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POST-COVID SYNDROME IN OTORHINOLARYNGOLOGY: A SYSTEMATIC REVIEW

21 July 2023

by Rumbidzai Chiware

Post-COVID Syndrome in Otorhinolaryngology: A Systematic Review

Master of Medicine (MMed) in Otorhinolaryngology

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1. ABSTRACT

Background:

The novel virus SARS-CoV-2 which is the cause for coronavirus-19 disease (widely known as COVID-19), has shifted health and healthcare worldwide. With the majority of COVID-19 cases having mild to moderate symptoms, and with improvement in treatment and survival of severe disease, there has been a rise in the number of patients presenting with prolonged, recurrent or new symptoms long after the time frame of active disease. This phenomenon has been given various terms which include post-COVID syndrome.

Post-COVID syndrome like acute disease has various clinical presentations that involve multiple systems in the body which include the ear, nose and throat. Due to the substantial increase in this population of patients with ongoing COVID-19 symptoms, the current focus is towards identifying and managing these patients early so as to improve outcomes and quality of life.

Objectives:

The aim of this systematic review was to bring awareness to post-COVID syndrome in the context of otorhinolaryngology with a description of the demographics, clinical manifestations and identifiable predisposing factors. The secondary objectives were to describe special investigations used for diagnosis and management of patients with post-COVID syndrome in otorhinolaryngology.

Methods:

A systematic review of all the available published literature (systematic reviews, cohort studies, case series and case studies) was conducted. The databases searched were PubMed, The Cochrane Database of Systematic Reviews, EMBASE, and Google Scholar. The search terms used were “post-COVID syndrome” OR ‘’post-acute COVID-19’’ OR ‘’long COVID’’ AND “chemoreceptor dysfunction” OR “Otology” OR “Rhinology” OR “Laryngology”. The search included articles from January the 1st 2020 to the 31st of July 2021. A total number of 13 561 articles were found of which 25 articles met the inclusion criteria.

The systematic review was a retrospective study of information already available in the public domain. Ethics clearance was received from the University of the Witwatersrand Human Research Ethics Committee (medical).

Results:

A total of 25 studies were included in the systematic review with a total of 1041 patients presenting with otorhinolaryngological symptoms associated with COVID-19. Patients who presented with symptoms in the post-acute COVID-19 period (more than 4 weeks) were 383 in total. The vast majority presented with chemosensory dysfunction (olfactory +/- gustatory) accounting for 82,5% (n=316). Patients with audiovestibular

symptoms (sensorineural hearing loss, tinnitus and/or vertigo) accounted for 7,6% (n=29) and patients with dysphonia 9,9% (n=38).

Fifteen percent of cases (152/1041) presented with otorhinolaryngological symptoms beyond 12 weeks (post-COVID syndrome). Chemosensory dysfunction still accounted for most cases in this group with 80,9% (n=123), 8,6% (n=13) had persistent or residual audiovestibular symptoms (sensorineural hearing loss, tinnitus, vertigo) and 10,5% (n=16) had persistent dysphonia.

The limitations of the systematic review were the lack of high-quality data due to the novelty of COVID-19, the risk of bias of individual studies and the heterogenous findings and outcomes.

Conclusion:

Post-COVID syndrome like acute COVID-19 manifests in multiple systems in the body which include the ear, nose and throat. Otorhinolaryngological symptoms that this population presents with include chemosensory dysfunction, audiovestibular dysfunction and dysphonia. Olfactory dysfunction is the dominant presentation with more data available in the literature as it presents more commonly. There is need for larger and more detailed future studies with focus on identification of specific risk factors that predispose individuals to post-COVID syndrome with the goal of improving outcomes and preventing long-term disability.

2. INTRODUCTION

The novel virus SARS-CoV-2 which is the cause for coronavirus-19 disease (widely known as COVID-19), has shifted health and healthcare worldwide with over 170 million cases and close to 4 million fatalities to date. The collective efforts of scientific and medical fraternities worldwide have led to ground breaking discoveries, treatment methods and preventative measures at a rapid rate.

At the outset of the pandemic, much attention was given towards understanding and treating active COVID-19. However with the majority of cases having mild to moderate symptoms[1], and with improvement in treatment and survival of severe disease, there has been a rise in the number of patients presenting with prolonged, recurrent or new symptoms long after the time frame of active disease.

This phenomenon of ongoing symptoms has different terms which include long COVID, persistent COVID, chronic COVID, post-acute COVID-19 and post-COVID syndrome.[2]

The National Institute for Health and Care Excellence (NICE) together with Royal College of General Practitioners (RCGP) and Scottish Intercollegiate Guidelines Network (SIGN) developed a series of definitions for the different stages of COVID-19.[3] These are:

- Acute COVID-19: signs and symptoms of COVID-19 up to 4 weeks
- Post-acute COVID-19 which is subdivided into:
    - Ongoing symptomatic COVID-19: signs and symptoms that continue beyond 4-12 weeks
    - Post-COVID syndrome: signs and symptoms that persist or develop 12 weeks after the acute phase of infection which are in keeping with COVID-19 and cannot be explained by an alternative diagnosis.

It is important to note that due to the novelty of COVID-19, the above definitions and classification are subject to change with time as better knowledge and more evidence is obtained.[3]

Due to the substantial number of post-acute COVID-19 cases that continue to rise, it is critical that this condition be addressed just as aggressively as acute COVID-19 as neglect may lead to increased morbidity and even mortality due to potential life threatening complications.

Post-acute COVID-19 like acute has various clinical presentations which involve multiple systems in the body. The common ongoing or new presentations in this post-acute period from review of the literature include fatigue, respiratory and neurological symptoms.[1]

3. LITERATURE REVIEW

The pathophysiology of acute and post-acute COVID-19 has been postulated to be as a result of direct invasion by SARS-CoV-2 into cells via Angiotensin-2 (ACE-2) receptors which have been found to be present in various tissues in the body including those of the head and neck. Other theories are that of an inflammatory response to the virus or as part of known systemic inflammatory conditions that develop as sequelae of COVID-19.[1]

In the context of otorhinolaryngology, the most common symptoms of post-acute COVID-19 reported include:

- Chemosensory dysfunction
    - Olfactory: hyposmia, parosmia or anosmia
    - Gustatory: ageusia or dysgeusia
- Audiovestibular symptoms: sensorineural hearing loss, tinnitus and vertigo
- Dysphonia
- Dysphagia
- Neck masses
- Facial paralysis

Common symptoms will be now be discussed in more detail.

3.1. Otology

Audiovestibular symptoms in COVID-19 have been reported in multiple case reports but not widely investigated.[4] This has had a negative impact on quality of life with reports of cochlear implantation in some cases as a result.[5,6] Oral corticosteroids and intratympanic corticosteroids are treatment options which have been of some benefit particularly when patients present early.[4]

Infection is an established cause of audiovestibular dysfunction in otorhinolaryngology, with examples of viral causes including Herpes Simplex Virus (HSV), Human Immunodeficiency Virus (HIV), Cytomegalovirus (CMV) and Rubella amongst others. In the era of COVID-19 and with studies that have been published, it has been suggested that COVID-19 be considered an additional infectious cause in the differential diagnosis of idiopathic audiovestibular dysfunction.[7]

Labyrinthitis or neuritis from upper respiratory tract invasion by SARS-CoV-2 is postulated to be the cause of sensorineural hearing loss. The virus triggers production of proinflammatory cytokines that results in inflammation and injury to inner ear structures such as neurons from neurotropism of the virus or damage to outer hair cells of the cochlea. Another possibility is the development of an autoimmune response due to cross-reaction resulting in antibodies attacking inner ear antigens.[7]

Other theories have been made with focus towards the blood supply to the inner ear. Microvasculature of the inner ear are the anterior inferior cerebellar arteries and basilar arteries which are the main blood supply as they branch into the anterior vestibular

and cochlear arteries. Occlusion of this microvascular system may possibly result in permanent hearing loss due to the inability to form collaterals. As COVID-19 causes a hypercoagulable state, microthrombi may form and cumulatively cause ischaemia and complete occlusion. Another possible cause is that although the SARS-CoV-2 virus is large in size and unable to pass through the microvasculature of the inner ear, the virus itself can still be a barrier that occludes vascular circulation. Intra-labyrinthine haemorrhage has been reported as an additional possible cause of sensorineural hearing loss, as well as central nervous system invasion of the virus into higher auditory centres in the temporal lobes.[7]

3.2. Rhinology

Rhinological symptoms that have most commonly presented in the post-acute phase of COVID-19 are that of a chemosensory nature which is a decrease, loss or distorted sense of smell and taste. Persistent anosmia has been rarely reported, with hyposmia and parosmia being more common.[8] A recent systematic review on post-infectious olfactory dysfunction (inclusive of COVID-19 as a cause) and its management revealed olfactory training to be best treatment.[9]

Chemosensory dysfunction in the form of olfactory and gustatory dysfunction has been an area of great interest in scientific studies as it presents as one of the most common or hallmark symptoms of COVID-19 particularly in mild disease which presents in the vast majority of cases.[10]

The pathophysiology of olfactory dysfunction has been postulated to occur in three different ways which are conductive, sensorineural or central which can occur in isolation or simultaneously. Conductive dysfunction occurs when there is a mechanical barrier such as mucosal oedema from inflammation which impedes odorants from reaching the olfactory neuroepithelium. Sensorineural dysfunction occurs due to direct invasion and injury to the neuroepithelium or olfactory sensory neurons by SARS-CoV-2. Central nervous system dysfunction occurs secondary to direct or indirect injury to higher cortical olfactory pathways.[11]

Studies have demonstrated from computed tomography (CT) and magnetic resonance imaging (MRI) evaluation that some patients with olfactory dysfunction had olfactory cleft obstruction which prevents odorants from reaching the olfactory epithelium.[11] Kandermirli et al [12] demonstrated in their study the persistence of olfactory cleft obstruction after a month of follow up in patients with ongoing olfactory dysfunction. 91.3% of cases in the study had abnormal olfactory bulb signal intensity by means of diffuse increased signal with scattered hyperintense foci or microhaemorrhages. Some cases had clumped olfactory filia which were thinned and decreased in number. Abnormal cortical signalling was detected in 21.7% of the cases studied. This study depicted that post-COVID-19 olfactory dysfunction is multifactorial.[12]

Injury to neural and non-neural cells of the olfactory epithelium which include sustentacular cells, microvillar cells, bowman gland cells, horizontal basal cells and olfactory bulb pericytes which express ACE-2 receptors (gateway of entry for SARS CoV-2) is believed to be the mechanism leading to olfactory dysfunction. The release of proinflammatory cytokines particularly tumor necrosis factor alpha, initially causes desensitization of olfactory sensory neurons but if inflammation persists can lead to

neuronal loss and sensorineural olfactory loss. When the inflammation resolves then resensitisation and regeneration of new olfactory neurons occurs. With ongoing olfactory dysfunction this resensitisation and regeneration either does not take place or is incomplete.[11]

Mechanisms of central nervous system involvement which have been investigated include studies on neuropilin-1 (NRP1). NRP1 is abundantly found in parts of the brain which are responsible for olfaction or which are part of the olfactory pathway e.g. olfactory tubules and para-olfactory gyri. NRP1 has been demonstrated in in-vitro studies to bind to primed S protein of the SARS-CoV-2 virus. Based on these findings, it can be postulated that SARS-CoV-2 can invade the brain by retrograde axonal transport from the nasal cavity. Future studies on this topic are however needed.[11]

3.3. Laryngology

Dysphonia is the most common laryngological symptom of COVID-19, and it is often neglected due to focus on other systemic symptoms which are more life-threatening.[13]

Theories for the pathophysiology of dysphonia include invasion of epithelial cells within the upper aerodigestive tract by the SARS-CoV-2 virus via ACE-2 receptors with resultant proinflammatory cytokine production causing local inflammation.[13] Another theory is an indirect mechanism which is an inflammatory response that occurs as part of a systemic inflammatory condition which develops as a complication of COVID-19. This concept has been demonstrated by Halfpenny et al [14] who reported dysphonia and dysphagia in some children with Paediatric Inflammatory Multisystem Response Syndrome Temporally Associated with SARS-CoV-2 (PIMS-TS).

Other causes for dysphonia may be through indirect mechanisms which include injury to the higher cortical centres in the brain or vagus nerve responsible for voice production. Injury to these structures may be due to SARS-CoV-2 virus itself or as part of the inflammatory response it triggers.[13] Psychogenic dysphonia has also been described in a case report which has highlighted the importance of having a holistic approach to managing patients.[15]

Voice fatigue has also been described in some patients with not only local factors as a cause, but also poor pulmonary reserve and muscle weakness which result in decreased expiratory flow needed for the voice production mechanism. Additional contributory factors to dysphonia also include laryngeal irritation by secretions from the upper and lower respiratory tracts.[13]

3.4. Other ENT Manifestations

Dysphagia as an isolated symptom in the post-acute period of COVID-19 has been described as multifactorial. In addition to aforementioned theories, an area of most interest and investigation in these patients is possible central neurological involvement of the glossopharyngeal and vagus nerves by SARS-CoV-2. Yoichiro et al [16] described an interesting case of a patient who developed dysphagia after twenty days of admission. An objective assessment revealed an absent gag reflex with decreased

pharyngo-laryngeal sensation on video-endoscopy. Such a presentation is of concern as it leads to complications such as aspiration pneumonia (which the patient developed) and malnutrition which further increase the morbidity and mortality risk if left untreated.[16,17]

Neck masses have been reported to occur as part of general systemic inflammatory conditions that patients develop as a long-term complication of COVID-19. An example is Paediatric Inflammatory Multisystem Syndrome Temporarily Associated with SARS-CoV-2 (PIMS-TS) or Kawasaki-like disease (KLD). This condition has presented mostly in the paediatric population although a few adult cases have been reported.[18] Such cases may initially present to the Otorhinolaryngology department with a neck mass or cervical lymphadenopathy with or without obstructive symptoms (upper airway obstruction and/or dysphagia) with subsequent referral to the relevant specialties once a diagnosis has been made.[19]

Facial paralysis in the acute and post-acute period of COVID-19 has been another clinical manifestation presenting to otorhinolaryngologists and other physicians. A systematic review by Gupta et al [20] reported multiple cases of patients with mild or asymptomatic COVID-19 who presented with facial paralysis not attributed to other causes. Viruses in the literature have been established to play a role in facial nerve disorders particularly Varicella Zoster virus (VZV) which causes Ramsay Hunt Syndrome characterised by facial nerve paralysis associated with an auricular vesicular rash.[21]

Viruses have also been postulated to be the cause of Bell's palsy which is an idiopathic facial nerve disorder with various possibilities such as HSV, VZV, EBV, CMV and HIV.[20] SARS-CoV-2 may well be a cause of facial nerve palsies and should be considered in the differential diagnosis. Similar theories of the pathophysiology for other neurological manifestations of COVID-19 also apply in the case of facial neuropathy in which there is either direct neural invasion of the facial nerve by SARS-CoV-2 or the nerve is indirectly injured as a result of the inflammatory response to infection.[20]

The otorhinolaryngologist plays an important role in the different phases of COVID-19.[22] With the advent of post-COVID syndrome, it is important to highlight the various clinical manifestations in otorhinolaryngology that these patients may present with and how to approach and manage them accordingly.

The aim of this systematic review was to bring awareness to post-COVID syndrome in the context of otorhinolaryngology with a description of the demographics, clinical manifestations and identifiable predisposing factors. The secondary objectives were to describe special investigations used for diagnosis and management of patients with post-COVID syndrome in otorhinolaryngology.

4. MATERIALS AND METHODS

A systematic review was conducted on post-COVID syndrome in Otorhinolaryngology. Due to the heterogeneity of study findings a meta-analysis was not done. Ethics approval was received from the University of the Witwatersrand Human Research Ethics Committee (medical). There was no active human participation in this study.

4.1. Eligibility Criteria

The inclusion criteria were applied as limits during each search which were studies related only to the human species, studies published in English, studies including data of post-acute COVID-19 period (symptoms >4 weeks) and studies conducted or published within the set dates for the systematic review.

The exclusion criteria were studies that were found because of keyword matching or tags but that were irrelevant to the study topic, studies exclusively investigating acute COVID-19 in Otorhinolaryngology, letters to editors, preprint articles which were not peer reviewed and studies we were unable to locate the full-text articles for.

4.2. Information Sources and Search strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was followed. A total of 13 561 articles were identified from electronic database searches which included PubMed (n=13 318), The Cochrane Database of Systematic Reviews (n=94), EMBASE (n=75) and Google Scholar (n=74). Search terms used were “post-COVID syndrome” OR ‘’post-acute COVID-19’’ OR ‘’Long COVID’’ AND ‘’Chemoreceptor dysfunction’’ OR “Otology” OR “Rhinology” OR “Laryngology”. The search was inclusive of articles from January the 1st 2020 to the 31st of July 2021.

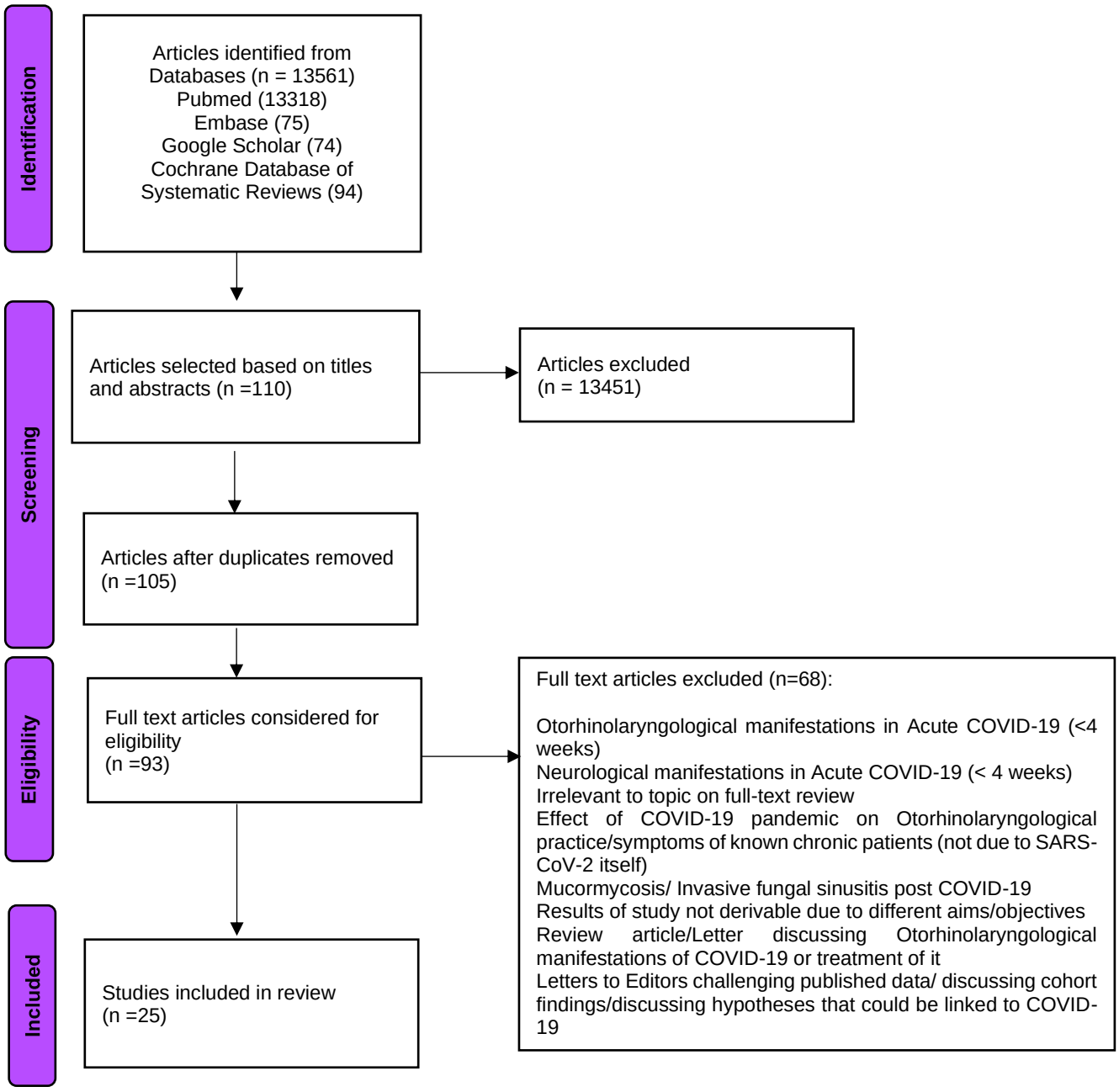
4.3. Selection Process

The articles were independently perused and rated by two researchers (RC and SHM). There were no disagreements encountered with the selection of studies. Of the 13 561 articles found, 110 were selected based on the titles and abstracts. This was further narrowed down to 105 articles after duplicates were removed. Twenty-five articles were finally selected that met the inclusion criteria for the systematic review.

4.4. Data Extraction

The variables which were extracted from the eligible studies (n=25) were the demographics (age and gender), co-morbidities, risk factors, clinical presentation or symptoms, duration of symptoms, special investigations, diagnosis, management and follow up where available. This data was collected and documented on a Microsoft Excel spreadsheet.

PRISMA FLOW DIAGRAM: POST COVID SYNDROME IN OTORHINOLARYNGOLOGY



4.5. Risk of Bias and Level of Evidence

The evidence based practice tool was used and was classification level IV.

5. RESULTS

A total of 25 studies were included in the systematic review with a total of 1041 patients [4,6,10,13,14,23–42] presenting with otorhinolaryngological symptoms associated with COVID-19. The studies were under the categories Otology (n=16)[4,6,23–30,37–42], Rhinology (n=5)[10,31–34], and Laryngology (n=4)[13,14,35,36]. Study types included were 6 case series (3 prospective and 3 retrospective)[25,26,29,31–33], 6 cohort studies (3 prospective and 3 retrospective)[10,13,14,34–36] and 13 case reports.[4,6,23,24,27,28,30,37–42] Countries in which the studies were conducted were 3 in Spain[28,34,35] and the United States of America[6,29,37], 2 each in Brazil[32,41], Italy[13,26] the United Kingdom[4,14] and Turkey[25,39] and 1 each in Belgium[27], Croatia[30], Egypt[42], Germany[10], India [23], Iran[31], Iraq[36], Ireland[40], Israel[33], Qatar[38] and Saudi Arabia.[24]

The total number of patients who presented with otorhinolaryngological symptoms that fell into the post-acute COVID-19 period (more than 4 weeks) in the studies where time frame was reported was 383 patients. The vast majority of these patients had chemosensory dysfunction (olfactory +/- gustatory) accounting for 82,5% (n=316). Patients with audiovestibular symptoms (sensorineural hearing loss, tinnitus and/or vertigo) accounted for 7,6% (n=29) and patients with dysphonia 9,9% (n=38).

The proportion of patients in the post-acute COVID-19 group presenting with otorhinolaryngological symptoms beyond 12 weeks (post-COVID syndrome) were a total of 152 patients. Chemosensory dysfunction still accounted for most cases in this group with 80,9% (n=123), 8,6% (n=13) had persistent or residual audiovestibular symptoms (sensorineural hearing loss, tinnitus, vertigo) and 10,5% (n=16) had persistent dysphonia.[4,6,10,14,23,25,28,31,33–35,37–42]

Out of all the patients in the included studies that presented with otorhinolaryngological symptoms related to COVID-19, approximately 15% (151/1041) were classified into the post-COVID syndromic group (beyond 12 weeks).

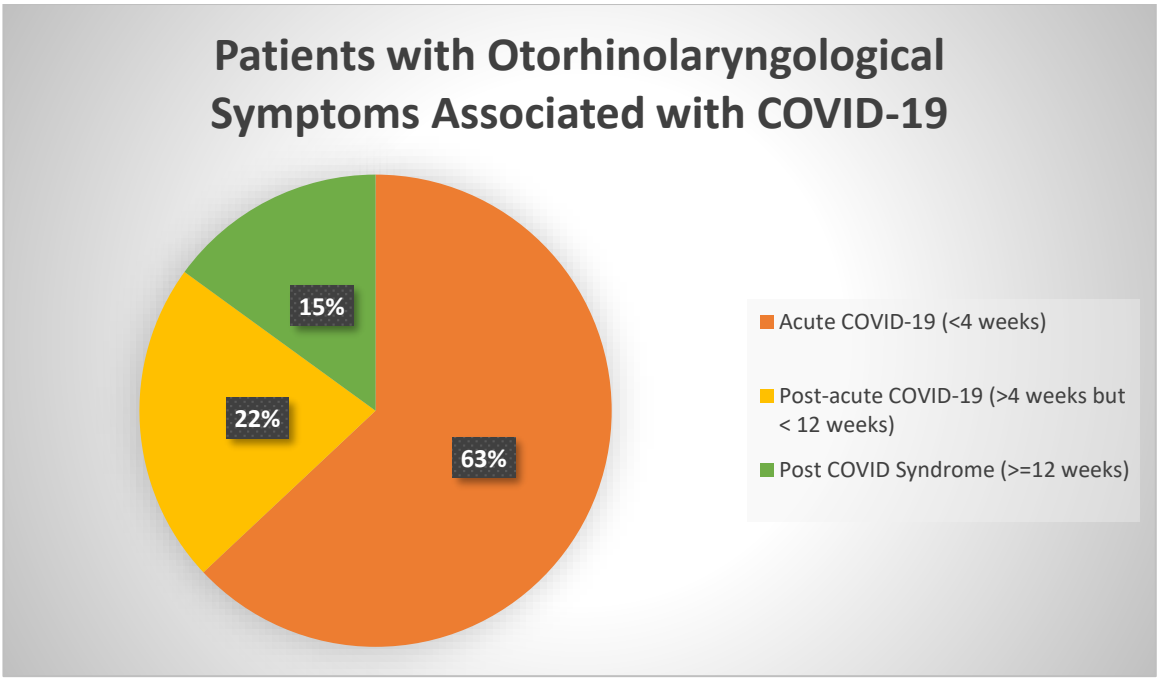


Figure 1: Pie Chart Illustrating Patients with Otorhinolaryngological Symptoms Associated with COVID-19

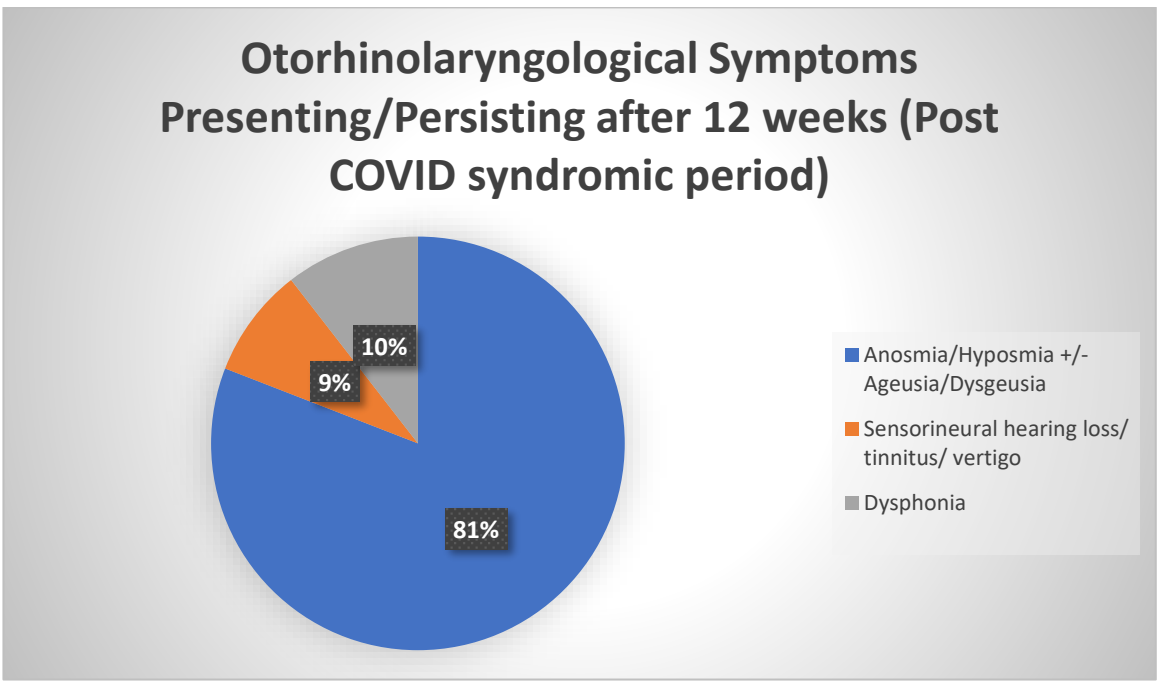


Figure 2: Pie Chart Illustrating Otorhinolaryngological Symptoms Presenting in the Post-COVID Syndromic Period

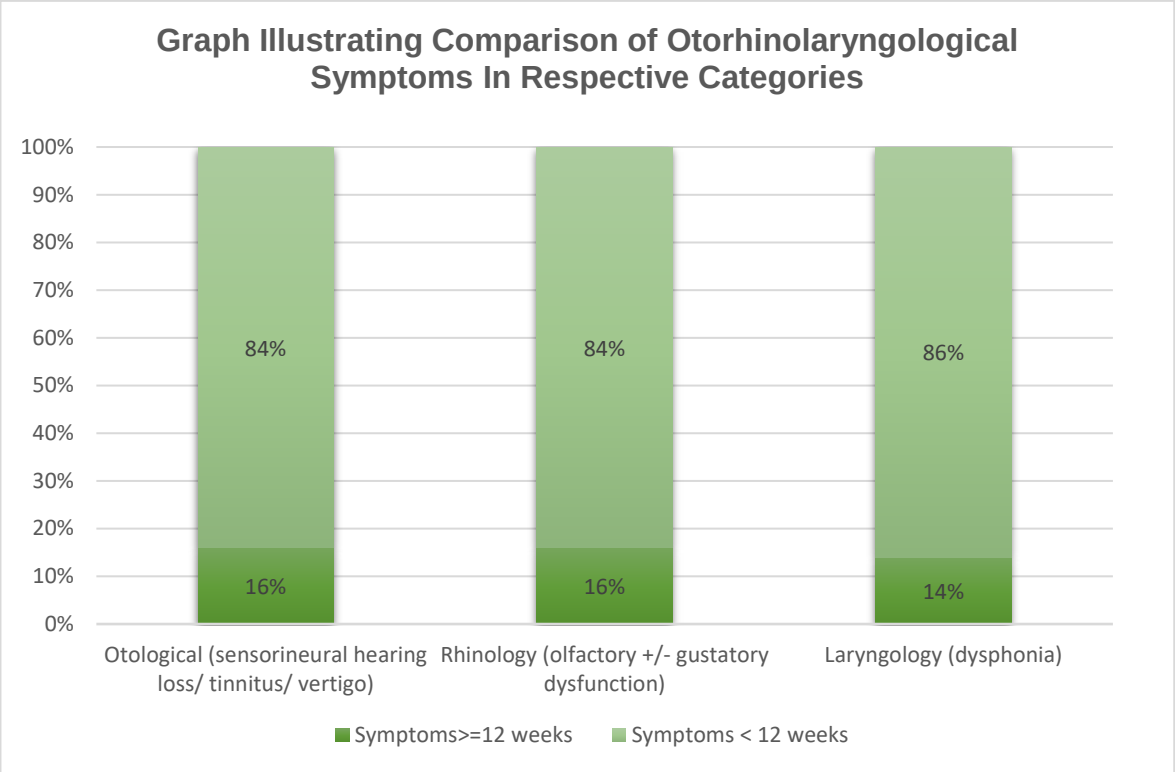


Figure 3 : Graph Illustrating Comparison of Otorhinolaryngological Symptoms In Respective Categories

5.1.OTOLOGY

Sixteen otological studies were included in the systematic review.[4,6,23–30,37–42] These studies were 3 case series[25,26,29] (1 prospective and 2 retrospective) and 13 case reports.[4,6,23,24,27,28,30,37–42] The total number of patients were 100 with an age range of 18-90 years. In the studies that reported gender 55% (16/29) were female and 45% (13/29) male.[4,6,23,24,26–30,37–42]

The symptoms that patients presented with often simultaneously included vertigo in 52% (52/100),[25,26,28–30,37] sudden sensorineural hearing loss in 34% ((34/100) 3 bilateral, 17 unilateral and 14 not stated, ranging from moderate to profound severity),[4,6,23–27,37,38,40,42] hyperacusis in 18% (18/100),[25,26] tinnitus in 11% (11/100)[6,24,26,38,40–42] and aural fullness in 3% (3/100).[26,37] The vast majority of patients had no pre-existing conditions with the exception of 7 patients (7% (7/100)).[6,23,24,26,28] The co-morbidities included Diabetes Mellitus (3)[23,24,26], Hypertension (2)[24,26], Asthma (1)[4], Rheumatoid Arthritis (1)[41], Sjogren's disease (1)[6] ,Gout (1)[6], Aplastic Anaemia (1)[28] and Mitral valve disease (1)[28] some occurring simultaneously.

Post-COVID Syndrome: Vestibulocochlear Dysfunction

16% (16/100) patients were reported to present with persistent or new onset audiovestibular symptoms beyond 12 weeks (see table 2).[6,7,23,25,28,29,37,41] The proportion (each in their respective category) of patients with symptoms extending to or presenting in the post-COVID syndromic period were approximately 24% (8/34) with sensorineural loss[6,7,23,25,37,41], 18% (2/11) with tinnitus[6,7,41], 13% (7/51) with vertigo[25,28–30,37] and 6% (1/18) with hyperacusis.[25]

Post-COVID Syndrome: Cochlear dysfunction

Cochlear dysfunction (sensorineural hearing loss, tinnitus and/or hyperacusis) beyond 12 weeks was reported in four studies.[6,23,25,37,41] Three studies which were case reports went into detail with demographics, clinical presentation, work up and management.[6,23,37,41] These three studies demonstrated males and females to be equally affected (50% (2/4) male and 50% (2/4) female) with an age range of 18-67 years and a mean of 42 years.[6,23,37,41] Fifty percent (2/4) had bilateral sensorineural hearing loss and 50% (2/4) unilateral sensorineural hearing loss with severity ranging from moderate to profound. All patients presented with new and sudden onset hearing loss more than 4 weeks after their initial COVID-19 diagnosis.

Co-morbidities were noted in 75% (3/4) of the patients which included Diabetes Mellitus(1)[23], Rheumatoid Arthritis(1)[41], Sjogren's disease and Gout(1).[6] One patient had a history of hydroxychloroquine use for four years for her Rheumatoid Arthritis.[41] Another patient had a history of treatment with hydroxychloroquine, furosemide and azithromycin during his admission in intensive care unit for COVID pneumonia approximately a month prior to the onset of his hearing loss.[6]

Sensorineural hearing loss was diagnosed by the use of Pure Tone Audiometry (PTA) in all the studies. Laboratory tests for this group were variable and collectively included full blood count, urea and electrolytes, Hemoglobin A1c (HbA1c)[23], D dimers, lactate dehydrogenase (LDH), C Reactive Protein (CRP)[6], albumin, Erythrocyte sedimentation rate (ESR), antinuclear antibodies (ANA) and COVID-19 IgG antibodies.[37] Magnetic resonance imaging (MRI) was also done which showed abnormalities in 75% (3/4) of the cases which were minimal bilateral opacification of the mastoid[6] in one case, multiple microhemorrhagic lesions in another[41] and a more significant finding of high signalling in the vestibulocochlear system in keeping with intralabyrinthine hemorrhage in the third case.[37]

Management was reported in three studies.[6,37,41] This included conservative treatment in all cases (3) and surgical treatment in one case. Conservative treatment included medication which was courses of corticosteroids administered orally, intravenously or through intratympanic injection. Corticosteroids resulted in minimal improvement in the cases. A hearing aid was given to one case which was ineffective resulting in surgical treatment with cochlear implantation ultimately which resulted in significant improvement in hearing and decreased tinnitus.[6] Other included studies which were not part of the post-COVID syndromic cases reported other treatment options such as hyperbaric oxygen therapy (HBOT) and mesoglycan which is a vascular glycosaminoglycan with subtle antithrombotic and profibrinolytic properties.[26]

Post-COVID Syndrome: Vestibular Dysfunction

The total number of patients who presented with persistent vertigo beyond 12 weeks were only 4 patients in three studies.[25,28,37] Demographics, clinical presentation and work up were described in two studies which were case reports.[28,37] These two cases were both healthy young women of 18 and 20 years old with no comorbidities. The case by Chern et al [37] presented with audiovestibular symptoms which were bilateral sensorineural hearing loss and vertigo, while the case by Garcia-Romo et al [28] presented with isolated vestibular symptoms which were dizziness and horizontal nystagmus. Both cases were of a sudden onset presenting at 3 weeks and 7 weeks post COVID-19 diagnosis respectively.

Special investigations done included laboratory tests which were full blood count, albumin, ESR, ANA, D dimer and IgG antibodies for COVID-19. PTA and MRI brains were done in both studies. MRI in the case by Chern et al [37] was diagnostic revealing intralabyrinthine hemorrhage as the cause of the patient's vestibulocochlear dysfunction. Vestibular testing was reported to be done in Garcia-Romo et al's [28] case which was normal.

Management was described by Chern et al [37] which was two courses of oral corticosteroids and one intratympanic corticosteroid injection. Other treatment options were described in other otological studies which fell into the acute and post-acute COVID-19 categories (i.e. less than 4 weeks and more than 4weeks but less than 12 weeks respectively).[29,30] The treatment options in these studies depended on the cause of the vestibular dysfunction. One study was a case series describing patients presenting with vestibular neuritis secondary to COVID-19 and treatment given included corticosteroids, dimenhydrinate, meclizine, anti-emetics, benzodiazepines and vestibular rehabilitation.[29] The other study described COVID-19 induced Benign Paroxysmal Positional Vertigo (BPPV) treated with canalith repositioning procedures which were Epley manouvres.[30]

5.2. RHINOLOGY

A total of 5 rhinological studies[10,31–34] were included in the systematic review which included 2 cohort studies[10,34] and 3 case series (1 retrospective and 2 prospective).[31–33] The predominant symptoms patients presented with were of chemosensory dysfunction associated with COVID-19 in the form of olfactory and/or gustatory loss or decreased acuity. The total number of patients in the studies was 763 with an age range of 18-88 years. In the studies that reported the gender of patients presenting with chemosensory dysfunction, females accounted for 61.3% (344/561) and males 38.7% (217/561).[31–33]

Risk factors and/or co-morbidities were mentioned in three studies.[31,32,34] Jalessi et al [31] reported approximately 22% of the patients presenting with olfactory dysfunction to be smokers. It was also reported that patients who presented with other associated symptoms of COVID-19 particularly gastrointestinal symptoms had an increased risk of severe olfactory dysfunction as well as delayed recovery (patients with diarrhoea

had 4.65 times increased risk). Other risk factors for delayed resolution from Jalessi et al's [31] analysis included patients presenting with rhinological symptoms (nasal congestion, rhinorrhoea, sneezing) and fever. The level of severity of chemosensory dysfunction and duration of symptoms were also reported to determine outcome with patients presenting with severe hyposmia or anosmia and patients with prolonged symptoms having a poorer prognosis.[31]

Co-morbidities were mentioned in two studies.[32,34] Kosugi et el [32] reported 36.4% of patients to have co-morbidities majority with rhinitis followed by asthma and hypertension. A variety of conditions were mentioned by Parente-Arias et al [34] which included hypertension, asthma, depression, diabetes mellitus, heart disease, oncological conditions or treatment, autoimmune disease, neurological disease and renal failure. Despite the variety of co-morbidities mentioned in the Parente-Arias at al's [34] study, the prevalence of chemosensory dysfunction in this group was actually less compared to the vast majority who were healthy patients.

Post-COVID Syndrome: Chemosensory Dysfunction

Approximately 16% (123/763) of patients had persistent chemosensory dysfunction which was predominantly hyposmia beyond 12 weeks.[10,31,33,34] Dysgeusia was reported to be persistent in one study in 46% of patients (30/65 with 25 patients with partial recovery and 5 patients with no recovery).[33] No cases of anosmia or ageusia beyond 12 weeks were reported in the studies included in the systematic review.[10,31,33,34] Only two studies went into detail on the demographics of this particular group.[31,33] Biadsee et al [33] reported females to account for the majority of cases with chemosensory dysfunction (65% (19/30) for gustatory dysfunction and 61% (22/36) for olfactory dysfunction). The mean ages of patients reported by Jalessi et al [31] and Biadsee et al [33] with delayed or no recovery of olfactory function were 32.48 +/- 7.34 years and 37.7 +/- 18.1 years respectively.

Special investigations were not reported in the included studies and only one study conducted an objective evaluation of patients with use of taste strips or sprays to assess gustatory function and the Sniffin' sticks test to assess olfactory function.[10] The other studies used subjective evaluation through questionnaires and telephonic interviews with various quantitative scales to obtain their data which included the Sino-Nasal Outcome Test-22 (SNOT 22) and non-validated scales.[31–34]

Management was reported in one study by Kosugi et al [32] although this study was conducted up to a follow up period of 31 days. A wide variety of treatment options were reported which included expectant treatment used by majority of the patients, nasal saline irrigation, analgesics/antipyretics, intranasal corticosteroids, oral corticosteroids, antibiotics such as hydroxychloroquine and antivirals such as oseltamivir.[32] Olfactory training was only used by 2% of patients. There was no statistical difference between the different treatment options in recovery or outcome.[32]

5.3. LARYNGOLOGY

Four studies discussing laryngological manifestations associated with COVID-19 were included in the systematic review.[13,14,35,36] All were cohort studies (2 prospective[13,35] and 2 retrospective[14,36]). The predominant symptom discussed was dysphonia which was postulated to be multifactorial and often discussed or investigated with dysphagia.

A total of 113 patients were reported to be dysphonic with an age range of 8-90 years.[13,14,35,36] Three studies discussed gender separate from the control groups.[13,35,36] Leis-Cofino et al [35] reported females as the predominant gender presenting with dysphonia accounting for 64.3% as opposed to Cantarella et al [13] and Al-Ani et al [36] who reported no statistical difference between males and females.

Co-morbidities were identified in one study which included obesity, diabetes mellitus, dyslipidemia and hypertension.[35] Smoking (previous or current) was reported in two studies which both demonstrated there to be no association with presentation or outcome of dysphonia.[13,36]

<u>Post-COVID Syndrome: Dysphonia</u>

Approximately 14% (16/113) of patients presented with persistent dysphonia beyond 12 weeks.[14,35] Leis-Cofino et al [35] reported female predominance with a mean age of 58.5+/-19.25 years and 56.75 +/- 18.14 years for previous intensive care unit (ICU) admissions and ward admissions respectively. Halfpenny et al's [14] study was a paediatric study which did not go into detail with the demographics of the dysphonic patients falling into the post-COVID syndromic period.

Objective evaluation of dysphonia in the above studies was by use of voice scales which included GRBAS (grade, roughness, breathiness, asthenia, strain) ,perceptual severity scores, vocal handicap index (VHI), vocal tract discomfort scale (VTDS) and maximum phonation time. The special investigation of choice in both studies was endoscopic evaluation of the upper aerodigestive tract with fibreoptic video laryngoscopy and stroboscopy.[14,35] Leis-Cofino's [35] most common findings were vocal cord weakness/paralysis and vocal cord atrophy in the ICU and ward admissions respectively. Halfpenny et al [14] reported generalised laryngopharyngeal weakness as the most common finding on laryngoscopy and stroboscopy. Other findings were laryngeal granuloma, inflammation, candidiasis and two patients with a normal investigation.[14,35]

Management of dysphonia was discussed by Halfpenny et al [14] and included conservative treatment for all patients which was voice therapy, anti-reflux medication and anti-allergy medication if indicated. Only one patient was treated surgically with vocal cord medialisation injection.[14]

Table 1 Various Outcomes of Treatment of Post-COVID Otorhinolaryngology Symptoms

OTOLOGY: SENSORINEURAL HEARING LOSS + TINNITUS +VERTIGO

Reference	Country	No of patients	Intervention	Outcome
Chern et al (2021)	United States of America	1	Steroids: oral, intratympanic	Minimal Improvement hearing thresholds on one side (had bilateral hearing loss)
Lang et al(2020)	Ireland	1	Oral steroids	No improvement in hearing thresholds
Lamounier et al (2020)	Brazil	1	Steroids: oral and intratympanic	No improvement in tinnitus Partial improvement in hearing thresholds
Koumpa et al (2020)	United Kingdom	1	Steroids: oral then intratympanic steroids (3 sessions)	Partial improvement in hearing thresholds
Rhman et al (2020)	Egypt	1	Intratympanic steroids (3 sessions)	Partial improvement hearing thresholds
Kilic et al (2020)	Turkey	5	Oral steroids Vitamin B, folic acid, proton pump inhibitors One study: hydrochloroquine (as per country's policy)	Complete resolution in 4 cases No improvement in one case
Alanazy SM (2021)	Saudi Arabia	1	Oral steroids Hearing aid	No improvement in hearing thresholds with steroids
Asfour L et al (2021)	United States of America	1	Cochlear implant	Partial improvement speech perception and decreased tinnitus within one month of activation

OTOLOGY: SENSORINEURAL HEARING LOSS + TINNITUS	Ricciardiello F et al (2021)	Italy	5	Oral steroids Mesoglycan Hyperbaric Oxygen Therapy Vestibular rehabilitation	Partial improvement of sensorineural hearing loss, vertigo and tinnitus
	Beckers E et al (2021)	Belgium	1	Oral and intravenous steroids	Partial Improvement hearing thresholds
RHINOLOGY: OLFACTORY DYSFUNTION	Kosugi M et al (2021)	Brazil	253	Options: expectant, nasal saline irrigation analgesics/antipyretics, intranasal steroids, antibiotics, oral steroids, hydroxychloroquine, oseltamivir, olfactory training	No comment or comparison made on efficacy of the different treatment options. General outcomes: 171 cases complete resolution, 76 cases partly resolved and 30 cases no resolution
LARYNGOLOGY: DYSPHONIA	Halfpenny R et al (2021)	Italy	8	Voice Therapy Surgical: One child had vocal cord medialisation injection	6 cases had complete resolution 2 cases persistent dysphonia

Table 2 : Post-Covid Syndrome Presentation in Respective Categories and Studies

Category	Study	Country	Symptoms	Outcomes of persisting symptoms at 12 or more weeks
Otology	Asfour L et al (2021)	United States of America	Sensorineural hearing loss Tinnitus	Follow up at 4 months: Case report (1) persistent sensorineural hearing loss
Otology	Chakraborty S et al (2021)	India	Sensorineural hearing loss	Follow up at 3 months: Case report (1) New onset sensorineural hearing loss
Otology	Eravci F et al (2021)	Turkey	Hearing loss Hyperacusis Vertigo	Follow up at 3 months: 4.9% (2/41) with persistent vertigo 6.3% (1/16) with persistent Hyperacusis 28.6% (4/14) persistent hearing loss
Otology	Chern et al (2021)	United States of America	Sensorineural hearing loss Tinnitus Vertigo	Follow up at or after 12 weeks: Case Report (1) Minimal improvement in hearing thresholds unilaterally Significantly improved vertigo (close to complete resolution)
Otology	Lamounier et al (2020)	Brazil	Sensorineural hearing loss Tinnitus	Follow up at approximately 3 months: Case Report (1) Persistent tinnitus Partial improvement hearing thresholds in low frequencies

Otology	Garcia-Romo E (2021)	Spain	Vertigo	Follow up at 4 months: Case report (1) persistent but improved symptoms with increased time between episodes (partial resolution)
Rhinology	Biadsee A et al (2021)	Israel	Hyposmia/Anosmia and Dysgeusia	Follow up at 8 months: 38.5% (25/65) partial recovery with residual dysgeusia 7.7% (5/65) no recovery. No ageusia cases 48% (31/65) partial recovery with residual hyposmia 7.7% (5/65) no recovery of hyposmia. No anosmia cases
Rhinology	Jalessi M et al (2021)	United Kingdom	Hyposmia/anosmia	Follow up at 4 months: 1.6% (4/239) severe hyposmia. 8.6% (21/239) moderate hyposmia. Mild hyposmia 18.5% (45/239) No anosmia cases
Rhinology	Niklassen AS et al (2020)	Germany	Hyposmia/anosmia	Follow up to 169 days: 18% (6/33) remained hyposmic. No anosmic patients
Rhinology	Parente-Arias P et al (2020)	Spain	Hyposmia/anosmia	Follow up at 91-108 days: 14.7% (11/75) remained hyposmic

Laryngology	Cofino CL et al (2021)	Spain	Dysphonia	Follow up at 3 months: Total 14 patients: 25% (10/70) of previous ICU admissions and 10.3% (4/79) previous ward admissions with persistent dysphonia
Laryngology	Halfpenny R et al (2021)	United Kingdom	Dysphonia	Follow up at 6 months: 2/8 Children with persistent dysphonia

6. DISCUSSION

The novel virus SARS-CoV-2 known to cause COVID-19 is under wide investigation by researchers worldwide with a large number of publications discussing its pathophysiology, clinical manifestations, investigations and management. In Otorhinolaryngology the clinical presentation of acute COVID-19 includes nasal congestion, rhinorrhoea, sore throat, chemosensory loss (olfactory and/or gustatory) and less commonly hearing loss (conductive or sensorineural), tinnitus, vertigo, facial weakness, neck masses, dysphagia and dysphonia.[18,43,44] With the progression of time, there has been a shift in focus towards the long-term effects of COVID-19 with the goal of identifying and understanding sequelae of the disease, to improve outcomes and to prevent the burden of lifetime morbidity. This to our knowledge is the first report providing a collective summary of chronic symptoms related to COVID-19 in the context of Otorhinolaryngology.

The results of our systematic review revealed the prevalence of post-COVID syndrome (new onset or persistent symptoms beyond 12 weeks) in the selected studies to be approximately 15%. Majority of the cases (80,9%) had chemosensory dysfunction specifically olfactory dysfunction which was hyposmia. This may be due to the higher incidence of olfactory dysfunction in COVID-19 cases with it documented as a hallmark symptom for COVID-19 diagnosis according to the World Health Organisation (WHO).

Studies have demonstrated olfactory dysfunction secondary to COVID-19 to carry a good prognosis with most cases resolving within 15 days. In the pre-COVID era the incidence of olfactory dysfunction secondary to infection was 11% with up to 39% presenting to specialist clinics.[9,10] However with the emergence of COVID-19 this figure has increased up to as high as 98% in some studies. [45]

Our systematic review revealed females to be most affected by delayed recovery of smell acuity. This is similar to previous studies on post-viral olfactory dysfunction which have demonstrated female predilection as well.[46] Risk factors which would present as potential predictive factors mentioned included smoking and co-morbidities such as hypertension, asthma, depression, diabetes mellitus, heart disease, oncological conditions or treatment, autoimmune disease, neurological disease and renal failure. Most of the aforementioned factors are known causes of olfactory dysfunction.[47]

Risk factors for delayed recovery of olfactory dysfunction include the elderly population due to increased expression of transmembrane serine protease, the presence of rhinological symptoms associated with COVID-19 (such as nasal congestion and rhinorrhoea), pre-existent sinonasal disease and severe hyposmia or anosmia at onset. Jalessi et al[31] also reported an interesting finding of gastrointestinal symptoms (diarrhoea) associated with a 4.65 times increased risk of delayed olfactory recovery which was statistically significant. This was postulated to be due to ACE-2 receptors which are high in concentration in gastrointestinal epithelium as well as nasal goblet cells and ciliated cells. The presence of a pre-existing risk factor together with the additive insult of SARS-CoV-2 as an aetiology may result in poor outcomes for recovery. There was no separation in the included studies between cases that

possessed risk factors and those that did not as a control group to determine and compare outcomes. This would be an area of focus for further studies. [31]

Only one included study used objective testing for assessment of chemosensory function while the other studies used subjective questionnaires.[10] The pitfalls of these subjective studies is recall bias and there is no universal scale used for grading chemosensory dysfunction which made comparison of the results of the studies difficult.

For the studies that included cases with persistent symptoms beyond 12 weeks management was not mentioned. There is currently no standard treatment for post-viral olfactory dysfunction. A systematic review by Addison et al [9] highly recommended olfactory training as treatment for post-viral olfactory dysfunction and its outcomes. There is good evidence for the efficacy of olfactory training to improve olfactory function and it is good as initial treatment as it potentially avoids the use of pharmacological agents which may have potential adverse effects.[9,11]

The most effective pharmacological treatment has not yet been determined and ongoing trials are still underway. As a potential preventative measure in vitro studies have shown that camostat mesylate which is a protease inhibitor can block entry of SARS-CoV-2 into the cells. There are also theories that nasal irrigation with ACE-2 antagonists or angiotensin receptor blockers may reduce or remove the viral load in active disease and decrease the incidence and severity of post-viral olfactory dysfunction. This may be an option for patients who have positive predictive factors for late recovery.[11]

Other otorhinolaryngological symptoms reported in our systematic review that persisted beyond 12 weeks were audiovestibular symptoms (sensorineural hearing loss, tinnitus, vertigo) and laryngological symptoms (dysphonia) accounting for 8,6% and 10,5% of cases respectively.

Cochlear dysfunction beyond 12 weeks of COVID-19 diagnosis revealed males and females to be equally affected with an age range of 18-67 years. All cases presented with a sudden onset of sensorineural hearing loss. The incidence of viral induced cochlear dysfunction is unknown, although our findings do agree with other studies on idiopathic sudden sensorineural hearing loss which show no gender preference and a wide age range with poorer prognosis observed in cases older than 60years.[48] Sudden onset hearing loss comes with great anxiety prompting an early presentation in most cases. This is of importance as the timing of presentation has prognostic implications with patients who present earlier carrying a better outcome.[49]

Majority (75%) of the cases had comorbidities which could have contributed to the hearing loss.[6,23,41] Two cases also received known ototoxic drugs for their comorbidities and in the case of one patient for the treatment of his severe COVID-19 which also may have contributed to the worsening in hearing.[6,41] The limitation of the studies in this regard was the lack of testing baseline cochlear function prior to contracting COVID-19 except in one case who had an audiogram a year prior to her COVID-19 diagnosis.[41] This case demonstrated pre-existing hearing loss on her

previous audiogram which may be attributed to her comorbidity of Rheumatoid Arthritis and her being on hydroxychloroquine a known ototoxic drug for 4 years.[41] This case after contracting COVID-19 had subsequent worsening in her hearing thresholds on serial audiograms and this could have been caused by SARS-CoV-2 itself which was an added insult.

All the cases with post-COVID syndrome with cochlear dysfunction had pure tone audiometry which was diagnostic for sensorineural hearing loss and the severity ranged from moderate to profound. Audiometry can be used to determine prognosis with patients presenting with profound hearing loss and a down-sloping pattern carrying the worst prognosis.[49] All patients had MRI scans as well for which there were abnormalities in 75% of cases which assisted with diagnosis particularly in one case with intralabyrinthine haemorrhage.[37]

The management reported in all studies for sudden sensorineural hearing loss was systemic and/or intratympanic corticosteroids. Corticosteroids resulted in minimal improvement in this particular group of patients with cochlear dysfunction beyond 12 weeks. This may be due to the patients presenting with severe or profound sensorineural hearing loss at onset as opposed to mild and moderate severity which would have carried a better prognosis.[49] Corticosteroids have been used as the standard treatment for sudden sensorineural hearing loss and has been shown to be beneficial with improvement in hearing thresholds in a number of studies.[50–52] Each patient however should be individualised when considering systemic corticosteroid treatment particularly in those who have high risk of adverse effects.[49]

Hyperbaric oxygen therapy has been used and advocated for in early treatment of sudden sensorineural hearing loss and is considered as salvage therapy together with evidence of improvement demonstrated in some studies.[53–55] It entails delivering 100% oxygen at a pressure higher than 1 atmosphere which results in improved oxygenation that manages ischaemia within the microvasculature of the inner ear. The down-falls are that it is expensive and not available in some institutions and it is also time consuming.[53,55] This may be a consideration for treatment of refractory cochlear dysfunction secondary to COVID-19. Another option would be hearing aids or following the surgical route through cochlear implantation.[5,6]

Vestibular dysfunction as a symptom persisting beyond 12 weeks was described in two studies, one in which the symptoms were isolated to the vestibular system[28] and the other in which audiological symptoms occurred simultaneously in addition.[37] Both cases described vestibular symptoms with potentially different mechanisms. Garcia-Roma et al [28] described a young healthy female presenting with dizziness and horizontal nystagmus of a duration 10-15 seconds with multiple episodes per day. Although a diagnosis was not indicated by the authors, the clinical picture described appeared to possibly be in keeping with Benign Paroxysmal Positional Vertigo (BPPV). Other included studies have also reported BPPV as a vestibular disorder associated with COVID-19.[30]

BPPV may occur secondary to multiple aetiologies of which viral labyrinthitis accounts for approximately 15%.[30] Two established theories of how BPPV occurs exist and these are cupulolithiasis and canalithiasis.[30,56,57] The possible mechanism through which cupulolithiasis and/or canalithiasis occur is molecular and metabolic

dysregulation leading to loss of the otolithic membrane integrity and escape of otoliths.[57] One possible reason for this dysregulation is as a response to inflammation and disruption by proinflammatory cytokines. This could be considered the case with SARS-CoV-2 in which one of the mechanisms of disease is induced by its inflammatory effects.[30]

BPPV has a predilection for elderly females which is contrary to the age of the case by Garcia-Romo et al [28] though there was agreement with the gender. The typical history of BPPV is a patient who presents with vertigo or dizziness and nystagmus associated with positional changes or head movement lasting less than one minute. It is diagnosed clinically through head positional manoeuvres such as the Dix-Hallpike test (for posterior semicircular canal BPPV) which are part of the vestibular examination.[57,58] Special investigations in the form of laboratory tests or imaging are rarely needed for diagnosis unless clinically indicated from history or examination to ascertain a specific aetiology in the case of secondary BPPV. Garcia-Romo et al's [28] case did undergo vestibular testing which was normal although they did not go into detail of the type of testing done.

As management for BPPV canalith repositioning manoeuvres which include Epley's repositioning manoeuvre amongst others are the gold standard of treatment which have a good outcome.[30,56–58] Management was not mentioned in Garcia-Romo et al's [28] study but was mentioned by Maslovara et al [30] who reported the use of the Epley manoeuvre as management of two cases with BPPV believed to be due to COVID-19. Studies have demonstrated Vitamin D supplementation to be of benefit in recurrent cases or cases with low serum levels.[58] This may be considered in patients presenting with post-COVID syndrome with vestibular dysfunction attributed to BPPV as an adjunct to repositioning manoeuvres.

Chern et al [37] described a young female who presented with vertigo associated with nausea and vomiting in addition to aural fullness, sensorineural hearing loss and chemosensory loss she experienced as a result of COVID-19. More detail on the vestibular symptoms was not provided in terms of the duration and vestibular examination findings however the underlying aetiology was revealed through MRI in which there were features of intralabyrinthine hemorrhage within the vestibule, lateral and superior semicircular canals bilaterally.[37]

Intralabyrinthine haemorrhage is a rare condition that usually occurs as a result of trauma, bleeding disorders or anticoagulant therapy.[59] Chern et al's [37] study was the first of its kind to present a virus which was SARS-CoV-2 as a possible cause for intralabyrinthine haemorrhage. It was postulated that the inflammatory response induced by SARS-CoV-2 causes dysregulation in the coagulation cascade that results in coagulopathy and microhemorrhaging in the inner ear. Another possible consideration is injury and loss of integrity of the endothelium from pro-inflammatory effects induced by SARS-CoV-2 at a molecular level which is especially significant to the inner ear which has delicate microvasculature.[60]

Intralabyrinthine haemorrhage regardless of the underlying cause from available literature has been treated with systemic and/or intratympanic corticosteroids which have demonstrated improved audiovestibular function.[37,59] This was the case in Chern

et al's [37] patient who although had minimal change to her hearing had a significant improvement of her vestibular symptoms.
These two cases with persistent vestibular dysfunction were both healthy and young with no risk factors. The mechanism of vestibular dysfunction was also different with these two cases. Further and more detailed studies on this particular population of patients are needed in order to identify the risk factors that would predispose certain individuals to vestibular disorders.

Post-COVID syndrome in laryngology presented as persistent dysphonia in two included studies, one of which was a paediatric study.[14,35] Leis-Cofino et al's [35] study revealed dysphonic patients to be predominantly female with mean ages within the 5th decade. These demographics are similar to previous studies done in the pre-COVID-19 era that investigated post-viral vagal neuropathy from other upper respiratory tract infections.[61,62] Two theories for the mechanism of vagal neuropathy have been postulated to be the direct invasion of laryngeal nerves by a virus or inflammation of the laryngeal nerves indirectly as a result of the inflammatory response mounted by a viral infection. Both theories ultimately lead to vagal neuritis and neuropathy.[61]

Risk factors were reported by Leis-Cofino et al [35] which were a current or previous smoking history and comorbidities such as obesity, diabetes mellitus, dyslipidemia and hypertension. These risk factors were however statistically insignificant when comparing patients with persistent dysphonia and the control group with no dysphonia.

Vagal neuropathy secondary to SARS-CoV-2 clinically manifests as dysphonia, voice fatigue, coughing, clearing of the throat, dysphagia and odynophagia.[63] Both studies reported cases with dysphonia and dysphagia with a higher incidence in those who were previously intubated.[14,35] This higher incidence is likely due to mechanical injury and subsequent inflammation of the upper aerodigestive tract from instrumentation and insertion of endotracheal tubes and nasogastric tubes. This is not only traumatic in the emergent setting but also during maintained intubation and during the process of extubation and suctioning thereafter.[64] Despite intubation being a known contributory factor for dysphonia and dysphagia, the potential effects of SARS-CoV-2 on the upper aerodigestive tract and its nerve supply cannot be ignored particularly in persistent cases and cases who were not intubated.[14,35]

Objective evaluation of the patients in the included studies were through use of established voice scales such as GRBAS. Definitive diagnosis was reached through endoscopic assessment of the upper aerodigestive tract with fibreoptic video laryngoscopy and stroboscopy.[14,35] The most common findings in Leis-Cofino's [35] study were vocal cord weakness or paralysis in the ICU admissions and vocal cord atrophy in the ward admissions. Halfpenny et al's[14] study on the contrary demonstrated generalised laryngopharyngeal weakness as the predominant finding in dysphonic children. The mechanisms as to how these possibly occurred have already been explained.

In Leis-Cofino's [35] study vocal cord atrophy was more common in ward cases who were not intubated. This was an interesting finding which would be an area for further research into the pathophysiology. Vocal cord atrophy is a rare condition which is commonly a result of aging in which case it is termed 'presbylaryngis'. Other causes

include hormonal changes, inflammation and ischaemia which lead to denervation and degeneration of the vocal cords.[65] Of these causes SARS-CoV-2 would be implicated in the inflammatory and ischaemic effects potentially.

Management was reported in Halfpenny's [14] study which was in keeping with standard principles of treatment for post-viral vagal neuropathy. Conservative treatment includes anti-reflux medication as laryngopharyngeal reflux is a condition that is prevalent in post-viral vagal neuropathy. Other conservative treatment icludes anti-allergy and anti-neuralgic medication if indicated and of great importance voice therapy.[14,61,63] Surgical options for treatment include medialisation procedures of which one patient in Halfpenny et al's [14] study received injection laryngoplasty and voice therapy thereafter.

This systematic review sought to present the clinical manifestations of post-COVID syndrome from an Otorhinolaryngological perspective and to identify positive predictive factors which were achieved mainly in the rhinological studies investigating olfactory dysfunction. This was most likely due to olfactory dysfunction occurring more frequently than other otorhinolaryngological manifestations and thus there being more available data and larger study numbers. The limitation however of the rhinological studies is the use of subjective testing in most studies which would possibly affect the credibility of results due to factors such as recall bias. Special investigations and management of patients appeared to follow the same principles as for other aetiologies of dysfunction in the respective categories.

There were a number of limitations encountered in this study of which the main limitation was the lack of high quality data due to the novelty of COVID-19. Majority of the data in the available literature and in the included studies of this systematic review were cohort studies, case series and case reports. Identification of positive predictive factors was challenging as not all studies went into detail with demographics, comorbidities and risk factors, and when potential risk factors were mentioned there was no distinction between the group of patients with persistent symptoms and the control groups with the exception of one study.[35] The data obtained may also not be an accurate statistical representation of patients with post-COVID syndrome in Otorhinolaryngology and may be an underestimation of its true prevalence as the data obtained was restricted to the timeframe of follow up reported by the authors with missing information on long-term outcomes.

7. CONCLUSION

Post-COVID syndrome like acute COVID-19 manifests in multiple systems in the body which include the ear, nose and throat. Otorhinolaryngological symptoms that this population presents with include olfactory dysfunction, audiovestibular dysfunction and dysphonia. Olfactory dysfunction is the dominant presentation with more data available in the literature as it presents more commonly. There is need for larger and more detailed future studies with focus on identification of specific risk factors that predispose individuals to post-COVID syndrome with the goal of improving outcomes and preventing long-term disability.

8. FUNDING

No funding was required. The costs for research, data collection and printing were covered by the researchers.

9. ACKNOWLEDGEMENTS

I would like to acknowledge and express my gratitude to my supervisor Professor. Maharaj for his guidance, support and patience during this project.

I would also like to acknowledge and thank my parents Misheck and Josephine Zvemusi Chiware, my sisters Ruth and Tendai Chiware and my friends Tariro Ngombe and Stacy Jose for their unwavering support and encouragement throughout my career and this project.

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Table 3 Studies Included in the Systematic Review

Title	Authors	Country	Study type	Number of patients	Demographics	Co-morbidities	Signs and symptoms
Bilateral Sudden Sensorineural Hearing Loss and Intralabyrinthine Hemorrhage in a Patient With COVID-19	Chern A et al (2021)	United States of America	Case Report	1	18 years Female	Nil	Bilateral Sensorineural hearing loss Tinnitus Aural fullness Vertigo Nausea and Vomiting
COVID-19 and Tinnitus	Chirakkal P et al (2021)	Qatar	Case Report	1	35 years Female	Nil	Unilateral Sensorineural hearing loss Tinnitus
COVID-19 and sudden sensorineural hearing loss, a case report	Rhman SA (2020)	Egypt	Case Report	1	52 years Male	Nil	Unilateral Sensorineural hearing loss Tinnitus
Sudden irreversible hearing loss post COVID-19	Koumpa FS et al (2020)	United Kingdom	Case Report	1	45years Male	Asthma	Unilateral sensorineural hearing loss Tinnitus

Could sudden sensorineural hearing loss be the sole manifestation of COVID-19? An investigation into SARS-COV-2 in the etiology of sudden sensorineural hearing loss	Kilic O et al (2020)	Turkey	Case Series	5	Age range 29-54 years mean age 40.8 years All males	Nil	Unilateral sensorineural hearing loss
A 67-Year-Old Woman with Sudden Hearing Loss Associated with SARS-CoV-2 Infection	Lamounier P et al (2020)	Brazil	Case Report	1	67years Female	Rheumatoid arthritis	Unilateral sensorineual hearing loss Tinnitus
Coronavirus disease 2019 and sudden sensorineural hearing loss	Lang B et al (2020)	Ireland	Case Report	1	30years Male	Nil	Unilateral sensorineural hearing loss Tinnitus
Hearing Loss in a post COVID-19 patient	Chakraborty S et al (2021)	India	Case Report	1	49 year old male	Diabetic	Bilateral Hearing loss
Bilateral Sudden Sensorineural Hearing Loss Post-COVID-19 'A Case Report'	Alanazy SM (2021)	Saudi Arabia	Case report	1	55year old female	Diabetic Hypertension	Tinnitus Bilateral severe sensorineural hearing loss
Neurotological Manifestations of Patients with COVID-19	Eravci F, Alafifi M, Dundar MA et al (2021)	Turkey	Case series	71	Age 18-90 Gender not mentioned		41 with vertigo 16 hyperacusis 14hearing loss.

Cochlear implantation for single-sided deafness after COVID-19 hospitalisation	Asfour L, Kay-Rivest E, Ronald T (2021)	USA	Case Report	1	34year old male	Obesity, Gout, Sjogren's disease	Unilateral profound Sensorineural hearing loss Tinnitus
Sudden Sensorineural Hearing Loss in Mild COVID-19: Case Series and Analysis of the Literature	Ricciardiello F, Pisani D, Viola P et al (2021)	Italy	Case Series	5	2 females age range 26-46years 3 males age range 22-61 years Mean 37.6 years	Nil	Tinnitus SSNHL Aural fullness Vertigo hyperacusis
Sudden sensorineural hearing loss in COVID-19: A case report and literature review	Beckers E, Chouvel P, Cassetto et al (2021)	Belgium	Case Report	1	53year old male		Sensorineural hearing loss
COVID-19 presenting with nystagmus.	Garcia-Romo E, Blanco R, Nicholls C et al (2021)	Spain	Case Report	1	20year old female		Vertigo

A case series of vestibular symptoms in positive or suspected COVID-19 patients	Malayala SV, Mohan G, Vasireddy D et al (2021)	USA 2021	Case Series	6	All female Age range 29-71 years, mean 47.7 years		Vertigo, nausea, vomiting, imbalance/instability
Post-COVID-19 Benign Paroxysmal Positional Vertigo	Maslovara S, Košec A (2021)	Croatia	Case report	2	2 females age range 28-41 years mean 34.5		Vertigo, nausea and vomiting
The outcome of olfactory impairment in patients with otherwise paucisymptomatic coronavirus disease 2019 during the pandemic	Jalessi M, Bagheri SH, Azad Z (20210)	United Kingdom	Case series	243 with olfactory dysfunction. 139 patients in post covid period residual sym	155 females 88male Mean age 32.96+/-9.47		Hyposmia, anosmia, fever, gastrointestinal (diarrhoea)

				ptoms >4 weeks(47.95 +/- 12.44days)			
COVID-19 Recovery from Chemosensory Dysfunction. A Multicentre study on Smell and Taste	Niklassen AS, Draf J, Huart C (2020)	Germany	Case series	Total 103 patients with chemosensory dysfunction: 79 had acute hyposmia/anosmia	59 male 52 female Mean age 44.5 Ages 18-39 (45pts) 40-69 (61) >70 (5) No statistical diff between the sexes or age groups		Loss of smell and taste

				and post infection 24pts still persistent/improved or new onset			
Incomplete and late recovery of sudden olfactory dysfunction in COVID-19	Kosugi EM et al (2020)	Brazil	Case Series	253 olfactory dysfunction patients	149 females 104 male median age 36 age range 30-45	62 patients with comorbidities	Smell loss
Eight-month follow-up of olfactory and gustatory	Biadsee A, Dagan O and	Israel	Cohort	65 with che	16women and 9 men	Not mentioned	Dysgeusia/ageusia Hyposmia/anosmia

dysfunctions in recovered COVID-19 patients	Ormianer Z et al (2021)			mos ens ory dysf unct ion	(25people) mean age 43 +/- 17.4years with partial recovery dysgeusia after 8months 3 women and 2men (5 people)no improveme nt 20women and 11 men (31 people) mean age 37.7+/- 18.1 years partial recovery hyposmia after 8 months 3men and 2 women (5 people) no improveme		

					nt hyposmia		
Recovery rate and factors associated with smell and taste disruption in patients with coronavirus disease 2019	Parente-Arias P et al (2020)	Spain	Cohort	99 have chemosensory dysfunction: 67.7% (67/99) anosmia or ageusia, 8.1% (8/99) parosmia, 24.2% (24/	Olfactory dysfunction group: 75 patients 63.2%<60 years 31.2% >= 60years , 59.1% female 32% male Gustatory dysfunction: 91 patients 68.3% female	Majority no comorbidities. Others: hypertension, asthma, depression, diabetes, cancer or cancer treatment, heart condition, autoimmune disease, neurological, renal failure,	Olfactory dysfunction, gustatory dysfunction or both

				99) dysgeusia			
Dysphonia and dysphagia consequences of paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS)	Halfpenny R et al (2020)	United Kingdom	Cohort	8	Male predominance noncaucasian (black, Asian, other) Median age 10yrs 8months Age range 8-15yo		Dysphonia Dysphagia (One had pre-existent which worsened with PIMS-TS)
Prevalence of Dysphonia in Non hospitalized Patients with COVID-19 in Lombardy, the Italian Epicenter of the Pandemic.	Cantarella G et al (2021)	Italy	Cohort	70	No difference with sexes Age range 16-90	Smoking, obesity (did not say how many of smokers or obese were dysphonic)	Dysphonia
Persistent Dysphonia in Hospitalised COVID-19 Patients	Leis-Cofino C et al (2021)	Spain	Cohort	Total 79 of which dyspho	48men and 31 women Median age ICU 64.5yo Female (60%)	Obesity (80%) Dyslipidaemia hypertension	Dysphonia Dysphagia

				nic were 14 (10 previous ICU and 4 previous ward admissions)	Male 40% Median age ward 56.75+/-18.4 Females (75%) Males 25%		
Prevalence of dysphonia due to COVID-19 at Salahaddin General Hospital, Tirkit City, Iraq	Al-Ani RM et al (2021)	Iraq	Cohort	21	Mean age 64.24+/-15.97	Smokers hypertension	