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## Review article

# Relationship between blood type and outcomes following COVID-19 infection

Young Kim<sup>a</sup>, Christopher A. Latz<sup>a</sup>, Charles S. DeCarlo<sup>a</sup>, Sujin Lee<sup>a</sup>,  
C. Y. Maximilian Png<sup>a</sup>, Pavel Kibrik<sup>b</sup>, Eric Sung<sup>a</sup>, Olamide Alabi<sup>c</sup>,  
Anahita Dua<sup>a,\*</sup>

<sup>a</sup>Division of Vascular and Endovascular Surgery, Harvard Medical School, Massachusetts General Hospital, 55 Fruit Street, Wang 440, Boston, MA, 02114

<sup>b</sup>Division of Vascular Surgery, Langone Medical Center, New York University, Brooklyn, NY

<sup>c</sup>Division of Vascular Surgery and Endovascular Therapy, Department of Surgery, Emory University School of Medicine, Atlanta, GA

## ARTICLE INFO

## ABSTRACT

Since the onset of the COVID-19 pandemic, a concentrated research effort has been undertaken to elucidate risk factors underlying viral infection, severe illness, and death. Recent studies have investigated the association between blood type and COVID-19 infection. This article aims to comprehensively review current literature and better understand the impact of blood type on viral susceptibility and outcomes.

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## 1. Introduction

The COVID-19 pandemic began in December 2019. An outbreak of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) began as a cluster of patients developing pneumonia of unknown origin linked to a seafood market in the city of Wuhan [1]. From there, COVID-19 quickly spread throughout the Wuhan region. Despite stringent measures to contain the viral outbreak, the illness continued to proliferate throughout China, overwhelming its hospitals resources and health care workers [2]. In January 2020, the first case of COVID-19 was reported in the United States [3]. SARS-CoV-2 continued to spread through person-to-person transmission and swiftly escalated into a global emergency [4,5].

Robust research efforts have been undertaken to determine risk factors for viral susceptibility and severe illness [6]. The importance of deciphering COVID-19–related risk factors has significant implications for triage and prognosis. To date, multiple, population-based studies have discovered patient-level factors associated with worse outcomes after contracting COVID-19, including sex, race, ethnicity, age, obesity, and preexisting medical conditions [7–16]. Recent studies have investigated blood type as a risk factor for COVID-19 [17–23].

Blood type has been identified as a risk factor in many disease processes, ranging from malignancy [24,25] to venous and arterial thromboembolism [26–28]. The most widely studied associations, however, have been in the realm of infectious diseases. Blood group antigens play a direct role in infection through various mechanisms. On a molecular level, they can serve as receptors and coreceptors for pathogens; and can also facilitate intracellular uptake of viral particles [29]. Clinically, blood types have been linked to bacterial, parasitic, and viral infections [30–37]. One study,

\* Corresponding author.

E-mail address: [adua1@mgh.harvard.edu](mailto:adua1@mgh.harvard.edu) (A. Dua).

**Table 1 – Current studies analyzing the association of ABO blood type and COVID-19 infection.**

Study first author	Study period	Country	COVID-19 subjects, n	Subject population	ABO type, n (%)			
					A	B	AB	O
Ray [21]	Jan–June 2020	Canada	7,071	All tested adults and children	2,420 (34.2)	1,378 (19.5)	390 (5.5)	2,883 (40.8)
Hoiland [17]	Feb–Apr 2020	Canada	95	Adult ICU patients	27 (28.4)	23 (24.2)	11 (11.6)	34 (35.8)
Zhao [22]	NR	China	2,173	All tested adults	797 (36.7)	577 (26.6)	232 (10.7)	567 (26.1)
Li [20]	Feb–Mar 2020	China	2,153	All tested adults	819 (38.0)	561 (26.1)	219 (10.2)	554 (25.7)
Barnkob [43]	Feb–July 2020	Denmark	7,422	All tested adults	3,296 (44.4)	897 (12.1)	378 (5.1)	2,851 (38.4)
Boudin [45]	Jan–Apr 2020	France	1,279	All crew members	521 (40.7)	135 (10.6)	54 (4.2)	553 (43.2)
Leaf [19]	Mar–Apr 2020	US	2,033	Adult ICU patients	666 (32.7)	328 (16.1)	89 (4.4)	950 (46.7)
Latz [18]	Mar–Apr 2020	US	1,289	All tested adults	440 (34.2)	201 (15.6)	61 (4.7)	587 (45.5)
Zietz [23]	Mar–Aug 2020	US	2,394	All tested adults	786 (32.8)	392 (16.4)	94 (3.9)	1,122 (46.9)

Abbreviations: ICU, intensive care unit; NR, not reported.

**Table 2 – Current studies analyzing the association of rhesus type blood type and COVID-19 infection.**

Study first author	Study period	Country	COVID-19 subjects, n	Subject population	Rhesus type, n (%)	
					Rh+	Rh–
Ray [21]	Jan–June 2020	Canada	7,071	All tested adults and children	6,389 (90.4)	682 (9.6)
Latz [18]	Mar–Apr 2020	US	1,289	All tested adults	1,161 (90.0)	128 (9.9)
Zietz [23]	Mar–Aug 2020	US	2,394	All tested adults	2,219 (92.7)	175 (7.3)

Recent population-based studies estimate that Rh-positivity in North America (US and Canada) is approximately 85% [53].

in particular, found that ABO polymorphism was associated with susceptibility to infection with SARS-CoV-1 [30]. Further investigations discovered a protective effect of anti-A antibodies against intracellular uptake of SARS-CoV-1 [38,39]. Using a cellular model of adhesion, Guillon et al [39] discovered that human anti-A antibodies inhibited interaction between angiotensin converting enzyme-2–dependent cellular adhesion to angiotensin converting enzyme-2–expressing cells. These results propose a molecular mechanism by which ABO polymorphism impacts susceptibility to SARS-CoV-1 infection and transmission [38]. These and other articles have led investigators to investigate whether an association exists between SARS-CoV-2 and blood antigen grouping [40].

Currently, 9 large studies have analyzed the effect of blood type and COVID-19–related illness (Tables 1 and 2) [17–23]. These studies span multiple countries with widely different patient populations. The majority of these studies report an association between blood type and viral infection, although they differ with regard to which blood type portends susceptibility to infection. Among these studies, 8 of 9 articles associated blood type with COVID-19 susceptibility. Four studies found a correlation between blood type and severity of COVID-related illness, and 5 studies did not. The key findings of these studies are detailed below.

## 2. Methods

There was a significant amount of literature published about the relationship between blood type and SARS-CoV-2 and this field continues to evolve as the pandemic continues. For this comprehensive review, we included only peer-reviewed

journal articles, articles in English, and those published from March 2020 to January 2021. All articles were identified via searches on PubMed for terms including COVID-19 or SARS-CoV-2 and *blood type*, *severity COVID* and *blood type*. The articles for reviewed by 2 reviewers for sample size, diversity of population, and methodology to ensure a thorough, diverse representation of the literature. To minimize bias, single case reports and small case series were excluded.

### 2.1. Data supporting blood type correlation with severity of illness

Ray et al [21] published the largest study to date in Canada, investigating the association of blood type with COVID-19. This population-based cohort study from Ontario included a total of 225,556 patients who underwent polymerase chain reaction testing for SARS-CoV-2. Among these, 7,071 (3.1%) tested positive for the virus. Adjusted relative risks (ARRs) were calculated after adjusting for patient demographic data and medical comorbidities. The authors found that individuals with type O blood were less likely to contract SARS-CoV-2 compared with non-type O blood groups (ARR = 0.88; 95% confidence interval [CI], 0.84–0.92). Rhesus (Rh)-negative individuals were also less likely to be diagnosed with SARS-CoV-2 (ARR = 0.79; 95% CI, 0.73–0.85). Interestingly, individuals with O-negative blood type were further protected against viral infection (ARR = 0.74; 95% CI, 0.66–0.83). Type O individuals were at decreased risk compared to non-type O individuals with regard to secondary outcomes, such as severe illness and death (ARR = 0.87; 95% CI, 0.78–0.97). Rh-negative individuals were also at lower risk of severe illness and mortality compared to Rh-positive patients (ARR = 0.82; 95% CI, 0.68–0.96). Taken

together, the authors concluded that type O and Rh-negative blood groups may be protective against SARS-CoV-2 infection and illness.

In China, Zhao et al [22] conducted a retrospective analysis on 2,173 patients who tested positive for SARS-CoV-2. Subjects were pooled from 3 hospitals in 2 cities. The majority of patient data were collected from Jinyintan Hospital in Wuhan, with the remainder from Renmin Hospital of Wuhan University and Shenzhen Third People's Hospital. The authors compared COVID-19-infected patients with healthy population controls within the same region. Using a random effects model, the pooled data were used to determine the risk of blood type on COVID-19 infection and death. Zhao et al found that blood type A patients were at significantly increased risk of infection compared with non-type A patients (odds ratio [OR] = 1.21; 95% CI, 1.02–1.43;  $P = .03$ ). Conversely, type O individuals were at lower risk of infection compared to non-type O individuals (OR = 0.67; 95% CI, 0.60–0.75;  $P < .001$ ). Types B and AB were not at increased risk of COVID-19 infection. In terms of mortality, blood type A patients were at increased risk of death (OR = 1.48; 95% CI, 1.11–1.97) and type O patients had a decreased risk of death (OR = 0.66; 95% CI, 0.48–0.91) ( $P = .01$  each). Similar to Ray et al [21], the authors concluded that type O blood group may be protective against SARS-CoV-2 infection and mortality.

Zietz et al [23] also found that blood type groupings were associated with both risk of intubation and death. Zietz et al performed a retrospective cohort analysis using electronic health record data from the New York Presbyterian/Columbia University database. A total of 13,051 patients were tested between March to August 2020; among whom 2,394 were diagnosed with SARS-CoV-2. Altogether, 399 patients (16.7%) required mechanical ventilation and 331 patients (13.8%) died of COVID-19-related illness. On multivariate analysis, after adjusting for race and ethnicity, individuals with type A blood were at increased risk of infection compared with type O individuals (absolute risk difference [ARD] = 1.3; 95% CI, –0.3 to 3.0). Blood type AB (ARD = 0.1; 95% CI, –2.8 to 3.2) and type B (ARD = 1.3; 95% CI, –0.7 to 3.3) patients were also at increased risk of infection, using type O as a reference. Rh-negative patients were at lower risk of infection compared with Rh-positive patients (ARD = –2.7; 95% CI, –4.7 to –0.8). With regard to intubation and death, type A blood was associated with decreased risk of both intubation (ARD = –2.9; 95% CI, –7.2 to 0.6) and death (ARD = –1.6; 95% CI, –4.9 to 1.6). Type AB individuals were at increased risk of both intubation (ARD = 1.8; 95% CI, –8.3 to 12.2) and death (ARD = 1.4; 95% CI, –6.9 to 8.9). Type B individuals were at increased risk of intubation (ARD = 2.5, CI –2.7 to 7.5), but lower risk of death (ARD = –2.6; 95% CI, –6.6 to 1.3). Compared with Rh-positive patients, Rh-negative patients were at decreased risk of both intubation (ARD = –5.2; 95% CI, –10.7 to 1.0) and death (ARD = –8.2; 95% CI, –11.7 to –3.7), corresponding with a lower risk of initial infection. Taken together, the authors surmised that blood type plays a substantial role in COVID-19 infection and outcomes.

In Canada, Hoiland et al [17] focused their investigation on patients with COVID-19 in the intensive care unit (ICU) setting. This multicenter retrospective analysis included 95 patients critically ill with COVID-19 in ICUs across 6 metropolitan Vancouver hospitals. Given previous reports of the

protective effect of anti-A antibodies in SARS-CoV-1 infection [38,39], Hoiland et al hypothesized that anti-A antibodies might also be protective against severe viral infection with SARS-CoV-2. Subjects were therefore grouped into blood types A/AB and types O/B. Multivariate analysis was performed adjusting for patient age, sex, and comorbidities. In this patient population, blood types A and AB were more likely to require mechanical ventilation, chronic renal replacement therapy, and prolonged ICU stay compared with types O ( $P < .05$ ) and B ( $P < .05$ ). However, no differences were noted in hospital length of stay or in-hospital mortality between groups.

Other studies have also supported correlation between blood type with infection and illness in smaller populations. In Turkey, Gökler et al [41] found that blood type A was associated with higher rates of infection without any impact on severity of illness ( $n = 186$ ). In a separate study, Kibler et al [42] found that patients with aortic stenosis status post transcatheter aortic valve replacement ( $n = 22$ ) with blood type A were more likely to become severely ill with COVID-19. Given the small size of these and other similar series, these studies did not weigh into our overall conclusions.

## 2.2. Data against blood type correlation with severity of illness

Five studies found that ABO blood type was not associated with severity of illness or mortality after infection. Barnkob et al [43] published the largest study to date overall, including a total of 841,327 subjects from Denmark. Among tested subjects, 473,654 had ABO blood type data available and 7,422 were positive for COVID-19. In this cohort, the majority (74%) of COVID-19-positive subjects had mild disease and did not require inpatient hospitalization. Data from tested subjects were compared with 2,204,742 nontested individuals, which accounted for nearly 40% of the total Danish population. The authors found that individuals with type O blood were relatively protected from viral infection (relative risk (RR) = 0.87; 95% CI, 0.82–0.91). Unlike previous studies, however, there was no difference between ABO blood type and progression of illness to hospitalization or mortality (each,  $P > .40$ ). Rh typing was not collected in this analysis.

In our investigation, we performed a multi-institutional analysis across 5 hospitals in the New England region [18]. A total of 7,648 patients were tested for SARS-CoV-2 during the study period, of which 1,289 (16.9%) were positive. Among positive subjects, 484 (37.5%) required inpatient admission, 123 (9.5%) were admitted to the ICU setting, and 108 (8.4%) required mechanical ventilation. On univariate analysis, ABO and Rh types were not associated with infection, hospital admission, or ICU admission rates. Blood antigen groupings did not correlate with peak inflammatory markers, including white blood cell count, lactate dehydrogenase, erythrocyte sedimentation rate, and C-reactive protein levels. Individuals with type AB (OR = 1.37; 95% CI, 1.02–1.83), type B (OR = 1.28; 95% CI, 1.08–1.52), or Rh-positive blood groups (OR = 1.23; 95% CI, 1.00–1.50) were more likely to test positive for SARS-CoV-2. Type O individuals, on the other hand, were protected against infection (OR = 0.84; 95% CI, 0.75–0.95). Neither ABO or Rh types were associated with risk of intubation or mortality. As a result, we concluded that blood types may be associated with

infection rates, but in contrast to other studies, no association was noted with progression to severe illness or death.

A second retrospective cohort study from China was published by Li et al [20] in July 2020. This study included 2,153 patients across 3 hospitals in Wuhan, including Jinyintan Hospital, Renmin Hospital of Wuhan University, and the Central Hospital of Wuhan. It is unclear whether these subjects overlap with those in Zhao et al's [22] article, given that 2 of the hospitals reviewed are the same. On univariate analysis, a greater proportion of patients infected with SARS-CoV-2 were of type A blood compared with healthy controls (38.0% v 32.2%;  $P < .001$ ). The proportion of infected type O individuals were significantly lower than healthy controls (25.7% v 33.8%;  $P < .001$ ). With these findings, Li et al [20] suggested that type A individuals might be at greater risk of infection, and type O individuals may be less susceptible. The authors did not report any association between blood type grouping and severity of illness, and covariate adjustment was not performed in this analysis.

In a confirmatory analysis, Dzik et al [44] analyzed ABO distribution among patients in both Wuhan and Boston. Using Wuhan data already published by Zhao et al [22] and Li et al [2], the authors did not find any associations between blood type and COVID-19–related severity of illness. This reaffirms the conclusions made by the original authors. In terms of their Boston data, Dzik et al's investigation is more comprehensively collected and analyzed in our study, as it uses the same database with fewer patients. Therefore, the study by Dzik et al did not weigh into our discussion or conclusions.

Leaf et al [19] investigated critically ill patients with COVID-19 in the ICU setting. In a multicenter cohort study, the authors examined SARS-CoV-2–positive patients admitted to ICUs from 67 hospitals across the United States. Among the 3,239 critically ill patients during the study period, a total of 2,033 patients had ABO blood group data available. Rh-type data was not reported in this analysis. Leaf et al found that the distribution of ABO phenotypes in critically ill patients differed substantially from the expected distribution in healthy subjects. Among White patients, type A individuals were over-represented (45.1% observed v 39.8% expected) and type O individuals were underrepresented (37.8% observed v 45.2% expected) compared to healthy subjects. No differences were noted between observed and expected distributions of ABO blood groups in Black or Hispanic patients. Leaf et al concluded that type A blood might be a risk factor among White patients with COVID-19–related critical illness, and type O blood might be protective. Within this critically ill cohort, the mortality rate was 39.3% within 28 days, and ABO blood type did not affect mortality rates.

In France, Boudin et al [45] studied a unique patient population impacted by SARS-CoV-2 infection. The authors investigated all crew members from the French Navy nuclear aircraft carrier, *Charles de Gaulle*, who were exposed to a viral outbreak while on board. Of the 1,769 crew members, 1,279 (76%) tested positive for COVID-19. After the ship returned to base, all members were quarantined and underwent medical monitoring for 2 weeks post landing. In contrast with other studies, the median crewmember age was 28 years, 87% were men, and no significant medical comorbidities were reported. No significant association was found between ABO

or Rh blood groups with viral infection, progression to severe illness, or death after infection.

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### 3. Summary of key findings and limitations

Eight of 9 studies demonstrated an association between blood type and susceptibility to infection with SARS-CoV-2. Four of these 9 studies also revealed an association with severity of illness. Ray et al [21] found that subjects with type O and Rh-negative blood were protected from viral infection, severe illness, and mortality. Although the data are convincing, this study was limited by the inability to test critically ill patients who died quickly after hospital admission. Zietz et al [23] also found that ABO and Rh types were associated with infection, mechanical ventilation, and death. This study was significantly limited by the circumstances of limited testing capability, however, with the majority of subjects being tested in an inpatient setting due to illness. Hoiland et al [17] focused primarily on critically ill subjects, reporting an association with blood types A and AB with risk of intubation, chronic renal replacement therapy, and prolonged ICU stay. This study was limited by a very small sample size, with missing blood group data in 25% of subjects.

In China, Zhao et al [22] reported type A subjects were at increased risk of infection and mortality, and type O subjects were protected from both outcomes. Li et al [20] also found type A–associated susceptibility to viral infection, but did not find an association with mortality. Both Zhao et al's and Li et al's articles were limited by a small sample size of a single ethnic group. In addition, given that both authors used data from the same hospitals during the same study period, there is potential for subject overlap between the 2 studies. A third study from China by Wu et al [46] supported these findings, noting an increased risk of infection with type A blood. Of note, this third study from China ( $n = 187$ ) was much smaller in scale compared to the investigations by Zhao et al and Li et al ( $n = 2,153$  and  $n = 2,173$ , respectively).

In the largest study to date, Barnkob et al [43] found a protective effect of type O blood with viral susceptibility. We also found that subjects with type O and Rh-negative blood appeared to be at decreased risk for infection on multivariate analysis [18]. Unlike previous reports, neither Barnkob nor our study found any association between blood type and progression to severe illness or death. Our investigation was limited by small sample size and lead-time bias, however, with subjects analyzed early in their hospital course. Similarly, Leaf et al [19] also found that blood type O and Rh-negative subjects were at decreased risk of infection, with no association with mortality rates. These results were also limited by small sample size, along with missing blood group data in approximately one-third of subjects.

Unlike other analyses, Boudin et al [45] did not find any association between ABO or Rh types with infection, severe illness, or death. These results were impacted by the healthy patient population and high rate of infection (76%); however, and might not be reflective of normal societal conditions. Finally, all 9 studies were retrospective analyses of observational data and, therefore, subject to selection bias. A summary of key study limitations are detailed in Table 3.

**Table 3 – Summary of key study limitations.**

First author	Limitations
Ray [21]	Inability to test patients who died quickly due to critical illness
Zhao [22]	Moderate sample size (n = 2,173), single ethnic group
Li [20]	Moderate sample size (n = 2,153), single ethnic group, no covariate adjustment, potential subject overlap with Zhao [22]
Hoiland [17]	Very small sample size (n = 95), limited to ICU subpopulation, blood group data missing in 25% of ICU-admitted patients
Leaf [19]	Moderate sample size (n = 2,033), blood group data missing in one-third of subjects
Latz [18]	Moderate sample size (n = 1,289), lead time bias
Zietz [23]	Selection bias for inpatient hospital population due to limited testing
Barnkob [43]	ABO data available for only 62% of tested individuals, female sex overrepresented at 71% of negative and 67% of positive subjects
Boudin [45]	Moderate sample size (n = 1,279), very high infection rate (76%), subjects not representative of general population (ie, young, healthy)

Abbreviation: ICU = intensive care unit.

As a group, one collective limitation among this set of articles is the significant variability in testing of ABO and Rh blood types. Only 3 of the 9 studies tested and analyzed Rh types, which are summarized in the next section. The proportion of ABO types represented appears to vary widely between studies (Table 1); however, this appears to reflect the natural ABO blood group distribution within each individual study population. For example, Zhao et al [22] and Li et al [20] both report an AB blood group prevalence of > 10%, but this is representative of the Chinese population. Each of these studies should therefore be taken in context of their individual study populations and limitations (Table 3).

### 3.1. Rhesus type and COVID-19

The impact of Rh-type on COVID-19 infection deserves a special focus (Table 2). Rh-type is the second most important blood group system after ABO typing. Like ABO types, Rh-type refers to proteins on surface of red blood cells [47]. Clinically, this system plays an important role in blood transfusion and erythroblastosis fetalis [47,48]. Recent studies also demonstrate a significant impact in COVID-19 infection and illness as well. As mentioned previously, of the 9 studies included in this review, 5 investigated Rh blood type. Four of 5 studies found significant associations with Rh-negative blood grouping [18,19,21,23]. Both Ray et al [21] and Zietz et al [23] found that subjects with Rh-negative blood type were at lower risk of viral infection, severe illness, and mortality after infection. Our study, along with Leaf et al's [19], also found that Rh-negative subjects were at lower risk of infection, but did not find any impact on COVID-19-related illness or mortality. Although overall results might be mixed, there is a consistent theme on Rh-type and susceptibility to COVID-19 infection.

### 3.2. Anti-A antibodies and COVID-19

As mentioned previously, Hoiland et al [17] reported an association with blood types A and AB with worse clinical outcomes. Although this study was limited by a very small sample size, the authors hypothesized that the presence of anti-A antibodies might play a key role in viral susceptibility. In their discussion, Hoiland et al refer to a growing body of scientific work comparing SARS-CoV-1 and SARS-CoV-2 viruses. Both viral

strains appear to share similar receptor-binding domains [49]. The anti-A antibody inhibits interaction between SARS-CoV-1 and the angiotensin converting enzyme-2 receptor [38], suggesting that the ABO antibodies might influence SARS-CoV-2 infection as well. Other scientific reports have implicated viral infection with other factors, such as anti-A immunoglobulin isotype [50], ABO-type differences in von Willebrand factor [51], and anti-A isohemagglutinin titers [52]. Interestingly, recent genomic analyses have identified specific gene clusters (3p21.31) as susceptibility markers in patients with COVID-19 and respiratory failure. Given the association of this specific locus with the ABO blood group locus, the authors suggest that this may be one mechanism for the involvement of ABO typing with COVID-19-related illness [40]. Although the complete mechanism has yet to be fully elucidated, future studies in this field may help the development of prophylactic and therapeutic interventions for COVID-19 infection.

## 4. Conclusions

Since the onset of the COVID-19 pandemic, a concentrated research effort has been undertaken to elucidate risk factors underlying viral susceptibility and illness. Among these efforts, several recent studies have investigated the association between blood type and COVID-19 infection. Each of these reports provides important information with regard to understanding the underlying disease process. Although these reports might be inconsistent in their findings, certain trends are evident. Many studies report that blood type A might predispose one to increased susceptibility of infection with SARS-CoV-2, and type O and Rh-negative blood groups might be protective. Although this appears to be an emerging trend, the impact of blood type on clinical outcomes remains unclear. At this point in time, there does not appear to be any relationship between blood type and COVID-19-related severity of illness or mortality. Current literature does not support blood type as part of a predictive model of viral illness or mortality, and ABO/Rh screening should not be used as a triage mechanism. Future investigations can focus on the creation of a global COVID-19 database to account for population-based differences in blood types and testing protocols. In addition, further studies are necessary to understand the

molecular mechanisms by which blood types might engender susceptibility to SARS-CoV-2 infection, and ultimately, develop countermeasures to viral infection and illness.

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