13,087 (7.3)	323 (13.2)
Anemia		41,580 (18.2)	915 (28.5)	32,602 (18.1)	715 (29.2)
Malignancy		56,407 (24.8)	996 (31.1)	44,441 (24.7)	783 (32.0)
Venous thromboembolism		7984 (3.5)	185 (5.8)	5,71 (2.9)	126 (5.2)
Any time before the SARS-CoV-2 specimen collection date					
Asthma		46,380 (20.4)	754 (23.5)	37,310 (20.7)	541 (22.1)
Chronic obstructive pulmonary disease		11,854 (5.2)	360 (11.2)	9639 (5.4)	285 (11.7)
Heart failure		16,376 (7.2)	512 (16.0)	12,536 (7.0)	343 (14.0)
Dementia, or frailty within the preceding year		56,079 (24.6)	1217 (38.0)	45,338 (25.2)	921 (37.7)
Diabetes mellitus		37,044 (16.3)	772 (24.1)	28,360 (15.8)	554 (22.6)
Chronic hypertension		68,627 (30.1)	1460 (45.5)	55,110 (30.6)	1136 (46.4)
HIV or organ transplant		1829 (0.8)	53 (1.7)	1423 (0.8)	42 (1.7)

Ab: non-ABO antibody; +VE positive; -VE negative.
[a] Area income quintile was missing for 602 (0.1%) of all participants.
[b] Residence was missing for 572 (0.1%) of all participants.

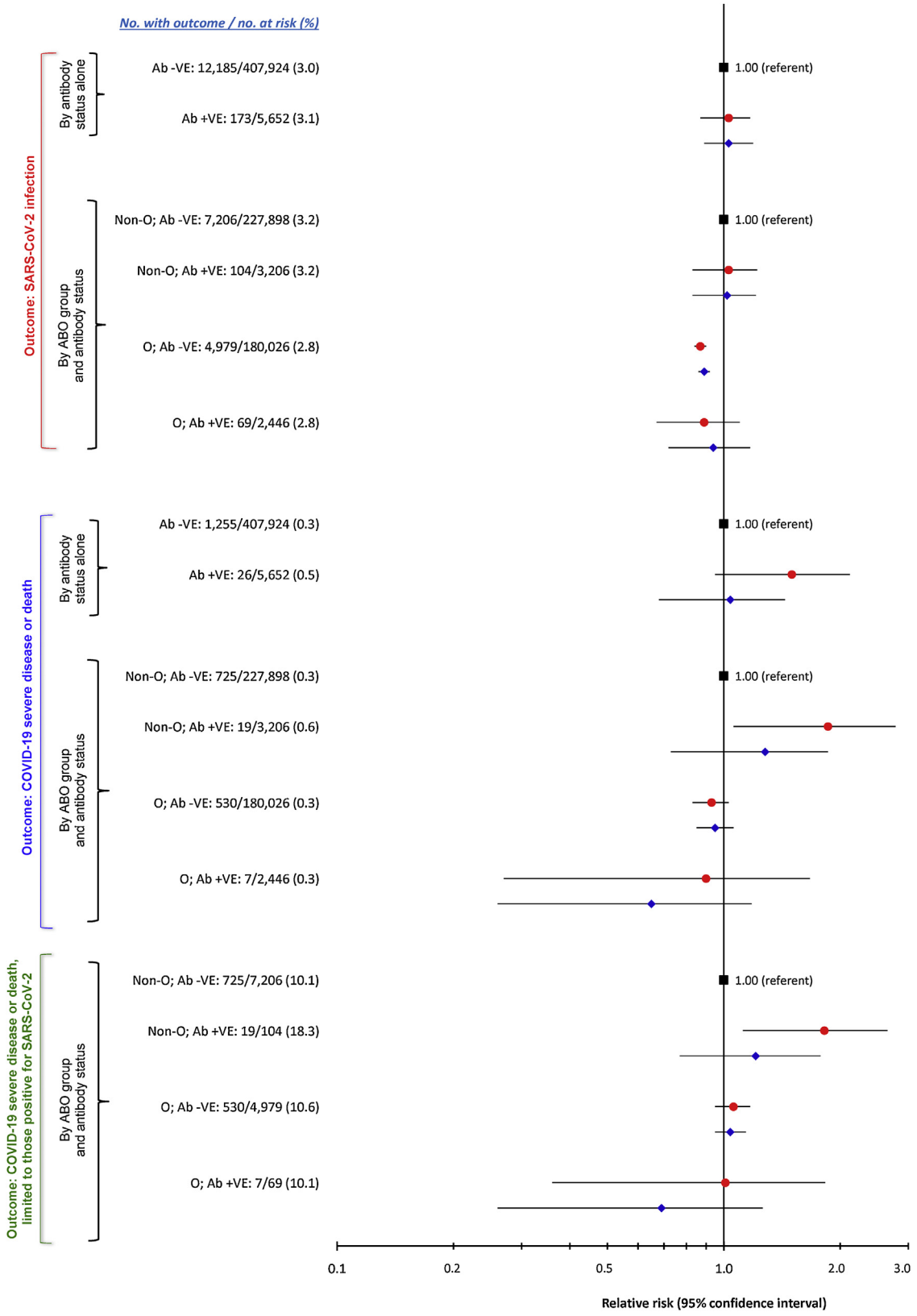

Figure 1. SARS-CoV-2 infection (top), and COVID-19 severe illness or death (middle), each in association with non-ABO antibody (Ab) positivity, including the co-presence of O and non-O blood groups. Also shown is the risk of COVID-19 severe illness or death among those with a positive SARS-CoV-2 test (lower). Relative risks are unadjusted (red circles) and adjusted (black diamonds) for age, sex, income quintile, rurality, local health integration network, diabetes mellitus, malignancy, heart failure, cardiac ischemia or arrhythmia, chronic kidney disease and venous thromboembolism – each prior to the SARS-CoV-2 specimen date.

opinions and statements expressed herein are solely those of the authors and do not reflect those of the funding or data sources; no endorsement is intended or should be inferred.

Ethical review

The use of data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a Research Ethics Board.

Declaration of interests

The authors declare that there are no known competing financial interests or personal relationships that could have appeared to influence the work described in this paper.

Author contributions

JGR, ALP: Study concept, analysis and interpretation of the data, drafting of manuscript, manuscript revision, approval of final version.

MC, MJS, MJV: Interpretation of the data, approval of final version.

Author agreement

All authors have seen and approved the final version of the manuscript being submitted. The article is the authors' original work, has not received prior publication, and is not under consideration for publication elsewhere.

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