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REVIEW ARTICLE

# SARS-CoV-2: Receptor and Co-receptor Tropism Probability

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## Abstract

The recent pandemic which arose from China, is caused by a pathogenic virus named "severe acute respiratory syndrome-related coronavirus-2 (SARS-CoV-2)". Its rapid global expansion has inflicted an extreme public health concern. The attachment of receptor-binding domains (RBD) of the spike proteins (S) to the host cell's membrane, with or without the help of other cellular components such as proteases and especially co-receptors, is required for the first stage of its pathogenesis. In addition to humans, angiotensin-converting enzyme 2 (ACE2) is found on a wide range of vertebrate host's cellular surface. SARS-CoV-2 has a broad spectrum of tropism; thus, it can infect a vast range of tissues, organs, and hosts; even though the surface amino acids of the spike protein conflict in the receptor-binding region. Due to the heterogeneous ACE2 distribution and the presence of different domains on the SARS-CoV-2 spike protein for binding, the virus entry into diverse host cell types may depend on the host cells' receptor presentation with or without co-receptors. This review investigates multiple current types of receptor and co-receptor tropisms, with other molecular factors alongside their respective mechanisms, which facilitate the binding and entry of SARS-CoV-2 into the cells, extending the severity of the coronavirus disease 2019 (COVID-19). Understanding the pathogenesis of COVID-19 from this perspective can effectively help prevent this disease and provide more potent treatment strategies, particularly in vulnerable people with various cellular-level susceptibilities.

## Introduction

Coronaviruses (CoVs) are among the most important pathogens that affect vertebrates, especially mammals and humans [1]. Until 2019, only seven highly pathogenic CoVs were identified to cause respiratory diseases in humans; as they more often affect the gastrointestinal system. Four human coronaviruses (HCoVs), including HCoV-229E, HCoV-OC43, HCoV-NL63, and HKU1, cause upper respiratory tract infections; however, the infections are mild, confined to the human population, and are typically responsible for a third of common cold cases [2]. Although the mortality rate of coronaviruses causing the common cold in winter was estimated between 0.5% and 1.5%; it can be severe if cytokine storms occur [3]. The three additional coronavirus strains that cause progressive respiratory failure and alveolar destruction in the human's lower respiratory system are severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), and SARS-CoV-2 [4, 5]. The mentioned strains have higher mortality rates: 9.6%, 34.7%, and 1–2.5%, respectively [6]. Even worse, SARS-CoV-2 as a catastrophic pandemic, emerged worldwide, surpassing

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any former coronavirus epidemics, and resulting in severe clinical symptoms leading to death [7]. Moreover, the interactions between the host and this virus can mediate the induction of a "cytokine storm", resulting in various immunopathological consequences, including immunothrombosis [8, 9]. For example, the lowered secretion of IFNs reduces the uptake of neutrophils into the infected area, making their presence more abundant in the blood stream. In fact, neutrophils, when drawn into the affected tissues, are involved in clearing the infection by secreting leukotrienes, reactive oxygen species (ROS), and neutrophil extracellular traps (NETs). The NETs are a collection of DNA, related proteins, and microbial enzymes, which play an important role in causing inflammation and thrombosis in SARS-CoV-2 infection [10]. In this regard, studies indicate that during sepsis and ARDS, platelet aggregation is increased with the secretion of NETs, resulting in immunothrombosis in SARS-CoV-2 infections [10]. Also, according to the studies on COVID-19 patients, the evidence of thrombotic microangiopathy have shown that immunothrombosis plays an important role in disease progression [11].

On the other hand, due to the 76% similarity of amino acid sequencing, SARS-CoV and SARS-CoV-2 use ACE2 as their cellular entry receptor and transmembrane serine proteinase 2 (TMPRSS2) as a priming protein for entering the host cell [12, 13]. The available data show that the overall expression of ACE2 and its distribution varies in different human tissues, especially in the lung and bronchial tissues. In such a way that the rate of ACE2 expression in kidneys and gastrointestinal tract is higher than the organs such as the lungs and trachea [14]. Although the expression of ACE2 is low in the lungs and trachea; the main symptoms and pathogenicity were related to the pulmonary and respiratory system infection [15]. Also, many human neutralizing antibodies bind to authentic SARS-CoV-2 spike proteins by the N-terminal domain (NTD) and do not interact or bind to a receptor-binding domain (RBD), which can be occupied with ACE2 receptors [16]. Thus, the importance of host receptors and co-receptors that allow SARS-CoV-2 to bind and enter the respiratory cells can be emphasized. On the other hand, the human coronaviruses tend to use a secondary receptor or co-receptor, which facilitate their entry into the host cell. A brief overview of the different molecules on the surface of host cells and how they operate as HCoVs' facilitation receptors or co-receptors, is given in Table 1. In addition, due to the propensity of SARS-CoV-2 to unique cellular receptors, and the similarity of human ACE2 to bats, pangolins, and several other species, there have been a significant increase observed in the development of strains capable of crossing barriers of host species [17]. According to the aforementioned statements, the most significant factor in defining viral host range and cross-species infection can be receptor recognition [18].

In this regard, due to the rapid prevalence and the lethal epidemics of SARS-CoV-2 mutants, we investigated the host cell details and different receptors/co-receptors used in the pathogenesis of SARS-CoV-2, which can lead to effective insights into treatment approaches and tackling this health problem.

## The Structure of SARS-CoV-2 Spike Protein (S)

The SARS-CoV-2 spike protein (S) is a trimeric glycoprotein, and the main presenting molecule on the surface of the virion's envelope, forming a crown-like structure [19]. The coronaviruses exploit protein–protein interactions to enter the target cell, utilizing the N-terminal of S1 via receptor-mediated endocytosis. The "S1" is one of the functional receptor-binding subunits of the coronavirus' homo-trimeric spike protein structure, containing four domains (S1-A, S1-B, S1-C, and S1-D). These domains are involved in the attachment of the virus via its RBD to the host cell receptors, which may include proteinaceous receptors or sugars [20] (Fig. 1). The spike protein has multifunctional properties, including facilitating the virus's binding to the host's surface cell receptors, causing its pathogenesis, and playing a role in virus tropism by targeting the host cells. However, virus entry and the formation of active S protein binding primer subunits, require cellular proteases such as lysosomal cathepsin L, cleaving the S1/S2 furin site (amino acids 682–685, RRAR) subunits on the SARS-CoV-2 S protein [21]. This process allows the merging of the viral envelope and the cell membrane facilitated by the S2's active site, which is located on the spike protein's C-terminal, and is responsible for the initiation of fusion [20]. Besides, the extracellular matrix continuously interacts with complex glycans and glycoconjugates, called the glycocalyx. The viral entry is regulated by the glycan-binding domains on the virion's envelope membrane proteins, interacting with receptors on the host cell's plasma membrane; due to the involvement of these receptors, subsequent fusing occurs [22]. Viruses can also utilize and bind to sialic acids at the end of glycans in glycolipids and glycoproteins [23], as well as interacting with heparan sulfate (HS) [24].

## Importance and Characteristics of ACE2 as the Primary Receptor

Following the entry of SARS-CoV-2 via respiratory droplets into the lung and airways, the life cycle of a virus begins [25]. The spike glycoprotein RBD of SARS-CoV-2 shows high tropism to ACE2, an exopeptidase expressed in vascular endothelial cells in the kidneys and the heart to regulate blood pressure through renin–angiotensin–aldosterone system (RAAS) [26]. The availability of the ACE2 gene sequence has made it possible to evaluate the

**Table 1** Summary of various Receptors and co-receptors of human coronaviruses

| Receptor/co-receptor | Tissue expression | Clinical feature in COVID-19 | Refs |
|---|---|---|---|
| ACE-2 | Heart | Multiple organ dysfunction | [6, 14, 31] |
| | Blood vessels | Cytokine storms | |
| | Kidneys | | |
| | Testes | | |
| | Gastrointestinal tract | | |
| | Brain | | |
| | Lungs | | |
| | Trachea | | |
| Integrins | β1 and β3 integrins expressed on human pulmonary epithelial cells | αVβ6 integrin Increased in idiopathic pulmonary fibrosis | [38, 39, 41] |
| GRP78 | Thyroid gland | Increasing levels of GRP78's gene expression in the blood of the patients with COVID-19 | [43–45] |
| | Olfactory cells | | |
| | Lung macrophages and pneumocytes | | |
| DPP4 /CD26 | Myeloid cells | Lymphopenia | [46, 48, 49] |
| | Blood capillaries | Exacerbation of cytokine storms | |
| | Myocardial cells | | |
| | CD4 + T cells | | |
| AXL | Pulmonary epithelia | Inflammation | [51] |
| | | Dysregulation of immune cells and responses | |
| CD147 | Nerve cells | Lymphopenia | [52, 56, 103] |
| | Lymph nodes | Cytokine storms | |
| | Tubular epithelial cells | Kidney injury | |
| | Platelets & RBCs | Thrombo-inflammatory responses | |
| | Myeloid cells | | |
| | Skin tissues | | |
| NRP-1 | Epithelial cells in the olfactory tissue | Reduction in the levels of calcium and phosphorus in the blood | [62, 64, 66, 104] |
| | Bone marrow-derived macrophages | Anosmia | |
| | | CNS infection | |
| Lectins (CD209L/CD209) | Human endothelia | Coagulation dysfunction | [71–73] |
| | Renal tissue | Altered platelet-induced immune responses | |
| | Lung epithelium tissues | | |
| | Megakaryocytes | | |
| | Human platelets | | |
| Heparan sulfate | Heart | Severe thrombosis | [81, 86] |
| | Arterial tissue | Heart damage | |
| | Capillaries | Endothelial dysfunction | |
| | Venous endothelial cells | | |
| Vimentin | Lung type II pneumocytes | Cytoskeleton rearrangement | [78, 79] |
| | Nasal goblet secretory cells | Mesenchymal alterations | |
| | | Cytokine storms | |
| Sialic acid | Epithelial cells | Infection in neuronal (especially CNS) tissues | [89, 102] |
| | Gangliosides of the brain | | |

*ACE-2* Angiotensin-converting enzyme 2, *GRP78* glucose-regulating protein 78, *DPP4* dipeptidyl peptidase-4, *AXL* Tyrosine-protein kinase receptor, *NRP-1* Neuropilin-1, Lectins [CD209L or L-SIGN, (liver/lymph node-specific ICAM-3-grabbing non-integrin) / CD209 or DC-SIGN, (dendritic cell-specific ICAM-3-grabbing non-integrin)], *RBC* Red blood cell, *CNS* central nervous system

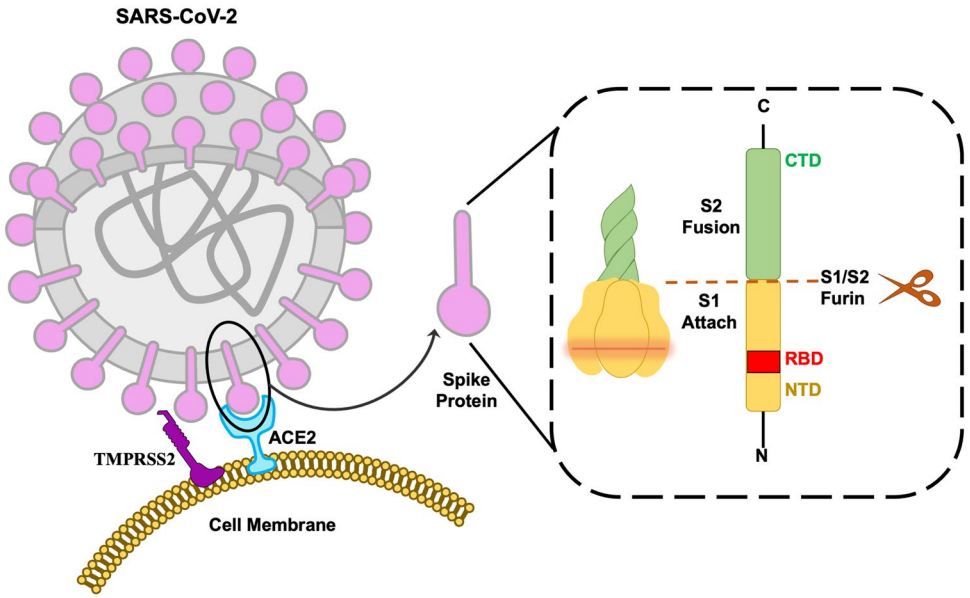


**Fig. 1** Schematic of the SARS-CoV-2 spike (S) protein, recognition of its specific receptor on the cell surface, and membrane fusion. The first step for the initiation of viral infectivity is the cleavage of the trimeric S protein into the S1 and S2 subunits. Through this process, the S1 subunits change position, and with the appearance of RBD on their surface, they can bind directly to ACE2. Followed by the mechanisms mentioned above, membrane fusion will be carried out by the S2 subunits

receptor-tropism capability from various species. This indicated that the high binding affinity of SARS-CoV-2 spike proteins for utilizing ACE2s might be the reason behind the interspecies transmission of this virus from its origin to a range of hosts [27]. However, SARS-CoV-2 recruits only ACE2s from specified species; even though ACEs are the virus's primary receptor [27]. This virus shows a close phylogenetic link to bat SARS-CoV, according to in silico analyses (RaTG13). Because of the phylogeny, and the protein–protein interactions of the antigenic spike protein with its receptor (i.e. ACE2), SARS-CoV-2 may have a zoonotic bat origin [28]. Furthermore, in a study by Choudhury and Mukherjee, it was discovered that surface proteins in humans, such as toll like receptors (TLRs), play a key role in disease development. It was claimed in this work that TLR4, one of the innate immune system receptors that triggers pro-inflammatory cytokines in response to antigen binding, has a higher affinity to bind the spike protein compared to TLR6 and TLR1. Protein–protein interactions, such as those between the spike protein and TLR4, may have a role in the severity of COVID-19 clinical symptoms. More importantly, these interactions have the potential to be used as a therapeutic method in the development of medications with a similar mechanism, or even designing TLR antagonists (especially TLR4); these strategies can be helpful during future SARS-CoV-2 outbreaks [28]. On the other hand, the virus has a high tendency to bind to alveolar pneumocytes expressing ACE2 on their surface, performing a series of functions. At the same time, changes in cellular factors and immune checkpoints within the host cell can influence the magnitude of the disease [25, 29]. Also, different interactions between ACE2 and RBD have been revealed in SARS-CoV-2 variants due to evolving and changing their structures [30]. SARS-CoV-2 variants that modify their structures to target the RBD-ACE2 interface can evade neutralizing antibodies. In humans, the expression of the mRNA which encodes ACE2 is high in almost all organs, including the heart, blood vessels, kidneys, and testes, leading to the infection of other tissues besides the lungs [31]. So, according to the previous statements, patients with high blood pressure, diabetes, and cardiovascular problems, are among vulnerable groups to a fatal COVID-19 injury. RNA-sequencing analysis of the human ACE2 genomic region showed that ACE2 can be transcripted into two isoforms due to its alternative splices: delta isoform (deltaACE2 or dACE2) and full-length isoform (flACE2) [32]. The delta isoform is shorter than the full-length isoform and lacks the first 356 amino acids on the N-terminal region, with no enzymatic activity [32]. Also, this isoform cannot be attached to SARS-CoV-2 spike proteins due to the lack of a primary binding site. The basal level expression of both dACE2 and flACE2 isoforms are similar in the lung and nasal tissues [33]. Spike binding and viral infectivity were affected by N-linked and O-linked glycosylation of the extracellular domain of the ACE2 receptor or the RBD of the S1subunit, which occurred near the binding interface [34]. The analysis of RBD-ACE2 structure revealed that RBD interacts primarily with the arch-shaped α1 helix of ACE2, and to a lesser extent with the $\alpha$2 helix and the loop bridging $\beta$3 and $\beta$4 antiparallel strands of ACE2 [35]. The results of mRNA analysis, immunohistochemistry (IHC), and mass spectrometry (MS) have confirmed low levels of ACE2 expression in the respiratory tracts. Nevertheless, it needs to be carefully clarified whether the same dysfunctional amount of ACE2 expression is sufficient to allow the proliferation and pathogenicity of SARS-CoV-2, or the viral infection requires a higher amount of ACE2-positive

cells (Fig. 2) [36]. It is worth noting that, the SARS-CoV-2 variants have emerged as a result of a slow, but continuous, mutations. Some of these mutations are expressed in spike protein's RBD, and have enhanced its binding affinity to the ACE2 receptor [37].

## SARS-CoV-2 Host Cell Entrance Mediators

### Integrin

Unlike other coronaviruses, the SARS-CoV-2 spike's binding sequence features a conserved RGD (Arg-Gly-Asp tripeptide) motif for binding its receptors. [38]. The SARS-CoV-2 can bind to the integrin family as a receptor in one or more other host species besides humans, with the minimum RGD peptide sequences required. Many human viruses use RGD binding sequences to bind to the integrin family and utilize them as receptors [39]. Integrins are cell surface receptors with a heterodimeric structure involved in cellular processes, such as migration, adhesion, and cell signaling. The trend of virus entry and infectivity in host cells is generally associated with the binding of specific RGD motif sequences of viral proteins to the integrin heterodimer structures, such as $\alpha V\beta 1$, $\alpha V\beta 3$, $\alpha V\beta 5$, $\alpha V\beta 6$, $\alpha V\beta 8$, $\alpha 5\beta 1$, $\alpha 8\beta 1$, and $\alpha$IIb$\beta 3$ [39]. This can subsequently activate the transmission pathway functions containing phosphatidylinositol-3 kinase (PI-3 K) or mitogen-activated protein kinase (MAPK), which lead to cell infectivity [40]. Experimental evidence shows that the SARS-CoV-2 spike protein (S1) binds to the $\beta 1$ and $\beta 3$ integrins, mainly expressed on the human pulmonary epithelial cells [38]. Patients with idiopathic pulmonary fibrosis were shown to have higher ACE2 and $\alpha V\beta 6$ integrin levels, and thus were linked to an increased risk of COVID-19 [41]. The folding of protein F's RGD on the surface of metapneumovirus, a pathogen mainly affecting children, was similar to SARS-CoV-2, with a small loop inserted between its two secondary structures (in this case, two β-sheets). Given these similarities, SARS-CoV-2's tropism to integrins may be possible; therefore, its binding to integrins may play a supporting and complementary role for signaling pathways. In this way, the virus can bind to ACE2, facilitating its endocytosis, and therefore increase its entry process into the host cells.

### Glucose-regulating Protein 78 (GRP78)

GRP78 is a heat shock protein (HSPA5), and is considered as an essential chaperone in many endoplasmic reticulum (ER) activities, including $Ca^{2+}$ binding, regulation of ER stress signaling, protein quality control, assembly, and

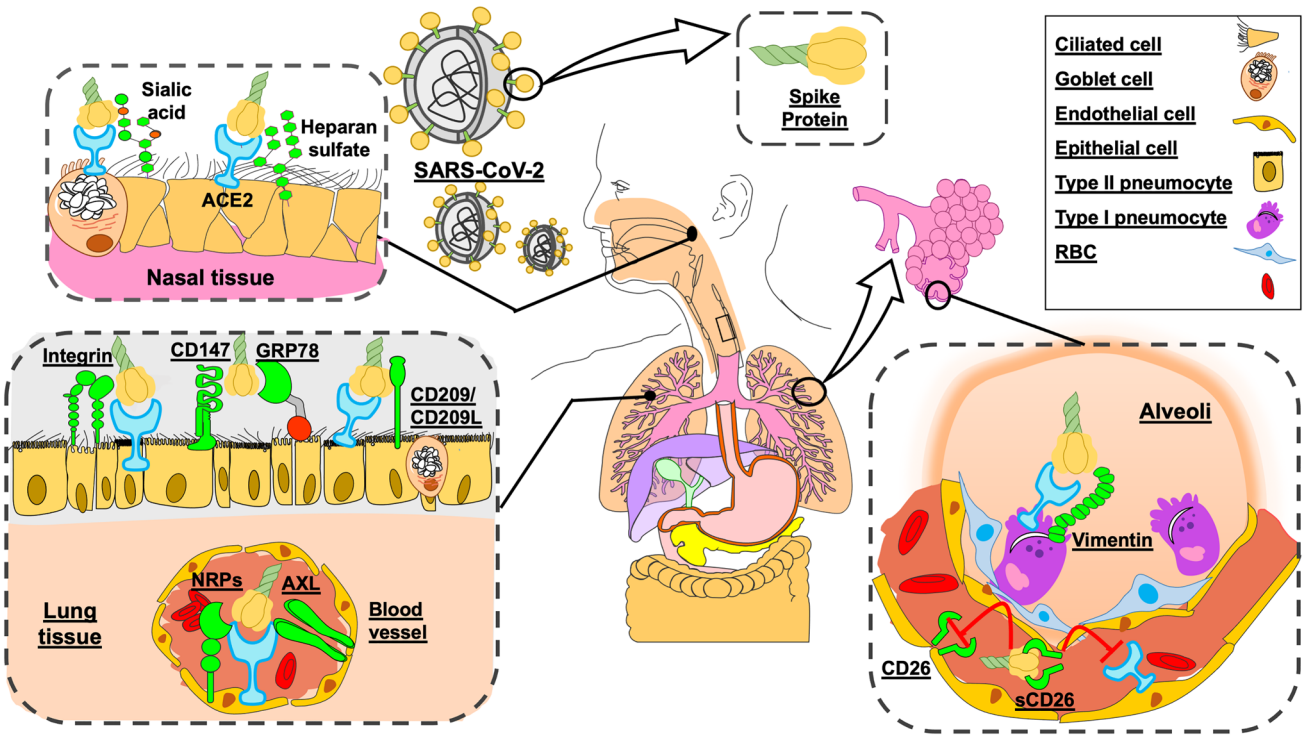


**Fig. 2** Alternative receptors and possible co-receptors of SARS-CoV-2. ACE2 is expressed in various tissues of the host's body. On the other hand, this leads to widespread respiratory system disorders alongside the engagement of other target organs. The use of various receptors and co-receptors expressed on the surface of different cells of the target organs leads to the advancement of the entry and initiation of the virus's pathogenesis, ultimately exacerbating the COVID-19 symptoms

folding. The overexpression of GRP78 on the cell surface has been described in various human malignancies due to its interaction with several ligands or protein receptors implicated in inflammation and autoimmunity [42]. Also, GRP78, as a binding immunoglobulin protein (BiP), can contribute to vital functions of cell organelles as well as participating in metastases and strengthening the recognition of respiratory CoVs, by its substrate-binding domain (SBD) region [43]. The critical component of SARS-CoV-2 is the RBD with 13 disulfide bonds in 13 cyclic parts; its interactions are required to translocate the virus into the target cell via receptor binding [21]. Although most type II alveolar epithelial cells have low or negative ACE2 expression [14]; HSPA5's mRNAs and proteins were modest in lung macrophages and pneumocytes according to the IHC of human lung tissues [44]. Increasing GRP78's gene expression in the blood of the patients with COVID-19-induced pneumonia on one hand, and the proven in vitro infection by detecting SARS-CoV-2 genes on the surface of respiratory epithelial cells containing GRP78 protein on the other, have confirmed that the GRP78 binding site overlaps with the ACE2 binding site, albeit slightly different [45].

#### Dipeptidyl Peptidase-4 (DPP4) /CD26

Given the evidence that the virus's outer membrane glycoprotein S1 employs dipeptidyl peptidase-4 (DPP4) when it penetrates the respiratory cells, this molecule might be regarded as a selective or a replacement option for virus entrance [46]. The DPP4 appears on cell surfaces with its dimeric form, as a serine exopeptidase. It is a multifunctional type-II transmembrane glycoprotein, also known as the T-cell antigen CD26, which participates in glucose metabolism, especially in mammalians [47]. When the intramembranous or cellular part is absent, it is produced in soluble form CD26 (sCD26), secreted in plasma and other body fluids, exerting its enzymatic activity [47]. Moreover, the DPP4 as a ubiquitous serine peptidase, is found in various epithelial and endothelial tissues, including the kidneys, liver, pancreas, villous-like membranes of the intestine, vascular endothelium, glandular epithelial cells, immune system cells, and T cell differentiation sites. DPP4 is widely expressed in myeloid cells, blood capillaries, and myocardial cells; it also expresses many functions as a protein binding and signaling agent in the cardiovascular system, inflammation processes, and angiogenesis [48]. Simulation of the homotrimeric structure of the SARS-CoV-2 spike protein creates a tight binding and a close interaction between the S1 domain and DPP4, which is probably done by sialization [23]. High DPP4 levels are inversely linked with age, fibrinogen, albumin, and ALT, as well as neutrophil counts [49]. For this reason, the elderly may be more susceptible to the virus infection. COVID-19 patients have been shown to have low DPP4 levels in their serum [49]. Lymphopenia is more prevalent in COVID-19 patients [50]. As a result, in these patients, a decrease in the number of lymphocytes, the major source of soluble DPP4 cells, can be linked to the decreased serum DPP4 levels. Moreover, serum sCD26 levels are severely reduced in high-risk cases, such as the elderly and type 2 diabetes mellitus (T2DM) patients. In this regard, high serum levels of sCD26 compete with cell surface CD26 receptors, thereby inhibiting virus binding to the host cell membrane and protecting against the viral infection. According to the findings, the presence of DPP4 (CD26 cells) in the human respiratory tract may facilitate viral entry, increase cytokine storms, and induce immune system complications in COVID-19.

#### Tyrosine-protein Kinase Receptor UFO (AXL)

Tyrosine-protein kinase receptor UFO, encoded by the AXL gene, is a tyrosine kinase receptor involved in vital physiological functions such as cell proliferation, differentiation, and dendritic cell (DC) maturation. AXL performs these processes by transmitting extracellular matrix signals into the cytoplasm. AXL is highly expressed in the human pulmonary and bronchial epithelial cells, and together with the exceeding ACE2 levels [51], cause the severity of SARS-CoV-2 infection in the primary pulmonary epithelium of COVID-19 patients [51]. The AXL association with the N-terminal region of the spike protein allows SARS-CoV-2 to enter human pulmonary epithelial cells, which is mainly independent of virion-associated phosphatidylserine [51]. On the other hand, the high expression of AXL in the bronchoalveolar lavage fluid cells of COVID-19 cases, increases the likelihood of additional host receptors, with or without co-receptors, facilitating the entrance of SARS-CoV-2.

**CD147** CD147 (basigin) is a membrane protein abundantly expressed on the surface of various cell types throughout the body, including activated lymphocytes, red blood cells, neural tissues, epithelial cells, myeloid cells, and skin tissues [52]. In addition to being the foundation of the blood grouping system, it can interact with extracellular and intracellular molecules [53]. Also, CD147, a basigin involved in producing matrix metalloproteinases, interacts with integrins, cyclophilins, monocarboxylate transporter proteins, and caveolin-1 [54]. It has been demonstrated that this receptor is involved in various diseases such as inflammatory disorders, microbial infections, and some cancers [55]. Statins have also been suggested to control viral entrance, replication, and elimination by promoting autophagy activation via SARS-CoV-2's CD147 receptor [55]. Besides, cyclophilins A (CypA) and B are the two major extracellular ligands that activate CD147, interacting with the nonstructured protein 1 (nsp1) of SARS-CoV [52]. Further-

more, circulating CypA is an essential intracellular mediator and a virtual interface for viral entry and T cell activation with CD147 [56]. Since CypA can prevent CD4+T cells from developing; CypA may be involved in the induction of lymphocytopenia in COVID-19 patients [56]. During the course of COVID-19, the expression of CypA is elevated in the tubular epithelial cells, podocytes, and parietal cells. As a result of the stimulation of the JAK-STAT and MAPK pathways [64], which promote the production of cytokines and chemokines, CypA is likely to be the most crucial pro-inflammatory mediator of cytokine storms in the severity of COVID-19 [56]. However, the entry of SARS-CoV-2 into red blood cells has not yet been reported [50]. Hematological symptoms in patients with SARS-CoV-2 infection raises the possibility that basigin might indirectly influence the clinical progression of COVID-19, and act as an accessory binding receptor for the immune system complications [57]. Given the platelet overreaction observed in COVID-19 and the presence of CD147 on the surface of red blood cells and platelets [52], CD147 may play a role in the defective thrombo-inflammatory responses. SARS viruses enter host cells after the receptor-spike protein binding, and are delivered into target cells by clathrin and caveolae-independent endocytosis [58]. Wang et al. discovered the presence of CD147 and Rab5 in the lung tissues of COVID-19 patients and BHK-21-CD147 cells, indicating that the CD147 receptors and the viral spike proteins may be drawn into the cells through endocytosis after their attachment; since they were found in primary endosomes [58].

#### Neuropilin-1 (NRP1)

NRPs are transmembrane glycoproteins with non-tyrosine kinase activity, expressed as dimeric receptors, forming a protective cortex for various molecules such as vascular endothelial growth factors (VEGF) in vertebrates [59]. NRPs play a vital role in different physiological processes, including angiogenesis, vascular permeability, immune cell functions, neuronal growth, and cellular proliferation [60]. The activation of NRP1 and NRP2 requires binding to the protected carboxylic terminus of the peptides/proteins known as "C-end-rule" (C end R), which are shown as R-XX-R. R represents the arginine (Arg) amino acid and can be replaced by lysine (Lys); but the X can be filled with any amino acids [61]. Studies have shown that the S proteins of SARS-CoV-2 have an "Arg-Arg-Ala-Arg" sequence at the S1–S2 junction, which corresponds to the C end R (RRAR) sequences, acting as a cleavage site for furin [59]. Also, the NRP1 shows a constant expression in the bone marrow-derived macrophages (BMMs) and brain macrophages [62]. The malfunction of osteoclasts, a particular cell line in the bone matrix, causes COVID-19-related calcium metabolic diseases [63]. This disorder leads to osteoporosis, characterized by reduced levels of calcium and phosphorus in the blood [64]. The expression levels of NRP1 and 2 in the respiratory epithelium surfaces are similar to ACE2. Staining of the infected epithelial cells in the olfactory tissue of COVID-19 patients has shown a high level of NRP1 [65]. According to these findings, SARS-CoV-2 infection may reach the central nervous system (CNS) through NRP1 in the olfactory epithelial cells; the virus can also affect the skeletal system by infecting macrophages [62]. COVID-19 patients show anosmia and olfactory abnormalities, which are uncommon in other respiratory diseases [66]. The origin of COVID-19's aberrant anosmia without inflammation and nasal discharge, might be related to the virus's entry into the CNS via the same NRP-1 found on the olfactory bulb's surface. Therefore, in addition to ACE2 and TMPRSS2, NRP1 can facilitate the entry of SARS-CoV-2 into the host cells.

#### L-SIGN (CD209L) and DC-SIGN (CD209)

Lectins, as a family member of carbohydrate-detecting proteins by their carbohydrate-recognition domain (CRD) of sulfated glycosaminoglycan (SGAG)-binding motif, selectively identify specific carbohydrate structures on proteins; hence can bind to many pathogens as pattern recognition receptors (PRRs) [67]. C-type (calcium-dependent) lectins are divided into several subgroups. CD209/DC-SIGN (dendritic cell-specific ICAM-3-grabbing non-integrin) and CD209L/L-SIGN (liver/lymph node-specific ICAM-3-grabbing non-integrin), are two of their subtypes [68]. In general, the physiological function of the CD209 family proteins is to mediate cell-to-cell adhesion by providing high-affinity receptors for the intercellular adhesion molecules 2 and 3 (ICAM2 and ICAM3/CD50) [69]. These receptors (CD209L and CD209) are the most common PRRs in the human genome, detecting various viruses. The presence of CRD at the C-terminus of the CD209 family is the key player in identifying structures containing mannose, glucose, or galactose on the pathogens. On the other hand, the analysis of the N-glycosylation of the SARS-CoV-2 spike protein showed a large amount of oligomannose-type glycans, which could increase the possibility of SARS-CoV-2 spike protein's binding to CD209L and CD209 [70]. Viruses appear to use host lectin receptors, such as CD209 and CD209L, to avoid detection, recognition, and being captured by the immune system without entering another cell. This phenomenon is referred to as a replication-independent mechanism, facilitating the distribution of the virus. Human endothelial cells are vulnerable to the invasion of SARS-CoV-2 infection; while there is a widespread expression of CD209L in the human endothelia [57]. Also, the RNA-seq data files of megakaryocytes and human platelets have shown the expression of CD209 / DC-SIGN and CD209L / L-SIGN, respectively [71]. In COVID-19, the interaction between SARS-CoV-2

and the platelets expressing L-SIGNs, changes the platelet-induced immune response homeostasis, causing coagulation dysfunctions [72]. L-SIGN is linked to the SARS-CoV-2 spike protein's high–mannose–type N-glycan, through a Ca2 + -dependent mechanism [73]. Vascular endothelial cells express little or no ACE2. Subsequently, L-SIGN, as a SARS-CoV-2 endothelial cell receptor, may be involved in the hypercoagulability state associated with COVID-19, including thrombosis and coagulation, which are prevalent consequences in patients with severe COVID-19.

### Vimentin

Vimentin is a member of the intermediate filament (IF) family, known as cytoskeletal proteins, and can also be located out-of-cell. Vimentin can create a binding site for viral proteins whereby the viruses can enter the cell [74]. The role of intracellular vimentin has also been investigated in virus fusion, proliferation, and the assembly processes [74]. Several physiological circumstances, including cell activation, apoptosis, inflammation, immune responses, and cellular stresses, can cause vimentin to be released into the extracellular space. Various cell types are the exogenous sources of vimentin, particularly macrophages, neutrophils, monocytes, apoptotic lymphocytes/T-lymphocytes, and endothelial cells [75]. During epithelial to mesenchymal transition (EMT), a stage in the conversion of tumor cells into acquiring metastatic abilities in the epithelium-derived malignancies, vimentin can be involved in migration as well as the elimination of epithelial barriers [76]. Since vimentin is a member of the "immediate-early genes" family, activated in inflammation and pre-infection phases; its expression is rapidly increased in response to viral infections and inflammatory stimuli. There are also high expressions of vimentin on the surface of lung type II pneumocytes and nasal goblet secretory cells, which contain the two main proteins (ACE2 and TMPRSS2) required for SARS-CoV-2's entry into the cells [77]. Thus, the existence of a possible mediator, enhances the probability of vimentin acting as a co-receptor. Evidence suggests that the increased expression of extracellular vimentin in response to inflammation or tissue damage induced by SARS-CoV-2, may facilitate SARS-CoV-2's entry by creating a direct interaction, increasing the severity of its pathogenesis [76]. The cytoskeleton is affected by SARS-CoV-2's infection via the involvement of vimentin and the phosphorylation of p38 MAPK (Mitogen-activated Protein Kinase 14) pathway [78]. Thus, vimentin is considered a possible target for preventing viral particles from attaching and entering to cells. Due to cytoplasmic vimentin's ability to be transmitted onto the cell surface during the epithelial-to-mesenchymal transition, this filament can be considered a co-receptor or binding site for several viruses.

### Heparan Sulfate (HS)

Heparan sulfate proteoglycan (HSPG) is a negatively charged, sulfated polysaccharide molecule with the ability to attach linearly to the cell membrane and extracellular proteins, owing to its two proteins (i.e. 6 Glypicans and 4 Syndecans) [79]. HS is a regulatory factor in many biological processes due to its interactions with different proteins in the body. In addition to participating in cell adhesion, it is also involved in inflammation and causing diseases [80]. Surface HS in viral infections can act as an anchor to facilitate the mechanism of endocytosis, by carrying additional positive charges for the receptor-mediated uptake of protein cargoes [81]. Also, the use of HS promotes the infectivity of the virus. HS contributes to the effective interaction between ACE2 and the virus's spike protein, by collecting SARS-CoV-2 and increasing its local concentration on the cell's surface [82]. The binding of HS to the spike is done using the full-length spike domain or RBD binding sites [82]. The RBD domain appears to contain a positively charged binding groove which can accommodate the negatively charged HS chain [83]. Based on microarray binding experiments, the binding of SARS-CoV-2's RBD to HS is determined by the optimal ligands of hexa- and octa-saccharides, forming the repeating motif units of idA2S-GlcNS6S [84]. Therefore, the role of the HS motif $(GlcNS6S\text{-}IdoA2S)_3$ in disease development and endothelial cell activation is well established; as a result, the severe thrombosis, which is caused by endothelial dysfunction in COVID-19 patients, is considered to be associated with SARS-CoV-2 and its connectivity to HS [85]. Severe thrombosis and heart damage has been documented in COVID-19 patients [57]. ACE2 is widely expressed in arterial, capillary, and venous endothelial cells to accompany HS [86]. HS consumption is caused by the increased expression of ACE2 in the heart and the interaction between SARS-CoV-2 and HS, which enable SARS-CoV-2's entrance into the host cell. When HS level is low, Anti-thrombin activation is reduced, causing a higher coagulability state [86]. Endothelialization and the subsequent endothelial damage, as well as the development of intracardiac thrombosis, can be caused by a loss of anti-inflammatory and anti-thrombin activity caused by low HS levels.

### Sialic Acid

Sialic acids (SA) are members of the neuraminic acid family (5-amino-3,5-dideoxy-D-glycerol-D-galactononulsonic acid), which are nine-carbon acidic sugars [87]. Sialic acid is a sugar that binds to distinct glycosidic bonds (2–3, 2–6, 2–8, and 2–9) at the end of glycans, and on the margins of oligosaccharides [88]. Glycans are commonly referred to as carbohydrates that bind to protein and lipid carriers. N-acetylneuraminic acid (Neu5Ac) and N-glycolylneuraminic acid

(Neu5Gc) are two derivatives of sialic acid, which are concentrated on the surface of mammalian cells, containing glycans, such as gangliosides, mucin-type O-glycan, and complex N-glycans. There is a high sialic acid production in epithelial cells, especially in lung and oral cavity cells, making it a potential receptor for respiratory viruses [89]. Sialic acids play a significant role in many physiological processes in the body by interacting with carbohydrates and proteins. They also contribute to pathological processes such as viral and bacterial infections, cell–cell communications, and tumor hyper specialization, leading to tumor growth and metastasis [88]. Glycans' role in providing a negatively charged flat surface as a facilitator of cell entry for HCoVs is also well established. Sialoglycans facilitate the binding between MERS-CoV and the cell membrane, leading to cell entry [89]. It is well proven that MERS-CoV's S protein can also utilize a two-step attachment mechanism by binding to the sialic acids within the NTD groove near the site of the central entry receptor (i.e. DPP4) [87]. Based on the results of biolayer interferometry, there is a strong affinity between SA-conjugated gold nanoparticles and the S1 domain of SARS-CoV-2 S protein, including the NTD and RBD [90]. SARS-CoV-2 binds to the sialic acids on the host cell's surface via the NTD region of the S protein. This virus-binding domain contains a flat ganglioside binding site, which can mediate virus binding on the lipid raft sites of the plasma cell membrane; the same place where the ACE2 receptor resides [91]. The human brain has tenfold higher concentrations of gangliosides compared to the other organs [92]. As a result, it is reasonable to expect that gangliosides can mediate SARS-CoV-2 infection in neuronal (especially CNS) tissues. Due to the involvement and the invasion that SARS-CoV-2 can inflict on the central nervous system (CNS), and other facilitating factors that the virus uses for its pathogenesis, it is also possible for sialic acids and gangliosides to be taken into account as receptors in other organs.

### Cell Surface Immunoreceptors/Toll-like Receptors (TLRs)

The probability of putative receptors for SARS-CoV-2 could be debatable for therapeutic prioritization, especially if they can trigger host's immune responses. In Fig. 3 and Table 1, the clinical characteristics of SARS-CoV-2 infection caused by binding to its receptors, with or without co-receptors, are presented in several organs. Severe pro-inflammatory reactions following COVID-19 result in a "cytokine storm" that can potentially lead to pulmonary distress, multiple organ failure, and death [29, 50]. The cell surface immune receptors are the most crucial primary immunological responders via recognizing molecular patterns. The human innate immune system plays an essential role as the first immune

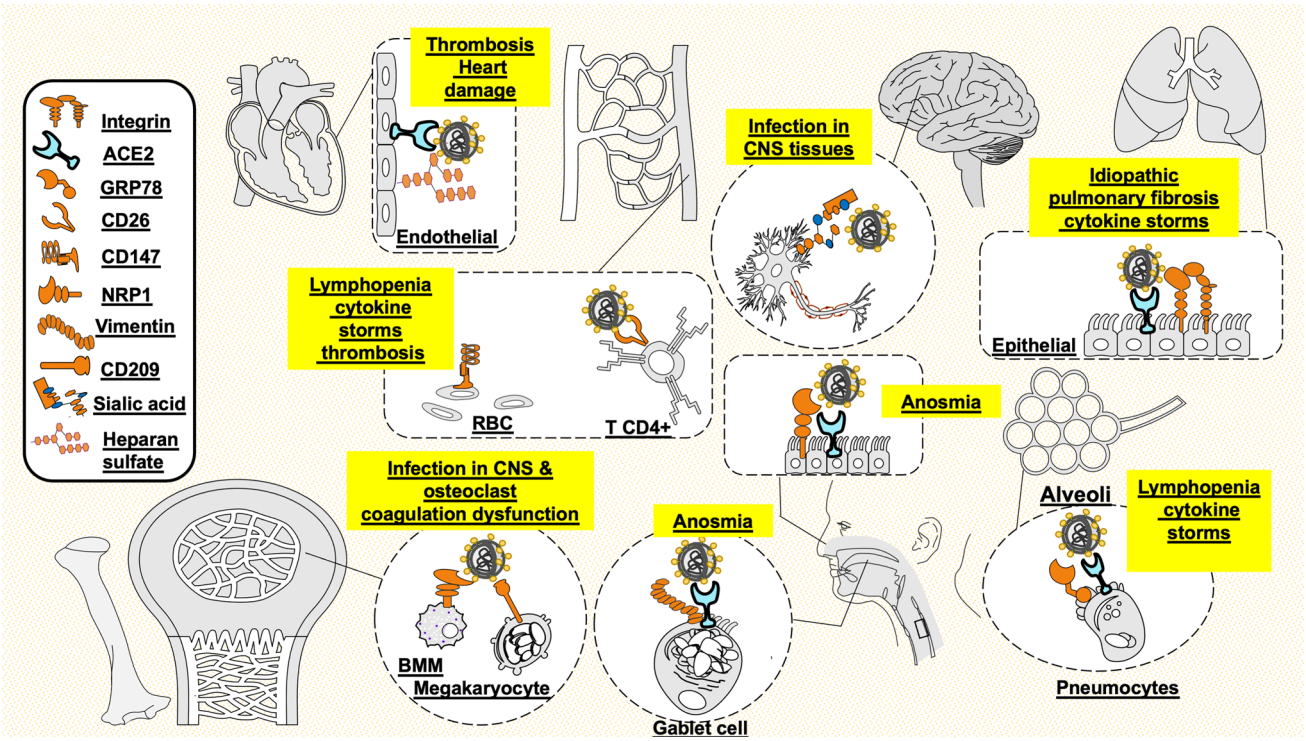


**Fig. 3** Clinical disorders in COVID-19. Infection of SARS-CoV-2 due to binding to receptors and/or co-receptors in various organs might justify the variability of ACE2's distribution

barrier in the inflammatory consequences that COVID-19 imposes [93]. A severe COVID-19 infection can be observed due to the increased pro-inflammatory cytokines, including interleukin-6 and tumor necrosis factor-alpha [9, 15]. The primary source of these cytokines is dependent on the toll-like receptors (TLRs) signaling pathways [28]. It has been found the extracellular domains of the surface TLR4, display a strong binding affinity to spike proteins, followed by TLR6 and TLR1 [28].

Furthermore, the function of intracellular TLRs (including TLR3, 7, and 9) in activating downstream cascade events when SARS-CoV-2 mRNAs attach to virus-associated molecular patterns, cannot be overlooked [93]. The interaction between TLR4 and its pathogenic ligand leads to cytokine storm and multi-organ disorders in COVID-19. It seems that the occupation of TLR4 using its antagonists might be an efficient therapeutic strategy against COVID-19. It is noteworthy to state that immunotherapies that target TLRs are double-edged swords; however, they disrupt the signaling pathways generated from TLRs which lead to the activation of mitogen-activated protein kinases, with or without the engagement of nuclear factor-kB [94]. One of the most important disadvantages of targeting TLRs, is that by reducing the induction of pro-inflammatory cytokines, the viral load can significantly increase.

## Therapeutic Perspective

Effective treatment strategies are needed to improve the prognosis of the affected individuals in the current pandemic, especially with the emergence of various mutations and novel strains generated by mutations. It's worth mentioning that one of the effective factors in controlling the infection, are receptors and co-receptors, which the virus targets to enter host cells; subsequently, the neutralization of these factors are among the suggested treatment strategies. The following drug categories, are some of the medications that can potentially be used to block the receptors and co-receptors involved in the pathogenesis of SAR-CoV-2:

1. **Anti-ACE2:** Protease inhibitors that retain ACE2's functional activation, such as camostat and ivermectin, might be used as therapeutic agents [8]. For example, Kow et al. in a meta-analysis study demonstrated that ivermectin exhibits a broad antiviral activity against a wide spectrum of RNA and DNA viruses in vivo and in vitro [95]. It's noteworthy that ivermectin treatment was not linked to a reduction in viral clearance time, length of hospital stay, death rates, or the need for mechanical ventilation in COVID-19 patients. However, more substantial clinical trials on the impact of ivermectin in disease progression can be carried out; since this drug has shown no major side effects during the treatment process [96].
2. However, given the numerous critical biological roles that ACE2 plays in regulating cardiovascular functions and the innate immune system, the use of ACE2 as a therapeutic target should be approached cautiously.
3. **Anti-HSPA5:** Medications that can inhibit the expression of HSPA5 on the cell surface, such as Bosutinib and Ponatinib, as well as the phytochemical orientin, may interfere with SARS-CoV-2's binding to target cells, and therefore are a good suggestion for targeting GRP78 [44].
4. **Anti-DPP4:** In COVID-19 patients, the use of DPP4 inhibitors, such as gliptins, can effectively prevent SARS-CoV-2's entry into T cells by regulating the activity of DPP4 / CD26, and blocking the host's CD26 receptor [97].
5. **Anti-CD147:** According to a clinical on meplazumab, a humanized therapeutic monoclonal antibody against basigins, this drug can considerably improve the clinical status of COVID-19 patients [98].
6. **Anti-CD209L:** In a study conducted by Kondo et al., it was shown that the interactions between SARS-CoV-2 and L-SIGNs can be suppressed by anti–L-SIGN antibodies, mannan, and recombinant L-SIGN/Fc proteins, as an alternative treatment approach for managing severe COVID-19 infections [73].
7. **Anti-vimentin:** The use of extracellular recombinant vimentin to inhibit the interaction between the SARS-CoV-2 spike's RBD and the cell surface membrane is another possible therapeutic approach; this can dramatically reduce the virus's ability to infect host cells [76]. Up to 80% of the cellular uptake of SARS-CoV-2 pseudo viruses was blocked by anti-vimentin antibodies [99]. Extracellular vimentin serves as a co-receptor for the SARS-CoV-2 spike protein; but it has a lower affinity for the spike protein compared to ACE2 [99]. So, new treatment techniques for preventing and delaying the infection of SARS-CoV-2 might be developed using vimentin-targeting agents.
8. **Anti-heparan sulfate:** Lactoferrin (LF), an endogenous natural protein which is found in numerous mucosal secretions and is a non-toxic iron-binding glycoprotein, plays a vital role in the first line of defense against human and animal viruses, acting against both DNA and RNA viruses [100]. It might be a viable anti-coronavirus agent for therapeutic purposes because of its anti-inflammatory properties, its synergistic antiviral activities with remdesivir, and its strong tendency to bind directly to HSPGs.
9. **Anti-sialic acids:** Acidic glycans mediate RBD's binding to ABH blood group antigens (particularly A and H), which might explain why people with these blood

types are more vulnerable to SARS-CoV-2 infection [101]. The mechanism of hydroxychloroquine, as the first medication suggested for controlling the infection, was to block the binding of spike's NTD to gangliosides [102]. Overall, although SARS-CoV-2 mainly affects the respiratory system; sialylated glycans can assist this virus in invading multiple other organ systems.

## Conclusion

The emergence of SARS-CoV-2 has demonstrated repeatedly that the coronaviruses' evolutionary history offers a diversity of strategies as well as new and more hazardous varieties. These viruses may adapt to new environments and hosts, as well as being transmitted between species by targeting alternative receptors. They have the ability to proliferate quickly by infecting new host populations through a variety of cellular proteins. Although ACE2 is considered to be the major receptor for SARS-CoV-2; additional variables and cellular components contribute to the virus's pathogenicity. As human ACE2 mRNAs are distributed differently in various tissues, and have a minimal expression level in the lungs, SARS-CoV-2 is more likely to use alternate receptors to enter cells. According to the findings of this review, the potential for antigenic alterations caused by mutations in the spike protein, which make antibody therapies ineffective in neutralizing the virus, necessitates the identification and analysis of the underlying orientation mechanisms. SARS-CoV-2 binds to a variety of receptors. This knowledge can help us fully comprehend how the infection is spread between the animals, and how it affects human cells and tissues. The different receptor distribution and expression on cells and tissue surfaces, which might operate as central or common receptors, may help explain and predict the heterogeneity of the clinical features observed in SARS-CoV-2 patients.

Correspondingly, therapeutic approaches can be developed by targeting cellular components such as glycans or polysaccharides that facilitate the early interactions between the viruses and host cells. As a result, a full understanding of SARS-CoV-2's entrance, pathogenesis, and transmission is critical in determining the disease's prognosis, therapy, and its potential preventive measures.

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**Data Availability** The data supporting this study's findings are available from the corresponding author upon request.

## Declarations

**Conflict of Interest** The authors declare no conflict of interest.

**Ethical Approval** Not applicable.

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