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Pathophysiology of SARS-CoV-2 Infection of Nasal Respiratory and Olfactory Epithelia and Its Clinical Impact

Jeremy Chee[1] · Beverlyn Chern[1] · Woei Shyang Loh[1,2] · Joaquim Mullol[3] · De Yun Wang[1,2,4]

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Abstract

Purpose of Review While the predominant cause for morbidity and mortality with SARS-CoV-2 infection is the lower respiratory tract manifestations of the disease, the effects of SARS-CoV-2 infection on the sinonasal tract have also come to the forefront especially with the increased recognition of olfactory symptom. This review presents a comprehensive summary of the mechanisms of action of the SARS-CoV-2 virus, sinonasal pathophysiology of COVID-19, and the correlation with the clinical and epidemiological impact on olfactory dysfunction.

Recent Findings ACE2 and TMPRSS2 receptors are key players in the mechanism of infection of SARS-CoV-2. They are present within both the nasal respiratory as well as olfactory epithelia. There are however differences in susceptibility between different groups of individuals, as well as between the different SARS-CoV-2 variants.

Summary The sinonasal cavity is an important route for SARS-CoV-2 infection. While the mechanism of infection of SARS-CoV-2 in nasal respiratory and olfactory epithelia is similar, there exist small but significant differences in the susceptibility of these epithelia and consequently clinical manifestations of the disease. Understanding the differences and nuances in sinonasal pathophysiology in COVID-19 would allow the clinician to predict and counsel patients suffering from COVID-19. Future research into molecular pathways and cytokine responses at different stages of infection and different variants of SARS-CoV-2 would evaluate the individual clinical phenotype, prognosis, and possibly response to vaccines and therapeutics.

Keywords COVID-19 · Olfactory · Smell · Nasal epithelium · Pathophysiology · Mechanism of action

Introduction

In December 2019, a novel coronavirus SARS-CoV-2 was first identified in a cluster of pneumonia cases in Wuhan, Hubei Province of China [1]. Spreading rapidly, the WHO declared a global pandemic in March 2020. It has since unfolded to become one of the deadliest and most consequential pandemics in our history. As of August 2022, there have been over 500 million confirmed cases and over 6 million deaths attributed to the virus [2]. Clinical manifestations range from asymptomatic to severe respiratory failure, multiorgan failure, and death [3].

A large proportion of the morbidity and mortality associated with SARS-CoV-2 infection is due to lower respiratory tract manifestations of the disease. However, the effects of SARS-CoV-2 infection on the sinonasal tract have also come to the forefront especially with the increased recognition of olfactory symptoms [4]. The objective of this review was to synthesize current evidence regarding sinonasal pathophysiology of SARS-CoV-2 and its clinical and epidemiological impact on olfactory dysfunction (OD).

✉ De Yun Wang
entwdy@nus.edu.sg

1 Department of Otolaryngology - Head & Neck Surgery, National University Health System, 1E Kent Ridge Road, Singapore 119228, Singapore

2 Department of Otolaryngology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore

3 Rhinology Unit & Smell Clinic, Department of Otorhinolaryngology, Hospital Clinic Barcelona, Universitat de Barcelona, IDIBAPS, CIBERES, Barcelona, Catalonia, Spain

4 Infectious Diseases Translational Research Programme, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore

Overview of SARS-CoV-2

Human coronavirus was first isolated in specimen viral cultures from a young child's nasal secretions in 1965 by Tyrell and Bynoe [5].They owe their name corona, which is the Latin word for crown, to their characteristic appearance of spike projection of glycoproteins under the electron microscope. There are seven formally recognized coronaviruses that are known to infect humans [6]. The known circulating Alpha coronavirus (229E, OC43, NL63, and HKU1) were only known to causes mild diseases. It was only in the past few decades that the spill over from wildlife has led to the emergence of the three pathogenic beta coronavirus species (SARS-CoV, MERS-CoV, and SARS-CoV-2) associated with higher case mortality [6]. SARS-CoV-2 genetic sequence is 80% similar to SARS-CoV-1 and 96.2% similar to bat coronavirus RaTG13 [7].

SARS-CoV-2 Structure

SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA virus and has the largest genome of all RNA viruses ranging from 27 to 32 kb. It contains 4 structural proteins (N, M, S, E) and 16 non-structural proteins (nsp1–16) [8]. The genome is tightly packed inside a helical capsid formed by the nucleocapsid (N) protein that is in turn enclosed within a lipid bilayer envelope. This envelope is formed by the membrane (M), spike (S), and envelope (E) protein [9]. The S protein is of particular clinical interest as it is required for virus entry and also gives the microbiological basis of viral tropism, making it a possible drug target for antivirals [9]. Synthesized as an inactive precursor, it undergoes sequential proteolytic cleavage to generate 2 domains: S1 and S2. S1 contains the receptor binding domain (RBD) while S2 contains the membrane fusion domain.

SARS-2-CoV-2 Replication Cycle

Entry into host cell marks the first step of viral infection. The S protein first undergoes proteolysis into S1 and S2 [10]. This may be mediated either by host cell furin, by serine proteases such as the transmembrane protease, serine 2 (TMPRSS2) [11], or by cathepsin proteases in the late endosome/endolysosome [12]. TMPRSS2 is a type II transmembrane serine protease that is widely expressed in epithelial cells of the respiratory, gastrointestinal, and urogenital tract [13]. Its expression level in the respiratory epithelium (RE) has been thought to be modulated by external factors such as air pollution or inflammatory airway conditions such as atopy or asthma [14].

Following S1/S2 site cleavage, the S1 protein binds to host ACE2 via the RDB to gain entry [15]. ACE2, a homologue of ACE, acts as a counter regulator in the Renin-Angiotensin (RAS) pathway by catalysing cleavage of Angiotensin II to Angiotensin I and Angiotensin I to Angiotensin [16]. ACE2 is expressed in type II alveolar cells and are found in numerous tissues including but not limited to lower respiratory tract, lungs, heart, gastrointestinal tract, blood vessels, and kidneys [17]. The S2 protein interacts with the membrane. It further undergoes structural conformational changes and exposes a second cleavage site S2', whose proteolysis is thought to trigger the membrane fusion [18, 19].

Following the entry and fusion at cellular or endosomal membrane, viral genome is released and uncoated into host cell cytoplasm. Viral genomic RNA is then translated into polyproteins which are further processed into individual non-structural proteins (NSPs). NSPs form the viral replication and transcription complex. Virus-induced double membrane vesicles are formed and viral genomic replication of full-length negative strand RNA and synthesis of subgenomic RNA occurs within the vesicles [20]. Transcription and translation of these negative RNA template forms structural proteins—N, M, S, and E proteins—which are then inserted into endoplasmic reticulum membrane and transit from endoplasmic reticulum to Golgi intermediate compartment [20].

The N protein complexes with the newly formed virion genome, while proteins M, S, and E are incorporated into the viral envelope. The newly assembled viral particles then bud into lumen of secretory vesicular compartments and are released from host cell by exocytosis.

SARS-CoV-2 Transmission

Just like SARS-COV-1 and MERS-CoV, SARS-CoV-2 likely originated from bats [21]. Initial zoonotic transmission from bats to human may have been via a yet-to-be-determined intermediate animal host [22]. Intermediate animal host transmission was seen in SARS-CoV with civets as intermediate host and camels for MERS-CoV [6].

The SARS-CoV-2 is a highly infectious virus that can survive in the air for 2 h. Incubation period of SARS-CoV-2 varies with variants; however, mean incubation period is estimated to be a week [23]. The primary mechanism of human transmission of SARS-CoV-2 is via close contact with infected respiratory droplets which are released via sneezing or coughing [24]. Transmission can also occur via direct contact with infected individual's oral, nasal, or conjunctiva mucosa, contact with fomites, and faecal oral transmission [24].

The presence of elevated ACE2 expression in nasal epithelial cells indicates that the nose and lung are the primary target organs of SARS-CoV-2 infection [25]. The virus then migrates from the nasal epithelium to the upper respiratory tract, and subsequently the lower respiratory tract, via the

conducting airways [26]. Sinonasal epithelium comprises olfactory (OE) and respiratory epithelium (RE). Within the nose, both OE and RE are major sites of viral infection and replication, mediated similarly by ACE2 and TMPRSS2 expression [27••, 28]. Unlike SARS-CoV [29], however, SARS-CoV-2 produces significant olfactory impairment [4]. Evidently, although host cell surface entry receptors and cofactors determine infectivity, they do not determine susceptibility nor pathogenicity [30].

Sinonasal SARS-CoV-2 Infection

Olfactory Epithelial Infection

Anatomy and Histology

The OE is estimated to be 2.5 cm^2 wide [31], and accounts for only 5% of the total luminal surface area of nasal epithelium [32, 33]. It is estimated that 10% of nasal airflow [34] comes into contact with the OE. Histologically, the OE is a layer of pseudostratified columnar epithelium. Cytologically, it is made of ciliated olfactory receptor neurons (ORNs), sustentacular supporting cells, globose and horizontal basal cells, occasional microvillar cells, and ductal cells of Bowman's glands, plus glandular cells of Bowman's glands in the lamina propria of the olfactory mucosa [33, 35]. SARS-CoV-2 infection results in focal atrophy, leukocyte infiltration of the olfactory mucosa, and ORN axonal damage [36, 37]. ORN may be structurally or physiologically affected given that sustentacular cells are known to take on supporting (including metabolic, nutritional, and homeostatic) roles in the OE [27••]. There has yet to be convincing evidence of direct ORN infection with SARS-CoV-2 [27••, 38].

ACE2 and TMPRSS2 Expression and Viral Infection

Studies have identified the expression of ACE2 and TMPRSS2 in sustentacular cells [27••, 28, 39], Bowman's glands [40], and duct cells [40]. In a comprehensive post-mortem analysis of SARS-CoV-2-infected OE combining ultrasensitive in situ RNA hybridization with immunohistochemistry, Khan et al. [27••] reported that the major target cell type in the OE is sustentacular cells, with vigorous replication within these cells. Molecular testing of OE has also shown subgenomic RNA transcripts, surrogate marker for active viral replication in a specific location [41]. Interestingly, the presence of eosinophilic rhinosinusitis has been found to be associated with ACE2/TMPRSS2 downregulation within the OE [42]. In contrast, ORNs appear to not be direct targets of SARS-CoV-2 infection, with no changes in ORN gene-expression levels seen in OE patches of high versus low viral load [27••].

Biopsies of SARS-CoV-2-infected OE have shown significant increases in the pro-inflammatory tumour necrosis factor alpha [43], a molecule known to promote olfactory receptor cell death [43, 44]. Interleukin-6 has also been implicated amongst COVID-19 patients with olfactory disorder, inhibiting the smell through apoptotic pathways through TNF-α or neuropilin [45]. Interestingly, there was no significant increase in interleukin-1-beta [43], a molecule often associated with lower respiratory tract pathology amongst COVID-19 patients.

Susceptibility

Despite the small surface area and relatively low nasal airflow of OE, OD in COVID-19 is especially prevalent. In a meta-analysis by Pang et al. [4], the frequency of OD via detection via validated smell testing was 0.76, and via survey/questionnaire reports was 0.53. Human autopsies have found SARS-CoV-2 spike protein in many OE sustentacular cells [46], with olfactory mucosa showing high viral loads [41]. Furthermore, it is reported that ACE2 expression in the olfactory epithelium is up to hundreds of times more than in the neighbouring respiratory epithelium [33, 39, 40].

Clearly, OE is highly susceptible to SARS-CoV-2 infection, with significant host response and clinical pathology. Both murine and human studies have shown that the ACE2 expression is more abundant in OE, up to hundreds-fold as compared to RE [39, 40, 47]. This increases the susceptibility of the sustentacular cells to SARS-CoV-2 infection. Liang et al. [33] further proposed that the coat of microvilli occupying the luminal OE surface may result in a multiplier effect for infectivity by vastly increasing the cellular surface area for binding or absorption [48].

While OD affects majority of patients, it is difficult to predict which patients will be affected. A recent multi ancestry genome study of 69,841 individuals by Shelton et al. [49] identified genome wide significant locus in UGT2A1/UGT2A2 in patients who reported anosmia and ageusia, highlighting a possible genetic predisposition. UGT2A1 and UGT2A2 are part of a family of enzymes that partake in the elimination of odorant particles and may play a role in the physiology of infected cells. Risk factors for OD include current smoking [50], history of allergy [50], female sex [51–54], younger age group [54, 55], Caucasian [39, 54], and presence of chronic cardiovascular diseases such as hypertension and diabetes [55].

Females have been shown to have more superior sense of smell [56], and this has been thought to be due to sex-specific differences in cytokine production following activation of toll-like receptors [57], and increased number of neurons and glial cells than males [56]. Caucasians have also been shown to express ACE2 and TMPRSS2 more frequently in OE and sustentacular cells of OE, allowing greater viral host

cell entry and infection. Even amongst Asians, microvascular disease from hypertension and diabetes is likely to further contribute to increased OD [58]. The presence of normal age-related decline in olfactory function [59] including atrophy of nasal epithelium, olfactory bulb volume shrinkage, and cortical degeneration is also theorized to result in decreased sensitivity to changes in olfactory ability in the older age group.

COVID-19-Induced Anosmia Versus Post-viral Olfactory Dysfunction

Viral upper respiratory tract infection is one of the most common causes of OD [60]. Post-viral olfactory dysfunction (PVOD) is not unique to SARS-COV-2, ranging from 18 to 42% following viral URTI [61]. Some of the more common viruses isolated are rhinoviruses, parainfluenza viruses, and coronavirus [62]. It is postulated that PVOD begins as nasal mucosa inflammation that causes conductive obstruction and decreased delivery of odorants to olfactory epithelium and can persist when there is direct damage to OE and olfactory bulb [63]. However, the exact pathophysiology of PVOD is poorly understood as patients often present late, difficulty in isolating causative viruses, and absence of standardized diagnostic tools [64]. In general, the clinical course of both SARS-COV-2 and other viral induced PVOD is similar. Both occur at the beginning of viral infection, with majority showing recovery 2–3 weeks of infection [65]. Huart et al. observed that SARS-COV-2 patients had worse global, sweet, bitter, and smell discriminatory performance [65]. The impairment of discrimination potentially points to greater involvement of central olfactory structures. This could be attributed to SARS-COV-2's relative neurological tropism [66]. SARS-COV-2-related PVOD also appears more severe than other viral PVOD. Haehner et al. observed that majority of SARS-COV-2 patients reported complete anosmia compared to 9–16% in other viruses [67].

Difference Amongst Variants

Epidemiological studies have shown that the prevalence of OD was the lowest amongst Omicron variants, followed by Delta variant, and then Alpha variant [68–72] (Fig. 1). Menni et al. reported that loss of smell was less common in participants infected during the Omicron than during the Delta prevalence (16.7% vs 52.7%) [70]. Cardoso reported that individuals with mild COVID-19 infected during the Gamma and Omicron waves had lower odds of reporting OD than individuals infected during the period of the original lineages (original lineages 52.6%, Gamma 27.5%, Delta 41.2%, Omicron 5.8%) [69]. Similarly, Vihta et al. reported that the Omicron variant had a lesser impact on smell and taste compared with the Delta and Alpha variants [71].

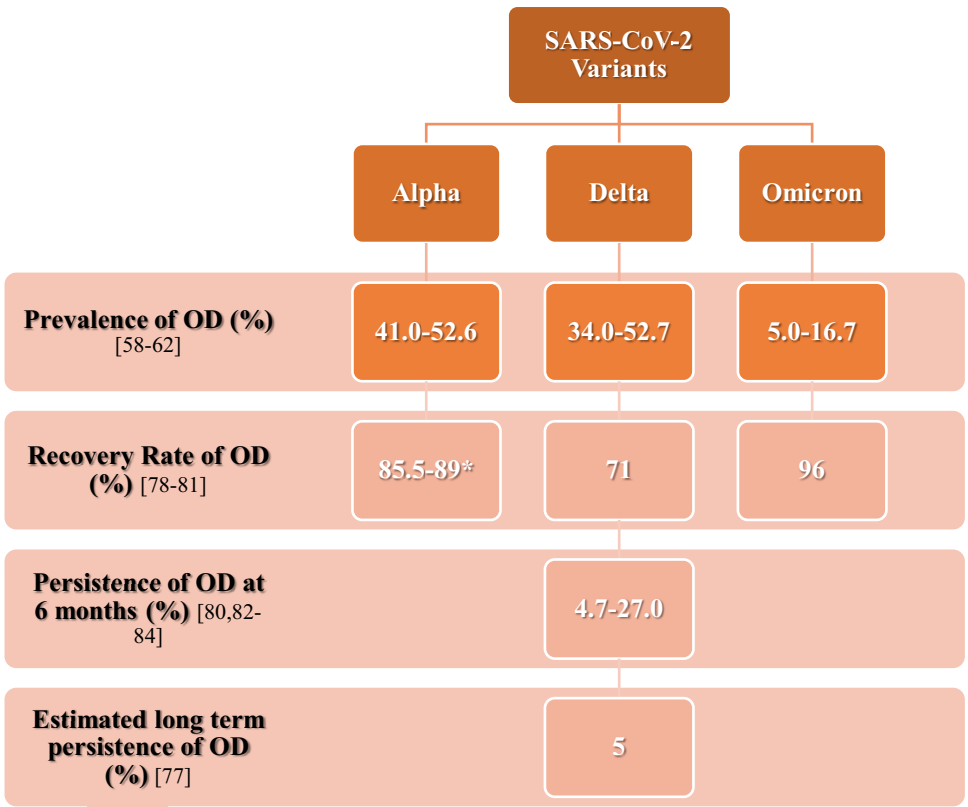

Fig. 1 Prevalence of olfactory dysfunction (OD) amongst patients infected by SARS-CoV-2 variants and recovery. *Data obtained from papers analysing OD recovery during period where the Alpha variant was predominant strain

An animal model study further reported that Syrian hamsters inoculated with the Delta variant results in severe necrotizing pan-rhinitis, while the Omicron variant acutely causes rhinitis with epithelial injury but with, of interest, OE sparing [73]. Histological analysis of the olfactory epithelium amongst Delta variant-infected hamsters showed global necrosis extending to the level of basal cells, with otherwise complete dissolution of the normal pseudostratified columnar layering of olfactory neurons and sustentacular cells [73]. This was despite no statistically significant differences in the viral loads between the two Syrian hamster subgroups [73]. This was also in spite of the findings of Kumar et al. showing the Omicron variant had a higher affinity for ACE2 than the Delta variant due to a larger number of mutations in the SARS-CoV-2 receptor-binding domain [74].

Alterations in Omicron spike protein have been found to result in reduced entry efficiency via TMPRSS2-dependent plasma membrane fusion [75, 76]. Butowt et al. [77] found that mutations made omicron more hydrophobic and alkaline than previous variants, which may reduce solubility and penetration of the mucus layer [78].

The different prevalence of OD during the different variants is likely multifactorial—less virulent virus characteristics, interaction with host and acquired immunity. From the Alpha wave to Omicron wave, previously acquired immunity from either vaccinations or previous infectious may have led to less local and systemic inflammation and hence lower self-reported OD. Antonelli et al. [79] and Malhotra et al. [80] observed that vaccinated patients who had re-infection with SARS-COV-2 had lower incidence of OD and shorter duration of symptoms.

It is interesting that the hospitalization [81–84], ICU admission [81], and mortality rates [85, 86] differ fairly significantly between the different SARS-CoV-2 variants (Table 1). These may once again reflect the differences in susceptibility to different mutations in the SARS-CoV-2 receptor-binding domain, or simply acquired immunity for either infections or previous infections.

Recovery and Prognosis of OD

Fortunately, a majority of patients with OD demonstrate recovery. Reyna et al. [87] reported that clinical recovery of OD was correlated with repair of the OE in the Syrian hamster model. Catton et al. reported that within 14 days, 64% of cases had resolved, and within 30 days, 87% had resolved, rising to 96% resolution within 90 days [88]. In a meta-analysis of time-to-event data by Tan et al. [89••], an estimated 74%, 86%, 90%, and 96% of patients self-reported smell recovery and 79%, 88%, 90%, and 98% self-reported taste recovery at 30, 60, 90, and 180 days, respectively. Recovery rates appeared to be highest amongst patients infected with the Omicron variant, followed by the Alpha variant, and then the Delta variant [90–93] (Fig. 1).

Persistent smell or taste dysfunction was reported in 4.7–27.0% [92, 94–96] of patients, and estimated to develop in about 5% of patients [89••] using parametric cure modelling. Female sex was associated with poorer recovery of both smell and taste, whereas greater initial severity of dysfunction and nasal congestion were associated with poorer smell recovery only. Zazhytska et al. [97] sought to explain the persistent OD that cannot be attributed to transient cell-autonomous effects of sustentacular cells. They observed downregulation of key transcription factors for olfactory sensory neurons and downregulation of olfactory receptor and olfactory receptor signalling genes in hamster cells infected by SARS-Cov-2. Similar changes were also observed in human OE autopsies obtained from infected patients. They postulated that the disruption in nuclear architecture in mature OSNs is irreversible; hence, olfaction may only recover after these mature OSNs are replaced, a process that will likely take weeks to months. Unfortunately, very limited evidence is available on the efficacy and harms of therapeutics for prevention and treatment of persistent OD [98, 99], and more work needs to be done in this area.

Table 1 Morbidity and mortality of COVID-19 caused by different SARS-CoV-2 variants

	Variants of SARS-CoV-2		
	Alpha	Delta	Omicron
Hospitalization (%) [81–84]	2.5–5.7	0.5–4.2	0.5–0.9
ICU admission (%) [81]	0.19–0.4	0.2–0.8	0.0–0.1
Mortality rates (%) [85, 86]	0.5–1.2	0.09–0.3	0.0–0.11

Olfactory Dysfunction and COVID-19 Disease Course

The presence of OD has been purported to be a marker of good prognosis. Mendonça et al. reported a significantly higher prevalence of OD amongst patients with more severe COVID-19 disease. Li et al. [100] reported that only a small proportion of patients with OD developed severe and critical illness was relatively small. Yan et al. [101] also found that patients who required admission for COVID-19 were significantly less likely to report OD. Patients who reported OD were 5-fold more likely to be managed in the outpatient setting. One proposed mechanism was that OD signified higher disease concentration in the sinonasal cavity rather than in the lower airway, indicating that a robust immune response has occurred in the nasal passages, with reduced spread to other parts of the body.

On the other hand, several other studies [102–105] found no association between the OD and disease severity. This may purely be due to recall bias, where patients with severe COVID-19 may be less cognizant of OD due to the presence of more bothersome symptoms such as dyspnoea [4].

Nasal Respiratory Epithelial Infection

Anatomy and Histology

In contrast to OE, nasal RE lines the majority of the inner surface of the nasal cavity[27••], occupying an area of approximately 120 cm^2 [106]. It is a ciliated, pseudostratified columnar epithelium comprising mainly of ciliated columnar epithelial cells, secretory goblet cells and basal cells [27••], as well as brush cells, small granule cells, ductal cells of glands, and glandular cells in the lamina propria [33, 106].

Sinonasal mucosal epithelium cells are firmly adhered to each other via cell junctions and tight junctions, forming a robust physical barrier [107]. Mucociliary clearance further traps microbes and particles in the mucus layer, and transports the debris to the oropharynx. Mucus also interact with components of innate immunity like IgA and defensins, generating proteins like lysozyme, lactoferrin, and defensins which assist in elimination of pathogens [108]. Within the nasal respiratory epithelium, there is also a network of innate and adaptive immunity made of macrophages, dendritic cells, IgA-committed B cells, and Th-1 and Th-2 cells.

ACE2 and TMPRSS2 Expression and Viral Infection

Ciliated columnar respiratory epithelial cells have been identified as the main target cell for SARS-CoV-2 infection, with high concentrations of ACE2 and TMPRSS2 expression [27••, 109–111]. Consistent with this, ciliated cells have been shown to harbour the bulk of the viral load in the RE [27••, 110]. In particular, ACE2 and TMPRSS2 were found to be localised to the plasma membrane including microvilli but excluded from cilia, with extracellular virions seen associated with microvilli and the apical plasma membrane [110]. Interestingly, Wang et al. reported regional differences in ACE2 expression in the sinonasal mucosa of patients with chronic rhinosinusitis, with decreased ACE2 mRNA and protein expression levels within the ethmoid mucosa and nasal polyps, as compared to the inferior turbinates [112].

The role of secretory goblet cells in viral infection, in contrast, is unclear. Evidence of ACE2 and TMPRSS2 expression within these cells is conflicting [40, 109, 113–115]. Pinto et al. found that evidence of intracellular virus replication could be clearly seen in ciliated cells but were rarely found in goblet cells [110]. Likewise, goblet cells were not identified as a target cell type by Khan et al. [27••]. However, some studies have documented SARS-CoV-2 infection of goblet cells [115, 116]. It is hence hypothesized that goblet cells lack adequate machinery for viral entry at the early stages of infection, but may gradually be vulnerable after longer periods of infection [110].

Susceptibility and Effect of Nasal RE Infection

Khan et al. identified ciliated cells as the major target cell type in RE [27••], concluding that the nasal RE is a major site of infection for SARS-CoV-2. Infected ciliated cells shed their ciliary axonemes [12, 18], which disables mucociliary clearance and likely enables disease progression.

SARS-CoV-2 replicates within the epithelial target cells and is release apically, thereby infecting neighbouring cells [113]. Infected nasal epithelial cells shed their ciliary axonemes [117] which causes dysfunction of mucociliary clearance and loss of barrier function, hence propagating infection. Active replication and release of viruses causes pyroptosis of host cell. This is recognized by neighbouring cells, resulting in production of cytokines and chemokines such IL-6, macrophage inflammatory protein 1 alpha which attracts monocytes, macrophages, and T cells [118]. Furthermore, pattern recognition receptors like toll-like receptors (TLR) and retinoic-acid-inducible gene 1 (RIG-1) receptors [119] recognize the viral particles and lead to activation of latent transcription factors including interferon regulatory factors, which kick-starts proinflammatory antiviral mechanisms [120].

It has been reported that while a large number patients with COVID-19 experience OD, most have a paucity of other sinonasal symptomatology [14]. Nasal RE is thought to have a dampened immune response to SARS-CoV-2. Blanco-Melo et al. reported that SARS-CoV-2 is secreted at lower levels as compared to other respiratory viruses [121]. This is also supported by the identification of loss of function mutations at TLR3 and TLR7 in patients with severe infection [122]. Gamage et al. measured several cytokines after SARS-CoV-2 infection of nasal epithelium, and, with the exception of CXCL, reported dampened cytokine secretion [123]. The reason for dampened innate response is unknown and investigations are underway. Some postulated explanations include ongoing exposure of the nasal RE to widespread microbes and their associated pathogen-associated molecular patterns may dampen the innate immune response. The relatively cooler temperatures in the nasal passages may contribute to dampened immunity [26].

Current Limitations and Future Perspectives

Since the beginning of the pandemic, great strides have been made in the understanding of sinonasal pathology in SARS-CoV-2 infection. However, the subjective nature of olfactory assessment and retrospective nature of the reviews [89••] may limit the accuracy of the estimate of the true impact on OD. Furthermore, hypotheses correlating the mechanism and pathophysiology of OD to recovery rates have yet to be proven, and require further research. It also remains unclear if the extent and subsequent recovery loss of sense of smell can serve as a prognostic indicator of severity of COVID-19 infection [124•].

The study of COVID-19 in the context of pre-existing sinonasal pathology such as chronic rhinosinusitis and its associated inflammatory environment has yielded interesting findings [125], and may serve as a platform for further research. Delving into molecular pathways and cytokine responses at different stages of infection and different variants of SARS-CoV-2 would also help to improve our understanding of the true effects of the virus, and help to more accurately prognosticate upper respiratory tract symptoms. With the evolving understanding of role of genetic variability in viral cell entry and immune response to virus infection, it will also be pertinent for future research to evaluate the genetic host background that impacts clinical phenotype and possibly response to vaccines and therapeutics.

Conclusion

The sinonasal cavity is an important route for SARS-CoV-2 infection. While the mechanism of infection of SARS-CoV-2 in nasal OE and RE are similar, there exist small but significant differences in the susceptibility of these epithelia and consequently clinical manifestations of the disease. Understanding the differences and nuances in sinonasal pathophysiology in COVID-19 would allow the clinician to predict and counsel patients suffering from COVID-19.

Author Contribution JC and BC contributed equally to this paper and are co-first authors. JC and DYW conceptualized the study. JC and DYW designed the study. JC and BC titles and abstracts for inclusion. JC, BC, WSL, JM, and DYW helped with interpretation from a clinical viewpoint. JC and BC wrote the first draft, which all authors revised for critical content. All authors approved the final manuscript. JC and DYW are the guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Data Availability Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Compliance with Ethical Standards

Ethics Approval Not required for this study.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Conflict of Interest The authors declare no competing interests.

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Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

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