ABO blood group and link to COVID-19: A comprehensive review of the reported associations and their possible underlying mechanisms

Eric Pereira [a], Stela Felipe [a], Raquel de Freitas [a], Valdevane Araújo [a], Paula Soares [a], Jannison Ribeiro [b], Luiz Henrique dos Santos [a], Juliana Osório Alves [a], Natália Canabrava [c], Mauricio van Tilburg [c], Maria Izabel Guedes [c], Vânia Ceccatto [a,*]

[a] *Superior Institute of Biomedical Sciences, State University of Ceará, Dr. Silas Munguba Av., Fortaleza, 60714-903, Ceará, Brazil*
[b] *Hematology and Hemotherapy Center of Ceará, José Bastos Av., Fortaleza, 60431-086, Ceará, Brazil*
[c] *Biotechnology and Molecular Biology Laboratory, State University of Ceará, Dr. Silas Munguba Av., Fortaleza, 60714-903, Ceará, Brazil*

ABSTRACT

ABO blood group is long known to be an influencing factor for the susceptibility to infectious diseases, and many studies have been describing associations between ABO blood types and COVID-19 infection and severity, with conflicting findings. This narrative review aims to summarize the literature regarding associations between the ABO blood group and COVID-19. Blood type O is mostly associated with lower rates of SARS-CoV-2 infection, while blood type A is frequently described as a risk factor. Although results regarding the risk of severe outcomes are more variable, blood type A is the most associated with COVID-19 severity and mortality, while many studies describe O blood type as a protective factor for the disease progression. Furthermore, genetic associations with both the risk of infection and disease severity have been reported for the ABO *locus*. Some underlying mechanisms have been hypothesized to explain the reported associations, with incipient experimental data. Three major hypotheses emerge: SARS-CoV-2 could carry ABO(H)-like structures in its envelope glycoproteins and would be asymmetrically transmitted due to a protective effect of the ABO antibodies, ABH antigens could facilitate SARS-CoV-2 interaction with the host' cells, and the association of non-O blood types with higher risks of thromboembolic events could confer COVID-19 patients with blood type O a lower risk of severe outcomes. The hypothesized mechanisms would affect distinct aspects of the COVID-19 natural history, with distinct potential implications to the disease transmission and its management.

1. Introduction

The Severe Acute Respiratory Syndrome-Coronavirus 2 (SARS-CoV-2), the causing agent of COVID-19, emerged in late 2019 and rapidly spread worldwide, becoming a global health threat that, in one year, accounted for about 70 million cumulative cases [1]. Its high infectivity [2], with the occurrence of asymptomatic transmission [3], may have contributed to such a scenario. Mainly characterized by symptoms like fever, headache, cough, fatigue, breathing difficulties, anosmia, and ageusia; COVID-19 can either remain asymptomatic or develop to severe and critical manifestations, like dyspnea, hypoxia, acute respiratory distress syndrome, and multiorgan failure [4]. Age and co-morbidities, like diabetes and cardiovascular diseases, increase the risk of severe outcomes [5]. However, given the poorly understood pathogenesis of

COVID-19 and the variability in clinical presentation and outcomes, there has been a search for other biological markers that could predict the susceptibility to SARS-CoV-2 infection and the risk of severe outcomes [4,6].

The ABO blood group, which comprises distinct carbohydrate epitopes at the surface of blood cells and other tissues, like the respiratory and gastrointestinal epithelium [7], has been considered as an influencing factor for the susceptibility to infectious diseases. For instance, associations between the ABO blood type and the risk or severity of infections have been described for the Human Immunodeficiency Virus (HIV) [8], hepatitis B [8,9], West Nile virus (WNV) [10], and *Helicobacter pylori* [11,12]. Blood group antigens can influence infections directly, acting as receptors or co-receptors for microorganisms and toxins; or indirectly, through the anti-blood group antibodies, which can

* Corresponding author.
E-mail address: vania.ceccatto@uece.br (V. Ceccatto).

be prompted by bacteria and enveloped viruses bearing blood group-like antigens [13].

After a first report [14], a wealth of studies have been investigating a possible association between the ABO blood group and SARS-CoV-2 infection, with conflicting findings. Some authors pointed to the ABO blood type as an influencing factor for SARS-CoV-2 infection [15,16] or even its severity [17] and mortality [18], while others failed to demonstrate such associations [19,20]. Generally, blood type A has been linked to higher risk of SARS-CoV-2 infection, and blood type O, to lower risk. It is noteworthy that a similar association was early described for SARS-CoV, in which blood type O was negatively associated with infection among a group of health workers [21].

Although these associations and their potential implications remain unclear; some underlying mechanisms have been hypothesized, like a protective effect of the ABO antibodies [22], the link between ABO blood type and cardiovascular risk [23], and a role for ABO(H) antigens in facilitating viral entry into target cells. Thus, this paper aims to review the associations between ABO blood group and COVID-19 and its possible underlying mechanisms.

2. ABO blood group system: an overview

The ABO blood group system consists of carbohydrate antigens forming four main blood types: A, B, AB, and O. Blood types A and B are determined by the presence of the homonymous antigens, while blood types AB and O, by the presence of both or none, respectively [24]. Discovered in the Red Blood Cells (RBCs); the ABO antigens were later found in several tissues and secretions, such as saliva, intestinal mucosa, endothelium [13], and the respiratory tract epithelium [7]. As an autosomally inherited trait, the ABO blood type is determined by the polymorphism of the ABO gene, located at the 9q34.2 *locus* [6]. Alleles A and B are codominant over allele O and determine the expression of the homonymous antigens. Allele O, in turn, is recessive and does not determine the expression of any antigen. Like carbohydrates, antigens A and B are secondary products of the ABO gene, which primarily encodes specific enzymes that catalyze the addition of monosaccharide motifs to an oligosaccharide backbone anchored to glycoproteins or glycolipids through N- or O-linked glycosylation. Such process depends on antigen

H, the acceptor of antigens A and B at the growing oligosaccharide chain [13,25–27].

Antigen H is synthesized through the addition of terminal fucose (Fucα1-2Gal) to lactosamine (GlcNac). On RBCs, platelets, and endothelium, this process is catalyzed by an α1,2-fucosyltransferase encoded by the FUT1 gene and forms a Fucα1-2Galβ1-4GlcNAc. FUT1 is independent of the ABO gene and its product uses insoluble oligosaccharides chains (type 2) as the acceptor structure for fucose, which generates insoluble antigen H. However, in epithelial cells, mucus, and secretions, antigen H is added to a soluble chain (type 1), which originates the secretor phenotype in a process catalyzed by an α1,2-fucosyltransferase encoded by the FUT 2 gene. The type 1 and type 2 chains differ in the link between galactoses: β1-3 and β1-4, respectively (Fig. 1) [7,27]. Although located at the same chromosome – 19q13 – FUT1 and FUT2 are independent genes with differential expression throughout the organism. The homozygous inheritance of FUT 1 null alleles produces the rare Bombay phenotype, on which the individuals are unable to synthesize antigen H and, thus, antigens A and B. In turn, the homozygous inheritance of FUT2 null alleles results in the inability to synthesize soluble antigen H and, therefore, in the non-secretor phenotype, characterized by the lack of ABO antigens in epithelial tissues and secretion. Unlike Bombay, the non-secretor phenotype is not rare and is found in about 20% of the western population [7].

Once antigen H is formed, antigens A and B are synthesized by the glucosyltransferases A (GTA) and B (GTB), respectively encoded by the A and B alleles of the ABO gene (Fig. 1) [26]. The O allele, in turn, produces a truncated protein instead of a functional enzyme [28]. Antigen A is determined by a N-acetyl-galactosamine (GalNAc) motif, and antigen B, by D-Galactose (Gal), respectively characterized by acetamido (AcNH) and hydroxyl (OH) groups (Fig. 2). Both are added to antigen H through an α1-3 glycosidic bond, forming the GalNAcα1-3(Fucα1-2)Gal- and Galα1-3(Fucα1-2)Gal-chains, respectively [26,27,29]. The specificity of GTA and GTB relies on a size-based complementarity with the nucleotide-sugar donors Uridine diphosphate(UDP)-GalNAc and UDP-Gal, respectively [30].

Another component of the ABO blood group system is the ABO antibodies, which are specific antibodies directed toward the missing A/B antigen even in the absence of a previous alloimmunization. Therefore,

Fig. 1. - Sequential synthesis the ABO antigens. Gal: D-Galactose, GlcNAc: N-Acetylglucosamine, GalNAc: N-Acetyl-galactosamine, Fuc: L-fucose, R: Radical group, GTA: Glucosyltransferase A, GTB: Glucosyltransferase B, β1,3: Type 1 chain, β1,4: Type 2 chain. (Two-column fitting image).
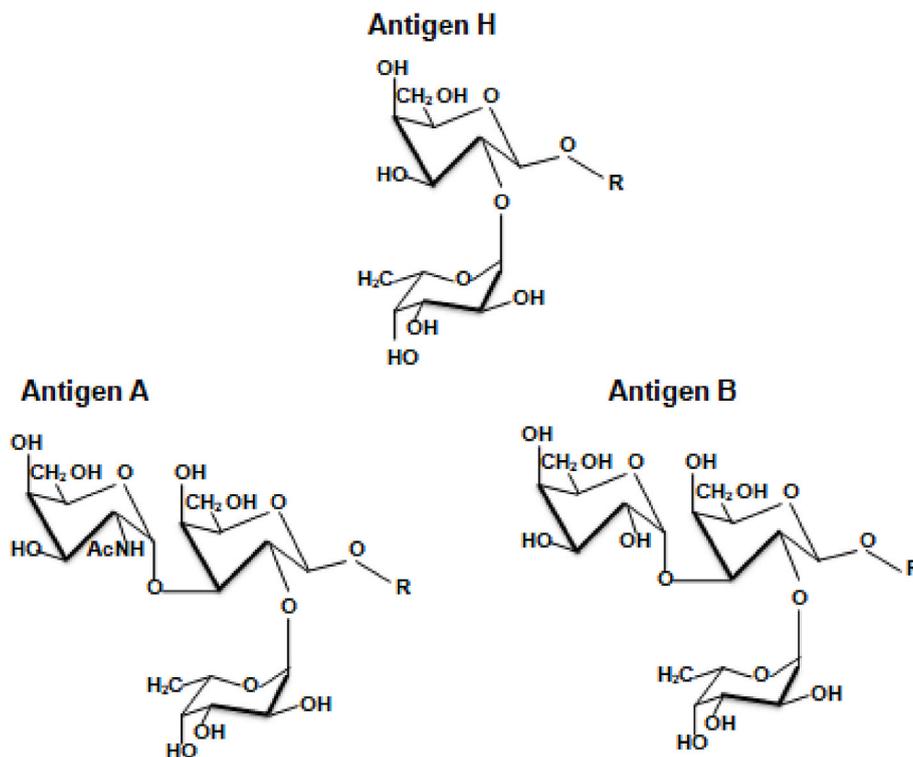
Fig. 2. - Structural representations of the ABO blood group antigens. (1.5-column fitting image).

A and O blood type individuals produce anti-B, B and O individuals produce anti-A, and AB individuals are devoid of both anti-A and anti-B [31]. The origin of ABO antibodies is still controversial, however, their synthesis seems to be mostly triggered by either microbiota or pathogenic microorganisms bearing ABO(H)-like antigens [32,33]. The ABO antibodies are able to induce complement-mediated lysis of RBCs and are mainly of IgM class [31].

3. ABO blood group and link to infections

ABO and FUT2 are clearly polymorphic genes and their products are highly present on epithelial cells in contact with the external environment. They are maximally expressed in mucins, which are thought to have a protective role in binding to microorganisms and are found in the body's exposed surfaces, like in the lungs and the gastrointestinal tract. Such features are suggestive of a possible function for ABO antigens in the interaction with environmental pathogens [7,34]. In addition, phylogeny of the ABO determinants showed that their firstly appeared as tissular antigens [35].

The widespread distribution of carbohydrates on cells' surfaces and their structural diversity place them as informational molecules able to act in cell recognition [36]. Indeed, pathogenic microorganisms and toxins can require binding to specific carbohydrate antigens to trigger infection and disease [37]. This was observed for *H. pylori,* whose infection was shown to depend on the expression of the Lewis b (Le[b]) antigen in the gastric mucosa [38], and for the uropathogenic *E. coli* R45 strain, which binds to galactosyl-globoside - a precursor of the type 1 chain exposed at the membrane of non-secretor uroepithelial cells - and its sialylated derivate [39]. Furthermore carbohydrate antigens akin to that found on the surface of hosts' cells can be synthesized by bacteria in a co-evolving process suggestive of molecular mimicry, in which pathogenic or symbiotic microorganisms mimic carbohydrate motifs found at the host species to evade their innate immune system [37]. Indeed, Georg et al. screened 282 gram-negative strains isolated from humans, of which 48% showed ABO blood group activity [40].

Likewise, enveloped viruses can also acquire carbohydrate antigens

from their previous host as part of their structures and be asymmetrically transmitted due to a protective effect of the naturally occurring antibodies [41]. During their synthesis, the viral proteins are glycosylated in the Golgi apparatus and the endoplasmic reticulum of the host cells by their glycosylation enzymes [42]. Hence, viral glycoproteins can bear the glycosylation pattern of the cell in which they were synthesized. This was experimentally demonstrated for the Human T-cell Lymphotropic Virus (HTLV) iii$_b$, which was neutralized by monoclonal anti-A antibodies after propagation in peripheral blood mononuclear cells (PBMC) from A-type individuals, but not after propagation in PBMC of B or O individuals [42]. A similar effect was observed for the *Measles* virus produced in cells transfected with cDNA encoding human A, B, or null "O" transferases. The viruses produced in A- or B-type cells were partially neutralized, in a complement-dependent manner, by human pre-immune serum containing anti-A or anti-B antibodies, respectively, while the viruses produced in type O cells were not neutralized [43]. Moreover, anti-A monoclonal antibodies and type O plasma inhibited the adhesion of transfected CHO cells co-expressing the A antigen and the Spike (S) protein of SARS-CoV to ACE2-expressing Vero cells [44].

The link between ABO polymorphism and infectious disease has been extensively studied and is detailed reviewed elsewhere [13]. Associations have been reported for instance, with HIV [8], hepatits B [9], West Nile Virus [10], and malaria [45]. Thus, the ABO polymorphism has been considered as an adaptive trait that could narrow the spread of infections within a given species. In turn, pathogenic microorganisms have been considered as a selective pressure generating diversity in the distribution of blood types among different populations, according to the exposition to distinct pathogens [37,46]. It is worth mentioning that associations between the ABO blood type and infectious diseases are most reliant on statistics, with few experimental data, and that illness may be multifactorial in nature, with the blood type constituting one of the multiple predisposing factors [34].

4. Associations between ABO blood types and COVID-19

4.1. Susceptibility to SARS-CoV-2 infection

Soon after the onset of the COVID-19 pandemic, an association between the ABO blood group and SARS-CoV-2 infection was firstly reported by Zhao et al., in which blood type A was significantly related to higher risk of COVID-19 infection in comparison to non-A blood types; while blood type O was significantly related to lower risk of COVID-19 infection compared to non-O blood types [14]. Subsequently, several studies have been reporting significant associations between blood type A and higher susceptibility to SARS-CoV-2 infection and/or blood type O and lower susceptibility [15,47–58]. A summary of the findings is described in Table 1.

As can be seen from Table 1, blood type A is frequently associated with higher risks of acquiring COVID-19, while blood type O is mostly described as a protective factor. Nonetheless, there are several disagreements, especially regarding the higher susceptibility. For instance, Muñiz-Diaz et al. evaluated the distribution of ABO blood types in two cohorts – convalescent plasma donors, with regular donors as the control group, and hospitalized COVID-19 patients, with general patients as the control group -. In the former, blood type A was significantly overrepresented compared to non-A blood types, while blood type O was significantly underrepresented compared to non-O types. However, no significant association was found in the later cohort [18].

Indeed, in a multiethnic cohort enrolling hospitalized COVID-19 patients - with general patients as the control group – no significant difference in ABO phenotype distribution was found [19]. In this study, the authors challenged the use of regular blood donors as the control group in studies concerning associations between ABO blood types and COVID-19 susceptibility. Blood type O individuals are preferentially recruited for blood donation and might be overrepresented among regular donors, which may have biased some previous results towards O-related protection. However, with a similar cohort choice, Wu et al. found significant associations between ABO blood group and the risk of SARS-CoV-2 infection, in which blood type A was associated with higher susceptibility to SARS-CoV-2 infection, and blood type O, to lower susceptibility [16]. Furthermore, studies using blood bank data do not always associate blood type O to lower risk of SARS-CoV-2 infection [59–62].

Table 1
Studies on associations between ABO blood types and the risk of SARS-CoV-2 infection.

Reference	Country	Study Design[b]	Cases Definition[c]	N	Controls Definition[d]	N	ABO Risk[a] A	B	AB	O
Zhao et al. [14]	China	I	I	2.173	I	27.080	↑	ns	ns	↓
Li et al. [15]	China	II	II	265	I	3.694	↑	ns	ns	↓
Muñiz-Diaz et al. [18]	Spain	II	III	854	II	75.870	↑	ns	ns	↓
Franchini et al. [53]	Italy	III	III	447	II	16.911	ns	ns	ns	↓
Dzik et al. [19]	USA	II	II	957	III	5.840	ns	ns	ns	ns
Wu et al. [16]	China	II	II	187	III	1.991	↑	ns	ns	↓
Padhi et al. [69]	India	IV	IV	–	I	–	ns	↑	ns	ns
Khalil; Feghali; Hassoun [20]	Lebanon	II	II	146	III	6.497	ns	ns	ns	ns
Liu et al. [74]	International	I	I	9.383	IV	54.218	↑	↑	ns	↓
Fan et al. [52]	China	II	II	105	III	103	↑	ns	ns	ns
Solmaz; Araç [54]	Turkey	V	II	1.667	I	127.091	↑	ns	ns	↓
Barnkob et al. [47]	Denmark	II	I	7.422	I	2.204.742	↑	ns	↑	↓
Boudin et al. [76]	France	II	I	1.279	IV	409	ns	ns	ns	ns
Latz et al. [68]	US	II	I	1.289	V	7.648	ns	↑	↑	↓
Levi et al. [66]	Brazil	II	I	2.037	VI	1.813.237	ns	ns	ns	ns
Yalaoui et al. [55]	Tunisia	III	I	51	II or IV	63.375 or 1.506	↑	ns	ns	ns
Göker et al. [56]	Turkey	III	V	186	II	1.881	↑	ns	ns	↓
Almadhi et al. [59]	Bahrain	V	I	2.334	II	4.985	ns	↑	↓	ns
Lehrer; Rheinstein [65]	UK	II	I	717	I	11.855	ns	ns	ns	ns
Mullins et al. [67]	US	II	II	227	I	–	ns	ns	ns	ns
Negro et al. [78]	Italy	II	VI	129	VII	38	↑	↓	ns	↓
Ray et al. [70]	Canada	II	I	7.071	IV	218.485	ns	↑	↑	↓
El-Shitany et al. [51]	Saudi Arabia/Egypt	V	I	726	IV	707	ns	ns	ns	↓
Kibler et al. [77]	France	II	VII	22	VIII	680	↑	ns	ns	Ref
Leaf et al. [63],[e]	US	II	VIII	2.033	II	3.100.000	↑	ns	ns	↓
Niles et al. [64],[e]	US	II	I	34.178	IV	242.358	ns	ns	ns	↓
Al-Youha et al. [71]	Kuwait	II	I	3.304	I	3.730.027	ns	↑	↑	↓
Muñoz-Culla et al. [57]	Spain	II	VI	412	II	17.796	↑	↑	↑	↓
Kotila et al. [72]	Nigeria	II	I	302	II	9.138	ns	↑	↑	↓
Mahmud et al. [58]	Bangladesh	II	V	438	I	–	↑	ns	ns	ns
Schetelig et al. [48]	Germany	V	I	6.257	IV	118.868	↑	ns	↑	Ref
Ozkarafakili, Gareayaghi & Kara [60]	Turkey	II	II	492	II	51.966	ns	ns	ns	ns
Gamboa-Aguilar et al. [61]	Mexico	III	V	2.416	II	5.000	↓	ns	↓	↑
Enguita-Gérman et al. [49]	Spain	II	IX	87.090	–	–	↑	ns	ns	↓
Jawdat et al. [73]	Saudi Arabia	II	I	373	I	9.939	ns	↑	↑	↓
Kander et al. [75]	Sweden	II	X	338	IX	29.174	ns	ns	↑	ns
Gurung et al. [62]	Nepal	III	I	1091	II	2.182	ns	ns	↑	ns
Jukić et al. [50]	Croatia	II	VIII	780	II, V and X	614.673	↑	ns	ns	↓

[a] vs. other blood types. Upward arrow: increased risk, downward arrow: decreased risk; ns: non-significant = p>0.05.

[b] I: Meta-analysis, II: Cohort study, III: Case-control study, IV: Mixed method, V: Cross-sectional study.

[c] I: SARS-CoV-2+ individuals (Mostly RT-PCR), II: COVID-19 hospitalized patients, III: Convalescent plasma-donors, IV: Officially reported cases, V: General COVID-19 patients, VI: Symptomatic cases, VII: COVID-19 patients underwent TAVR (Transaortic valvular replacement), VIII: Critically ill patients, IX: General population, X: COVID-19 patients admitted to ICU (Intensive care unit).

[d] I: Local anthropological data, II: Blood donors, III: Non-COVID-19 hospitalized patients, IV: SARS-CoV-2- individuals, V: Individuals tested for SARS-CoV-2, VI: Patients in general, VII: Asymptomatic COVID-19 cases, VIII: Patients underwent TAVR, IX: Non-COVID-19 patients admitted to ICU, X: Pregnant women with ABO typing.

[e] Adjusted for ethnicity.

Other studies enrolling multiethnic cohorts in the U.S reported no significant association between ABO blood group and the risk of acquiring COVID-19 [63] or significantly higher odds for blood type O [64]. Nonetheless, after adjusting for ethnicity, blood type A was significantly associated with a higher risk of SARS-CoV-2 infection [63], and blood type O, with lower risk [63,64], among white non-Hispanic participants, but not in the Hispanic and black non-Hispanic groups. Indeed, a more recent study conducted in Mexico described a significantly higher risk of SARS-CoV-2 infection among blood type O-individuals, while blood type A was significantly related to lower risk [61]. Ethnicity constitutes, therefore, a potential confounding factor in studies concerning ABO blood types and the risk of SARS-CoV-2 infection and should be considered in the interpretation of their results.

While several studies failed to reproduce significant associations between ABO blood-type and SARS-CoV-2 infection [20,60,65–67], others reached significant associations for blood types other than A and O. Blood type B was related to significantly higher risk of SARS-CoV-2 infection in some studies [59,68–73]; and a meta-analysis indicated that blood type B is associated with higher risk of SARS-CoV-2 infection in Asian, but not in European cohorts [74]. AB blood type, in turn, has been significantly related to either higher [47,62,68,70–73,75] or lower [59,61] risk of acquiring COVID-19.

Moreover, some authors studied the association between ABO blood types and the risk of SARS-CoV-2 infection in more specific backgrounds. Boudin et al. found no significant difference in ABO phenotype distribution between infected and uninfected crewmembers exposed to

Table 2

- Studies on associations between ABO blood types and the risk of severe COVID-19 outcomes.

Reference	Country	Study Design[b]	Cases Definition[c]	N	Type of Association	ABO Risk[a] A	B	AB	O
Muñiz-Diaz et al. [18]	Spain	I	I	965	Mortality	↑	ns	ns	↓
Dzik et al. [19]	USA	I	II	957	Mortality	ns	ns	ns	ns
Padhi et al. [69]	India	II	III	–	Mortality	ns	↑	ns	↓
Khalil; Feghali; Hassoun [20]	Lebanon	I	IV	146	Severity and mortality	ns	ns	ns	ns
Solmaz; Araç [54]	Turkey	III	II	1.667	Admission to ICU[d] and death	ns	ns	ns	ns
Barnkob et al. [47]	Denmark	I	V	7.422	Hospitalization and death	ns	ns	ns	ns
Latz et al. [68]	US	I	IV	1289	Hospitalization, admission to ICU, intubation, and death	ns	ns	ns	ns
Almadhi et al. [59]	Bahrain	III	IV	2.334	Admission to ICU	ns	ns	ns	ns
Lehrer; Rheinstein [65]	UK	I	V	717	Mortality	ns	ns	ns	ns
Mullins et al. [67]	US	I	II	227	Severity, admission to ICU, intubation, dialysis, hospital or ICU LOS[e], and death	ns	ns	ns	ns
Negro et al. [78]	Italy	I	V	167	Severity and mortality	ns	ns	ns	ns
Ray et al. [70]	Canada	I	V and VI	218.485	Severity and mortality	ns	ns	ns	↓
El-Shitany et al. [51]	Saudi Arabia/ Egypt	III	IV	726	Oxygen saturation, artificial respiration, myalgia, and recovery time	↓	↓	ns	↑
Garibaldi et al. [85]	Brazil	I	VII	72	Severity and risk of death (SOFA[f] and SAPS-3[g])	↑	ns	ns	↓
Hoiland et al. [86]	Canada	I	VIII	95	Mechanical ventilation, CRRT[h], and ICU LOS	↑	↓	↑	↓
Kibler et al. [77]	France	I	IX	22	Hospitalization and death	↑	ns	ns	ns
Sardu et al. [87]	Italy	I	X	164	Cardiac injury and death	ns	ns	ns	↓
Solhpour et al. [17]	Iran	I	XI	93	Severity	↑	ns	ns	↓
Valenti et al. [80]	Italy	I	VII	505	Mechanical ventilation and admission to ICU	ns	ns	ns	ref
Göker et al. [56]	Turkey	IV	IV	186	Admission to ICU, intubation, and death	ns	ns	ns	ns
Al-Youha et al. [71]	Kuwait	I	V	3.304	Respiratory support, admission to ICU, and death	ns	ns	ns	ns
Badedi et al. [79]	Saudi Arabia	I	V	404	Symptom presentation, hospital admission, disease duration and severity	ns	ns	ns	ns
Muñoz-Culla et al. [57]	Spain	I	VII, XII, XIII	213	Severity	ns	ns	ns	ns
Garg et al. [84]	India	I	IV	383	Severity	↑	↑	↓	↓
Szymanski et al. [88]	US	I	IV	4.968	Mortality	↑	ns	ns	ref
Ozkarafakili, Gareayaghi & Kara [60]	Turkey	I	II	492	Admission to ICU and death	ns	ns	ns	ns
Gamboa-Aguilar et al. [61]	Mexico	IV	IV	2.416	Hospitalization and death	ns	ns	ns	ns
Enguita-Gérman [49]	Spain	I	V	6.771	Hospitalization and death	ns	ns	ns	ns
Jawadat et al. [73]	Saudi Arabia	I	V	373	Hospitalization and admission to ICU	ns	ns	ns	ns
Nafakhi et al. [89]	Iraq	V	VII and XIII	169	Respiratory support, admission to ICU, death, and long-term symptoms	ns	↑	↑	ref
Gursoy & Avci [81]	Turkey	I	II	969	Hspital LOS, admission to ICU, ICU LOS, and death	ns	ns	ns	ns
Bokhary et al. [82]	Saudi Arabia	I	II	316	Admission to ICU and death	ns	ns	ns	ns
Jelinek et al. [83]	United Arab Emirates	III	VII	193	Severity	ns	ns	ns	↓
Alabsi et al. [90]	Saudi Arabia	III	XIV	100	Chronic chemosensive dysfunction	–	–	–	↑

[a] Risk of severity and death vs. other blood types. Upward arrow: increased risk, downward arrow: decreased risk, ns: non-significant = p>0.05.

[b] I: Cohort study, II: Mixed method, III: Cross-sectional study, IV: Case-control study, V: Longitudinal observational study.

[c] I: COVID-19 patients transfused during hospitalization, II: Hospitalized COVID-19 patients, III: Officially reported death rates, IV: General COVID-19 patients, V: SARS-CoV-2-positive individuals (Mostly RT-PCR), VI: SARS-CoV-2-negative individuals, VII: Severe COVID-19 patients, VIII: Patients admitted to intensive care unit (ICU), IX: COVID-19 patients underwent TAVIR, X: Hypertensive COVID-19 patients, XI: COVID-19 patients with severe hypoxia, XII: light COVID-19, XIII: Mild COVID-19, XIV: Patients recovered from COVID-19.

[d] Intensive Care Unit.

[e] Length of Stay.

[f] Sequential Organ Failure Assessment.

[g] Simplified Acute Physiology Score 3.

[h] Continuous Renal Replacement Therapy.

SARS-CoV-2 during an outbreak in an aircraft carrier [76]. Conversely, blood type A was significantly associated with higher risk of developing COVID-19 among patients who underwent transcatheter aortic valve replacement (TAVR) [77]. Furthermore, after no association between ABO phenotype and SARS-CoV-2 positivity was found, Negro et al. sought to investigate whether ABO blood type correlates with the symptomatic disease in SARS-CoV-2-positive individuals. A significant positive association was found between blood type A and the development of symptomatic COVID-19, while blood types B and O were significantly related to lower risks of developing symptomatic infection [78].

Although studies concerning ABO blood types and the risk of SARS-CoV-2 infection are highly heterogeneous, we were unable to find any trend in susceptibility according to the study design or the type and size of the case and control groups. However, among the studies summarized here, a dichotomy between blood types A – higher risk – and O –lower risk – was more clearly observed in European and East Asian settings, while the involvement of blood types B or AB has been mostly observed in Middle Eastern, Indian, and North American settings (Table 1). Data from Africa and Latin America are scarce, but it is noteworthy that in both the settings, blood type A was not associated yet with higher susceptibility to SARS-CoV-2 infection [61,66,72] and, in the case of Latin America, blood type O was not associated yet with lower susceptibility [61,66].

4.2. COVID-19 severity and outcomes

In addition to the risk of SARS-CoV-2 infection or symptomatic disease, the ABO blood group has also been associated with severe outcomes. Severity is usually defined as hospitalization, admission to Intensive Care Unit (ICU), mechanical ventilation requirement, or decease. The association of ABO blood types with COVID-19 severity is generally performed by comparing the blood type distribution between distinct subgroups of patients. Studies on this subject were mostly designed to uncover associations for both the risk of infection and severity, with fewer studies designed to evaluate associations for severity only. A summary of the findings is described in Table 2.

As can be seen from Table 2, results regarding severity and outcomes are more variable than those regarding the risk of infection. Several studies that reported associations between ABO blood type and the risk of SARS-CoV-2 infection failed to describe any association for severity [47,49,54,56,57,59,61,68,71,73,78] or reached distinct associations [51,70]. Other studies also reported no association between ABO blood types and severe COVID-19 outcomes but in accordance with the finds reported for the risk of infection [19,20,60,65,67]. Further studies also failed to report any association between the ABO blood group and severe COVID-19 outcomes [79–82].

Nonetheless, blood type A has been the most associated with severe outcomes, while blood type O frequently appears as a protective factor against the disease progression [17,18,69,70,77,83–88]. For instance, although failing to describe a significant difference in ABO phenotype distribution between hospitalized COVID-19 patients and the control group, Muñiz-Diaz et al. described a significant positive association between blood type A and mortality, and a significant negative association for blood type O [18]. Blood type A was significantly associated with hospitalization and mortality among COVID-19 patients who underwent TAVR [77] and to severe hypoxia among young COVID-19 patients without co-morbidities [17]. Blood type O, in turn, was significantly associated with lower risks of cardiac injury and death, and with lower pro-thrombotic indexes, among hypertensive COVID-19 patients [87].

Enrolling COVID-19 patients admitted to ICU, Hoiland et al. described significantly higher odds of requiring mechanical ventilation and Continuous Renal Replacement Therapy (CRRT), as well as a higher ICU length of stay (LOS), for A and AB groups; while B and O groups were negatively associated with these outcomes [86]. Conversely,

El-Shitany et al. reported an association between blood type O and unfavorable outcomes, such as lower oxygen saturation and mechanical ventilation requirement, while blood type A was linked to lower odds of requiring artificial ventilation, and blood type B, to shorter recovery periods [51]. Significant associations with severity [84] and mortality [69,89] were also reported for blood type B, while blood type AB has been linked to either favorable [84], or unfavorable [89] outcomes. More recently, some studies sought to investigate whether ABO blood types are associated with long-term symptoms presentation after COVID-19 recovery. Blood type AB was significantly associated with long-term palpitation and dizziness [89], and blood type O, with subjective loss of smell [90].

Studies regarding associations between ABO blood types and COVID-19 severity and outcomes are even more heterogeneous than those concerning the risk of infection. The studies evaluated distinct outcomes and some of them had a unique design, which makes it more difficult to establish trends. Among the studies summarized here (Table 2), the majority did not reach statistical significance, and we were unable to identify any trend in the outcomes according to the size of the enrolled groups. However, it is possible to observe a trend towards significance when the enrolled group consisted of critically ill COVID-19 patients – like those requiring ICU admission [86] or blood transfusion [18] and those presenting severe hypoxia [17] - or patients with cardiovascular co-morbidities [77,87]. Taken together, in these groups of patients, blood type A was the most associated with unfavorable outcomes and blood type O constituted a protective factor. Conversely, in broader enrolled groups, like general hospitalized COVID-19 patients or individuals with a positive test, there was a trend towards non-significant results (Table 2).

4.3. Genetic link with susceptibility and severity

Several studies have been designed to uncover single nucleotide polymorphisms (SNPs) that could predict COVID-19 susceptibility or severity, and associations have been reported for the ABO *locus*. In a meta-analysis of two Genome-Wide Association Studies (GWAS) enrolling COVID-19 patients with respiratory failure, Ellinghaus et al. analyzed 8.582.968 SNPs and described a cross-replicating association with the Reference SNP (rs)657152 at *locus* 9q34, which corresponds to the ABO gene [6]. Other GWAS also reported associations for the ABO gene. An association with rs9411378 at chromosome 9q34.2 was identified by Shelton et al. in contrasting SARS-CoV-2-positive and –negative individuals, while no association with this SNP was identified when comparing severity phenotypes [91]. In this study, blood type O was shown to be protective regarding susceptibility, while blood types A, B, and AB did not differ from each other. An association with rs91280525 for susceptibility was replicated in a meta-analyses of previous GWAS [92]. Nonetheless, a GWAS enrolling critically ill COVID-19 patients failed to identify any association with the ABO *locus* [93].

More recently, Vargas-Alarcón et al. evaluated the allele distribution of six SNPs located at the ABO gene among COVID-19 patients and healthy hospital staff members. Two SNPs located at the coding region - rs8176740 and rs512770 – were found to be associated with the risk of developing COVID-19, with the risk alleles being related to O blood type [94]. The rs8176740 polymorphism was also associated with high platelet blood levels [94]. In contrast, after finding significantly lower levels of blood type O among critical COVID-19 patients (vs. non-critical patients), Jelinek et al. performed a candidate gene approach based on previous GWAS data and examined 240 SNPs in the ABO gene for association with critical COVID-19 presentation. 8 SNPs located at the ABO 3'untranslated region were significantly associated with disease severity, with significantly lower frequencies of the risk alleles in non-critical patients with blood type O [83].

Furthermore, some studies sought to genotype the ABO and/or FUT2 genes in COVID-19 patients and control groups. AB-related alleles were significantly associated with SARS-CoV-2 infection and O-related alleles

were significantly less represented among the patients' group, while no association was described for FUT2 [95]. Conversely, a study found no significant difference in the distribution of the rs8176719 deletion allele – the main O blood type-determinant – between patients and controls nor between severe and non-severe patients [96], while the rs601338 G>A variant – the main non-secretor determinant – was associated with lower risks of ICU admission, mechanical ventilation and decease, especially in blood type A-individuals [80]. Another study described associations of the A/B-related rs8176747 with higher susceptibility to COVID-19 infection and the O-related rs8176719 with lower susceptibility, failing to describe any association with the FUT2-related rs1047781. Nonetheless, when comparing ABO secretor individuals vs. O and non-secretors, significant results were obtained, with the former group being more prone to COVID-19 onset [97].

Data from previous GWAS have been integrated to protein (p) or expression (e) quantitative trait loci (QTL) and colocalization analysis in Summary-Based Mendelian Randomization studies. In a multi-omics-based study, a protein-increasing allele of the ABO gene (rs505922) co-localized with susceptibility and severity-associated loci in both lungs and blood; and increased levels of blood ABO proteins was associated with higher risk of COVID-19 and its severity [98]. Likewise, in a Mendelian Randomization study based on previous GWAS, the blood level of ABO proteins was associated with hospitalization, respiratory support requirement, and decease [99]. Further QTL-based studies have also been reporting associations between the expression of ABO proteins (rs505922) and COVID-19 severity phenotypes [100,101]; however, pQTL for rs505922 was also associated with the levels of several other proteins [100,101], which suggests potential pleiotropic effects. Interestingly, among the proteins associated with rs505922, CD209 antigen

was recently described as a receptor for SARS-CoV-2 S protein in lung and kidney epithelium and endothelial tissue [102]. Moreover, genetically predicted ABO levels were significantly associated with COVID-19 clinical phenotypes driven by the circulatory system, such as deep vein thrombosis, pulmonary heart disease, and acute pulmonary infarction [103]. Genetic associations between the ABO locus and COVID-19 are summarized in Table 3.

5. Hypothesis linking ABO blood type and COVID-19: underlying mechanisms and their contribution to the interpretation of reported associations

Since an association between the ABO blood group and COVID-19 was firstly reported, several underlying mechanisms have been hypothesized [22,23]. The proposed hypotheses are most reliant on what is already known for other enveloped viruses, including SARS-CoV [21, 44], or in the previous associations between ABO blood group and other COVID-19 risk factors and co-morbidities [23,104]. The hypothesized mechanisms could affect either the risk of infection or the disease severity and outcomes, with distinct potential implications to the transmission dynamics or disease management.

5.1. ABO antibodies and host's glycosylation pattern

Upon entry in the human body, SARS-CoV-2 can infect and replicate in the upper respiratory tract [105,106], several cell types of the bronchial epithelium, and the alveolar type 1 pneumocytes [107], as well as in the enterocytes [108]. Epithelial cells of both the human airways and digestive tract are known to express host factors used by SARS-CoV-2,

Table 3

- Genetic associations of the ABO *locus* with COVID-19 infection and severity.

Reference	Country	Study Design	Sample size (n)	SNP	Outcomes
Ellinghaus et al. [6]	Italy/Spain	COVID-19 with RF[a] vs. blood donors, and non-COVID-19 controls	1.610 cases vs.2.205 controls	rs657152	Severe COVID-19 with respiratory failure
Pairo-Castineira et al. [93]	UK	Critically ill COVID-19 vs. matched controls	2.244 cases vs.1.157.277 controls	–	None
Cordero et al. [98]	International	Integrative genomics	–	rs505922	Susceptibility and severity
Valenti et al. [80]	Italy	Non-O vs. O COVID-19 with RF	Non-O 256 vs.O 153	rs601338 (FUT2)	Mechanical ventilation, ICU[a] admission, and mortality
Matzhold et al. [95]	Austria	Hospitalized COVID-19 patients vs. blood donors	336 patients vs. 250.298 controls	Several SNPs corresponding to variants of ABO alleles, FUT-2 rs601338, FUT3	Suscetibility to infection, hospitalization, ICU admission, mechanical ventilation, and mortality
Coto et al. [96]	Spain	Hospitalized COVID-19 patients vs. matched healthy controls	318 patients vs. 350 controls	rs8176719	Susceptibility and severity
Zhou et al. [100]	International	Hospitalized COVID-19 patients vs. healthy controls.	14.134 cases vs.1.2 million controls	rs505922	Severity
Zhu et al. [101]	International	Hospitalized COVID-19 patients vs. healthy controls.	6.492 patients vs.1.012.809 controls	rs505922	Susceptibility, hospitalization and severity.
Pathak et al. [103]	International	COVID-19 hospitalized patients vs.controls	7.885 cases vs. 961.804 controls	–	Severity
CHGI [92]	International (multiethnic)	COVID-19 patients vs. matched controls	49.562 cases vs. 2.000.000 controls	rs91280525	Susceptibility and severity
Shelton et al. [91]	US/UK	SARS-CoV-2 positive vs. controls	12.972 cases vs. 101.268 controls	rs9411378	Susceptibility
Vargas-Alarcón et al. [94]	Mexico	COVID-19 patients vs. healthy hospital staff members	415 cases vs. 288 controls	rs8176740 and rs512770	Susceptibility and platelets concentration
Jelinek et al. [83]	United Arab Emirates	Critical vs. non-critical COVID-19 patients	193 cases vs. 453 controls	rs199969472, rs34266669, rs76700116, rs7849280, rs34039247, rs10901251, rs9411475, and rs13291798	Severity
Nishida et al. [97]	Japan	COVID-19 patients vs. healthy controls	461 cases vs. 1.193 controls	rs8176719 and rs8176747 (ABO) and rs1047781 (FUT2)	Susceptibility
Palmos et al. [99]	International	Mendelian Randomiation	–	Several SNPs related to the ABO gene.	Severity

[a] Intensive Care Unit.

like ACE2 and TMPRSS [109–111], in addition to A/B transferases in secretor individuals [7,112].

During the replication cycle of SARS-CoV-2, viral RNA is synthesized within double-membrane vesicles that bud from the host endoplasmic reticulum following extensive remodeling [113], and the structural proteins assemble to the viral genome at the reticulum-Golgi intermediate compartment (ERGIC) to form progeny virions, which are released from the cell surface by exocytose [114]. The passage of virions through the secretory pathway raises questions concerning the processing of the viral surface glycoproteins [115], due to the presence of glycosylation enzymes at this pathway [116].

Indeed, the SARS-CoV-2 spike (S) protein is a highly glycosylated trimer, with 22 canonical N-linked glycosylation sites per protomer [117]. Glycomics-oriented studies revealed a high occupancy of N-linked sequons and the presence of O-linked glycosylation sites with low occupancy in recombinant S protein of SARS-CoV-2 produced in either mammalian [115,117–119] or insect [120] cell lines. In addition, mass spectrometry approaches showed that the glycosylation profile of the S protein is highly heterogeneous and cell type-dependent. In recombinant S protein produced in insect Sf9 cells, a predominance of less processed glycans, like oligomannose, was found [120]; while a more complex glycan processing, like fucosylation, galactosylation, and sialylation, was shown to take place in mammalian HEK 293 cells [115, 117,119]. Nonetheless, these glycans do not fully represent those found at the envelope glycoproteins of virions emitted from the human respiratory or digestive tract and cannot be decorated with ABH antigens, since Hek293 cells do not synthesize ABH transferases [25].

Aiming to uncover whether the S protein can be decorated with ABH antigens when synthesized in ABO- and FUT2-expressing cells, Deleers et al. produced recombinant S protein in transfected CHO cells expressing either the A or B transferase and the FUT2 gene. This approach showed that the S protein can carry ABH antigens according to the glycosyltransferase repertoire of the previous host cell [121]. Hence, ABO antibodies could constitute a barrier to SARS-CoV-2 infection according to the rules of blood transfusion. When transmitted in ABO-incompatible situations, SARS-CoV-2 could be partially neutralized by anti-A or anti-B antibodies, which can explain the lower incidence of COVID-19 in type O individuals, who display both anti-A and anti-B. Nonetheless, such protection would only be initial as, once the infection is established, the virions would carry the host's ABO profile and the autologous ABO antibodies would no longer be effective [122]. Therefore, this possible underlying mechanism can only explain associations between the ABO blood type and the risk of SARS-CoV-2 infection and does not apply to the reported associations concerning severity and outcomes.

The ABO antibodies hypothesis has some implications for the dynamics of COVID-19 transmission. Firstly, the reduced risk of viral infections in case of ABO-incompatible transmission does not constitute individual protection, but rather collective protection that could delay the spread of newly emerging viruses and slow down the epidemics, in addition to the required behavioral changes [44]. Nonetheless, as the epidemic progresses, more and more ABO-compatible transmission might occur, and the final number of cases may not be reduced to a great extent [25]. This could explain, for instance, the lack of association reported by Boudin et al. [76], in which the study participants consisted of crewmembers in close enough contact within an aircraft carrier that may had facilitate ABO-compatible transmission and reduced any O-related protection.

Moreover, the protection provided by ABO antibodies in ABO-incompatible transmission would critically depend on the relative frequency of ABO phenotypes in a given population. Such protection would be more effective in populations with low coefficients of variation between the ABO phenotypes and is expected to be inefficient in populations with high coefficients of variation, in which more ABO-compatible transmission may occur [25]. Importantly, although blood type O is likely more protective to SARS-CoV-2 infection due to the presence of both anti-A and anti-B antibodies, this advantage seems to disappear in populations in which this blood type is highly predominant, like in some Central and South American countries [25].

Following this rationale, differences in ABO phenotypes distribution between distinct cohorts can explain some interstudy discrepancies. For instance, the frequency of the B phenotype is increased in Asia at the expense of both A and O phenotypes, which, together, are largely predominant in Western Europe, with the Middle East displaying an intermediary distribution [25]. Such difference could explain the association between blood type B and the increased risk of SARS-CoV-2 infection reported by some Indian or Middle Eastern studies [59,69, 71,73]. Likewise, the lack of association between ABO blood type and the risk of SARS-CoV-2 infection [19,63] or a significant positive association with blood type O [64] in U.S multiethnic cohorts before adjusting for ethnicity can be explained by the fact that ethnic groups among who blood type O is predominant, like Hispanics and black non-Hispanics, have been disproportionally affected by the COVID-19 pandemic in the U.S [19,64]. In addition, the association between blood type O and the risk of COVID-19 onset described in a Mexican study can be explained by the high prevalence of this blood type in the Mexican population [61].

More recently, Boukhari et al. sought to investigate the impact of ABO compatibility on a secondary attack rate among the spouses of hospital staff members who were symptomatic for COVID-19. The risk of symptomatic COVID-19 transmission was significantly lower for ABO-incompatible couples, while ABO compatibility was associated with higher transmissibility regardless of the ABO blood type of the partner. This supports that all blood types are equally susceptible to COVID-19, and the protection provided by ABO-incompatibility may be due to ABO antibodies [123].

Furthermore, one should consider the variability of the ABO antibodies titer. The levels of ABO antibodies decrease with improving hygiene and tend to be low in developed countries [124], which may pose a challenge to its protective effect against viral infections and constitutes a potential confounding factor in association studies. Indeed, a study enrolling COVID-19 patients and asymptomatic controls showed that, for both A, B, and O blood types, the patients' group displayed significantly lower IgM agglutination scores compared to the control group [121]. In this way, some authors have been suggesting the promotion of anti-glycan antibodies through dedicated microbiota to enhance the natural anti-viral protection and slow down the spread of newly emergent viruses [121,125].

5.2. S protein priming and SARS-CoV-2-host cells interaction

The S protein of SARS-CoV-2 harbors a multibasic S1/S2 cleavage site, which constitutes a target for furin, a proprotein convertase. The furin-mediated S1/S2 cleavage generates two subunits – S1 and S2 – and is pivotal for the S protein's activation. S1 binds to cellular receptors, while S2 is further cleaved by TMPRSS2 and promotes virus-cell membrane fusion. The furin cleavage site was shown to be required for SARS-CoV-2 infection of the human lung cells Calu-3 and for the S protein-mediated cell-cell fusion, which promotes a systemic viral spread [126]. Although no correlation was yet reported for the furin levels and ABO polymorphism, an association between blood type O and lower levels of the furin-related proprotein convertase subtilisin-kexin type 9 (PCSK9) was previously reported [127]. Therefore, Abdelmassih et al. hypothesized that furin levels may follow the same pattern as PCSK9 and be decreased in blood type O individuals, which might reduce S protein priming and SARS-CoV-2 entry into host cells [128].

S1, in turn, is subdivided into the S1A and S1B domains. The former corresponds to the amino-terminal portion of the polypeptide chain, namely NTD (from N-terminal domain), and, in some coronaviruses, interacts with glycolipids and glycoproteins displaying terminal sialic acid motifs at the host cells' surface [129]. The latter constitutes the Receptor-Binding Domain (RBD) and binds to the ACE2 receptor [130].

In silico studies based on molecular docking simulations [131] and electronic density mapping surface [132] predict the existence of a sialic acid-binding pocket in the SARS-CoV-2 NTD similar to that found in MERS-CoV, which might confer to SARS-CoV-2 the ability to infect human cells in a dual manner, resulting in a higher diffusion speed [132].

ABH antigens are known to modulate the clustering of sialylated glycans at the cell's surface through carbohydrate-carbohydrate interactions and to regulate their interaction with cognate-binding proteins. A model was proposed in which antigen A is peripherally located at the sialylated glycan clusters, allowing for continuous clusters with increased sialic acids concentrations. Conversely, antigen B is mostly located at the center of the cluster, which may pose a steric hindrance for sialic acids-binding proteins, while in type O cells, the clusters are small and lack H antigens [133]. Following this rationale, it was hypothesized that ABO blood group may correlate with COVID-19 susceptibility and severity through carbohydrate-carbohydrate interactions between ABH antigens and sialylated glycans at the cells surface. According to such hypothesis, antigen A maximizes the interaction of SARS-CoV-2 with the target cells by promoting the clustering of sialylated glycans and increasing the likelihood of NTD biding [134].

Moreover, in a glycan microarray with ABH antigens, the SARS-CoV-2 RBD bound preferentially to the type I structure of antigen A, like the SARS-CoV RBD, which suggests a possible role for antigen A in coronaviruses entry into respiratory or digestive tract cells [48]. A similar result was described by Wu et al., who also demonstrated sequence similarities between the SARS-CoV-2 RBD and galectins, a family of carbohydrate-binding proteins [135]. This could explain, for instance, the genetic association reported by Valenti et al. between non-secretor status and lower risk of severe outcomes among blood type A-individuals [80]. Conversely, Boukhari et al. failed to detect any preferential biding of recombinant RBD to both A type I saccharide and lung tissue from A and O donors, as well as to salivary mucin from secretor-phenotype saliva [123]. Furthermore, although individuals with blood type A1 display more than fourfold higher A epitope density compared to those with A2 subtype, comparable rates of infection between A1 and A2 participants were reported by Schetelig et al., which suggests that the A antigen itself does not facilitate viral entry [48].

Hypotheses linking the ABO blood type to S protein priming or SARS-CoV-2 cellular entry remain largely elusive and need further studies. These hypotheses could explain both the higher SARS-CoV-2 infection rates and higher disease severity reported for blood type A, as well as the lower rates of infection and lower disease severity reported for blood type O. Unlike the ABO antibodies hypothesis, the possible role of ABO antigens in regulating virus-cell interaction may be mostly reliant on the antigen itself and may not depend on the ABO coefficient of variation at a population level. In addition, the possible pleiotropy effect of the ABO gene (rs505922) over the CD209 receptor gene [101] could also be considered into the framework of these hypotheses.

5.3. ABO blood group and cardiovascular risk

Associations between non-O blood types and increased risk of cardiovascular disorders are well documented and are detailed reviewed elsewhere [136–138]. Associations have been reported, for instance, with venous thromboembolism, myocardial infarction, peripheral vascular disease, cerebrovascular stroke, and pulmonary embolism. A possible explanation relies on the ~30% lower levels of von Willebrand factor (vWF) and coagulation factor VIII (FVIII) in blood type O individuals [139,140]. vWF mediates platelet aggregation and adhesion and can be released in response to inflammatory stimuli, like infections. It also plays a role in hemostasis by complexing with FVIII and stabilizing it at the circulation [141]. As a glycoprotein, vWF carries ABO (H)-like structures in Asp-linked sugar chains [142], which are likely to mediate its homeostasis. Indeed, glycosylation is likely to mediate the clearance of vWF, which is largely performed by lectin receptors [143,

144]. A and B antigens were shown to protect vWF from proteolysis by the ADAMTS13 metalloprotease [145]. Furthermore, the ABO blood group indirectly modulates the circulating levels of FVIII by affecting the clearance of the vWF/FVIII complex, accounting for about ~30% of its variation [140].

Likewise, some adhesion molecules, like the intercellular cell adhesion molecule 1 (ICAM1) and P-selectin, are protected by antigen A from enzymatic cleavage, prompting the attachment of leucocytes to them at the vascular wall, which increases inflammation and decreases circulation [23]. In addition, a study enrolling COVID-19 hypertensive patients reported significantly higher values of pro-thrombotic indexes - vWF, FVIII, D-dimer, and activated pro-thrombin time - in non-O vs O patients, which was consistent with the higher rates of cardiac injury and death in the former group [87]. Blood type O individuals are therefore less prone to thromboembolic events that constitute relevant outcomes in COVID-19 disease, especially among ICU-admitted patients [146, 147].

The link between ABO blood group and cardiovascular disorders does not affect the susceptibility to SARS-CoV-2 infection and cannot explain the reported associations between ABO blood type and the risk of infection. However, it constitutes a possible underlying mechanism for the lower risk of severe outcomes associated with blood type O and, at a lesser extent, the higher risk related to blood type A in some studies (Table 2), especially among patients with cardiovascular co-morbidities [77,87]. Into the framework of this hypothesis, the reported associations rely on constitutive tracts related to ABO blood type, which is in line with a study that reported associations between genetically-driven ABO expression levels and COVID-19 clinical phenotypes driven by the circulatory system [103]. Following this rationale, a risk stratification for cardiovascular complications in COVID-19 patients based on the ABO phenotype has been suggested, as well as the introduction of early anticoagulant therapy in non-O hypertensive patients [87].

6. Conclusions

A literature survey of epidemiological studies suggests that the ABO blood type may be an influencing factor for both SARS-CoV-2 infection and COVID-19 severity. Although the findings are conflicting and quite variable, blood type O is mostly associated with lower risk of SARS-CoV-2 infection, while blood type A, with higher risk. Blood types B and AB were also associated with higher risk of infection in some studies. Although the majority of the studies regarding COVID-19 severity and outcomes failed to report any association with the ABO blood group, associations with lower risk of severe outcomes have been frequently described for blood type O, while blood type A has been frequently described as a risk factor for severe outcomes. Moreover, genetic links with both susceptibility to infection and severity have been reported for the ABO *locus*.

Driven by the previous knowledge about ABO blood group biology and its role in the pathogenesis of infectious diseases, some underlying mechanisms that could explain the reported associations emerge; like a protective effect of the ABO antibodies against viral infections, a role for ABO(H) antigens in facilitating viral entry into host cells, and the association between non-O blood types and higher risk of thromboembolic events. These underlying mechanisms may affect different phases of the natural history of COVID-19, with distinct implications to the SARS-CoV-2 transmission dynamics and to COVID-19 outcomes. Nonetheless, there are little experimental data on this subject and more studies are needed to elucidate the mechanisms underlying the reported associations, which is pivotal for a deeper understanding of the relationship between the ABO blood group and COVID-19 and whether or not it can be translated to disease prevention or management strategies.

agencies in the public, commercial, or non-profit sectors.

Ethics approval

Not applicable.

Consent to participate

Not applicable.

Consent to publish

Not applicable.

Code availability

Not applicable.

CRediT authorship contribution statement

Eric Pereira: Writing – original draft, Formal analysis, Data curation, Conceptualization. **Stela Felipe:** Writing – review & editing, Conceptualization. **Raquel de Freitas:** Writing – review & editing. **Valdevane Araújo:** Data curation, Conceptualization. **Paula Soares:** Data curation, Conceptualization. **Jannison Ribeiro:** Supervision, Data curation, Conceptualization. **Luiz Henrique dos Santos:** Conceptualization. **Juliana Osório Alves:** Writing – review & editing. **Natália Canabrava:** Conceptualization. **Mauricio van Tilburg:** Supervision, Conceptualization. **Maria Izabel Guedes:** Supervision, Conceptualization. **Vânia Ceccatto:** Writing – review & editing, Supervision, Data curation, Conceptualization.

Declaration of competing interest

The authors have no financial or non-financial competing interests to disclose.

Data availability

No data was used for the research described in the article.

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