

Otological Sequelae In RRT-PCR Proven Covid-19 Patients: A Comparative Study

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Abstract

Background

This is a prospective study which was conducted from April 2021 – May 2022 was undertaken with a aim to evaluate the Otological sequelae in Real-Time Reverse Transcription-Polymerase Chain Reaction proven COVID -19 patients. Seventy patients of either sex in age group of 18-45 years were enrolled in the study after obtaining their consent. The patients were divided into two groups. Group A comprised of thirty five rRT-PCR proven patients (after the patients were rRT-PCR negative) and group B comprised of thirty five healthy adults (with no history of COVID-9 infection).

Results

In group A: Out of 35 rRT-PCR proven COVID-19 patients, only 07 (20%) presented with complaint of hearing loss, 11 (31.43%) with Tinnitus and only 01 (2.86%) presented with vertigo. In group B the control group, no case had any complaint related to hearing, vertigo or tinnitus. Though only 07 (20%) patients presented with complaint of hearing loss, pure tone audiometry revealed hearing loss in 13 (37.14%) patients and out of them 7 cases (53.84%) had mild hearing impairment and 6 cases (46.15%) had moderate hearing impairment (41-60 dB). A significant trend noted in the study was the frequency specific involvement. In our study the hearing loss was more significantly affected the higher frequency and more so in 8 KHz. In group A, Out of total 35 patients, 11 (31.43%) patients had tinnitus and among them 07 patients belong to Grade-1 tinnitus & 04 patients belong to Grade-2 tinnitus according to Tinnitus Handicap Inventory grading system.

Conclusions

Hence, COVID-19 infection could have deteriorating effects on the cochlear hair cells function despite being asymptomatic. It primarily causes SNHL and mainly effects higher frequencies. Recovered COVID-19 patients should be inquired & assessed for possible otological involvement.

Keywords

SNHL, Hearing loss, COVID-19, Tinnitus, otological sequelae, ear manifestation of covid-19, Dizziness

Date of Submission: 03-01-2025

Date of Acceptance: 13-01-2025

I. Background

Coronavirus belongs to family of Coronaviridae. These are single stranded enveloped RNA viruses. The size of virus ranges from 60nm to 140 nm in diameter and it has spike like projections on its surface which gives these viruses a crown like appearance under the electron microscope. In 2003 a novel coronavirus was recognized in humans as the etiological agent of the outbreak of severe acute respiratory syndrome (SARS).¹ The SARS outbreak demonstrated that coronaviruses can be serious human pathogens. In 2012 the Middle East Respiratory Syndrome (MERS) coronavirus emerged and provided another example of the ability of coronavirus's to cause severe human disease.² Coronavirus disease 2019 is caused by a new coronavirus first identified in Wuhan, China in December 2019. An official name was announced by World Health Organization for the disease, on February 11, 2020. The name of the new disease, abbreviated as COVID-19, where 'CO' stands for 'corona', 'VI' for 'virus' and 'D' for disease. Formerly, this disease was referred as "2019 novel coronavirus" or "2019-nCoV". It is also called severe acute respiratory syndrome corona virus 2 (SARS CoV2).³

The symptoms usually noticed between 2-14 days after COVID-19 exposure. The clinical presentation may range from asymptomatic infection, mild infection to severe respiratory distress. The common clinical features include fever, cough, fatigue, gastro-intestinal disturbance, loss of taste, loss of smell and respiratory difficulty. COVID-19 is an evolving situation and with each passing month new symptoms attributable to the virus are reported. The virus has been associated with chronic malaise, respiratory difficulty and myocarditis even after recovery from the initial infection and many symptoms tend to persist even after the patient becomes negative on (rRT-PCR) test.^{4,6}

Nose and mouth are the commonest entry points of the virus and cough, rhinorrhea, loss of taste and loss of smell are common presenting symptoms. Otological involvement associated in COVID-19 patients has been reported recently. Many case reports and studies have suggested that COVID-19 is associated with hearing loss and tinnitus. The hearing loss may be unilateral or bilateral and mostly of sensorineural hearing loss (SNHL).⁷ In fact several viral infections are associated with hearing loss which includes mumps, measles, herpes virus which can result in unilateral or bilateral hearing loss which can be permanent.⁵ The present study was undertaken to assess the degree and type of hearing loss in COVID-19 patients, the association of tinnitus using Tinnitus Handicap Inventory and to compare the results of hearing loss and tinnitus with the control group of healthy adults with no history of COVID-19 infection.

II. Methods

The prospective study was conducted in Department of Otorhinolaryngology, Pt. B.D. Sharma PGIMS, Rohtak from April 2021 – May 2022. Seventy patients of either sex in age group of 18-45 years were included. Thirty five rRT PCR proven COVID - 19 patients who presented to the outpatient department were selected for the study & were included in the case group (group- A) while thirty five healthy volunteer from PGIMS staff and students with no history of COVID-19 infection were included in control group (group B). This study was approved by Institutional review board.

Patients in both groups underwent a detailed evaluation based on history, general physical examination as well as complete ear, nose and throat examination. All the cases were subjected to an otoscopic examination to evaluate the condition of the external ear and middle ear (tympanic membrane condition and mobility)

Pure-tone audiometry was done in all cases in group-A and group-B. Air conduction pure tone thresholds were tested at 250Hz, 500Hz, 1000Hz, 2000Hz, 4000Hz, and 8000Hz. Bone conduction pure tone thresholds were tested at 500Hz, 1000 Hz, 2000Hz and 4000Hz. The average of pure tone thresholds at 500Hz, 1000 Hz, 2000Hz and 4000Hz were used to estimate the level of hearing impairment. This is in accordance with the WHO criteria for hearing loss.⁸ Hearing average up to 0-25 were taken as normal. Patients with average hearing between 26-40 db were grouped in slight (mild) hearing impairment, 41-60 db as moderate impairment, 61-80 db as severe impairment and ≥ 81 db as profound impairment.

Inclusion Criteria

Group A

1. rRT-PCR proven COVID -19 patients (after the patients become negative on rRT-PCR).
2. age group of 18-45 years

Group B

1. Healthy adults with no history of COVID-19 infection
2. age group of 18-45 years

Exclusion Criteria

1. Patients with previous history of hearing loss and tinnitus.
2. Patients who have undergone any ear surgery in the past.

3. Underlying diseases which are associated with hearing loss such as diabetes, hypertension and chronic renal failure.

III. Results

Age And Sex Distribution

Group A

35 patients were involved in this group. There were 19 male (54.29%) and 16 female (45.71%). Patients ranged from 18 years to 45 years. Maximum patients belonged to age group 31-45, 21 cases (60%) (Table 1)

TABLE 1: age and sex distribution in group A

	18-30 years	31-45 years	Total	Percentage (%)
Male	4	15	19	54.3
Female	10	6	16	45.7
Total	14 (40%)	21 (60%)	35	100

Group B

Thirty five healthy volunteers were involved which included 12 male (34.3%) and 23 female (65.7%). All healthy volunteers belonged to the age group 18-30 years, 35 cases (100%). (Table 2)

TABLE 2: age and sex distribution

	18-30 years	31-45 years	Total	Percentage (%)
Male	12	00	12	34.3
Female	23	00	23	65.7
Total	35	00	35	100

Symptomology Of Cases

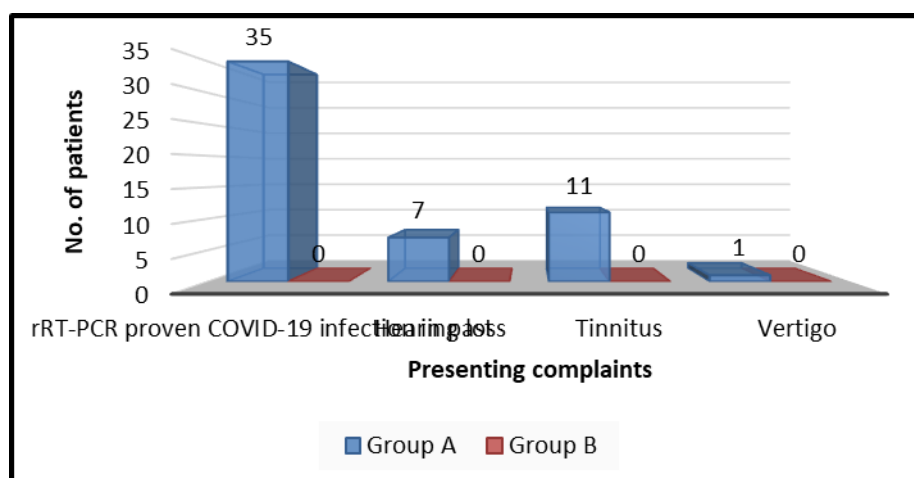
Presenting complaints: (Table 3 & graph 1)

In group A all the patients in this series had a history of rRT-PCR proven COVID-19 infection in the past, while group B comprised of healthy volunteers with no previous history of rRT-PCR proven COVID-19 infection.

In group A: Out of 35 rRT-PCR proven COVID-19 patients, only 07 (20%) presented with complaint of hearing loss, 11 (31.43%) with Tinnitus and only 01 (2.86%) presented with vertigo .In group B the control group, no case had any complaint related to hearing, vertigo or tinnitus (table 3 & graph1).

TABLE 3: Presenting complaints group A & group B

Presenting Complaint	No. of patients	
	Group A	Group B
rRT-PCR proven COVID-19 infection in past	35 (100%)	00
Hearing loss	07 (20%)	00
Tinnitus	11 (31.43%)	00
Vertigo	01 (2.86%)	00



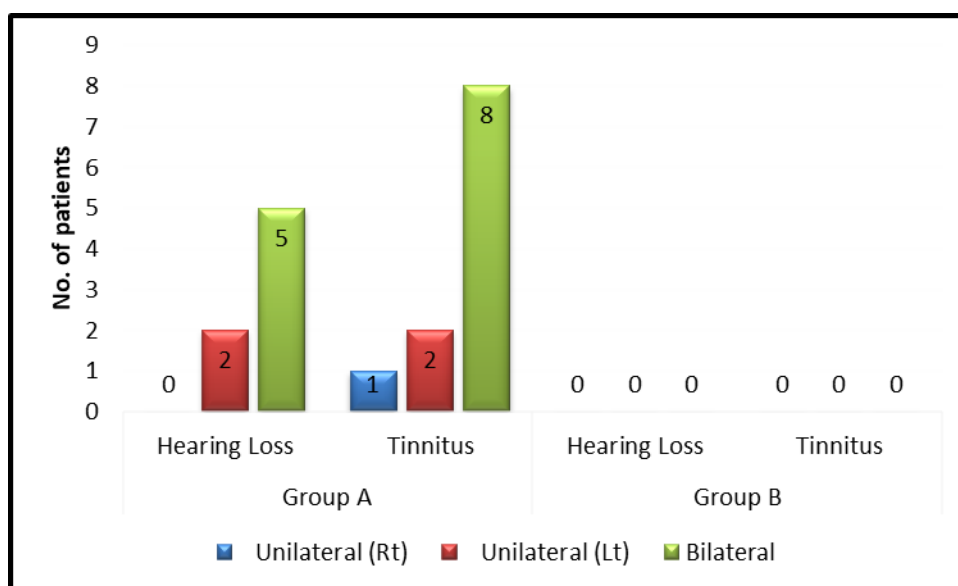
Graph 1: Bar diagram showing presenting complaints in group-A & group-B.

Ear Involvement

In group-A most of the cases were bilateral involvement of ear. Out of 07 (20%) patients presented with hearing loss, 05 had involvement of bilateral ear. Out of 11 (31.43%) patients presented with tinnitus, 08 patients had involvement of bilateral ear. (Table 4 & Graph 2)

TABLE 4: Ear Involvement of group-A & group-B

Ear involved	Total number of cases			
	Group A		Group B	
	Hearing Loss	Tinnitus	Hearing Loss	Tinnitus
Unilateral (Rt)	00	01	00	00
(Lt)	02	02	00	00
Bilateral	05 (71.43%)	08 (72.73%)	00	00
Total Cases	07 (20%)	11 (31.43%)	00	00



Graph 2: Bar diagram showing involvement of ear in both study groups

Otoscopic Examination

(A) Condition Of EAC

In both groups, no pathology was noted.

(B) Condition Of Tympanic Membrane (Table 5)

Group-A: 34 patients had normal appearing tympanic membrane and 1 patient had retracted tympanic membrane.

Group-B: All 35 healthy volunteers had normal appearing tympanic membrane.

TABLE 5: Condition of the tympanic membrane

Condition of tympanic membrane	Total number of cases	
	Group A	Group B
Normal intact	34 (97.14%)	35 (100%)
Retracted	1 (2.85%)	-
Dull	-	-

Audiological Assesment

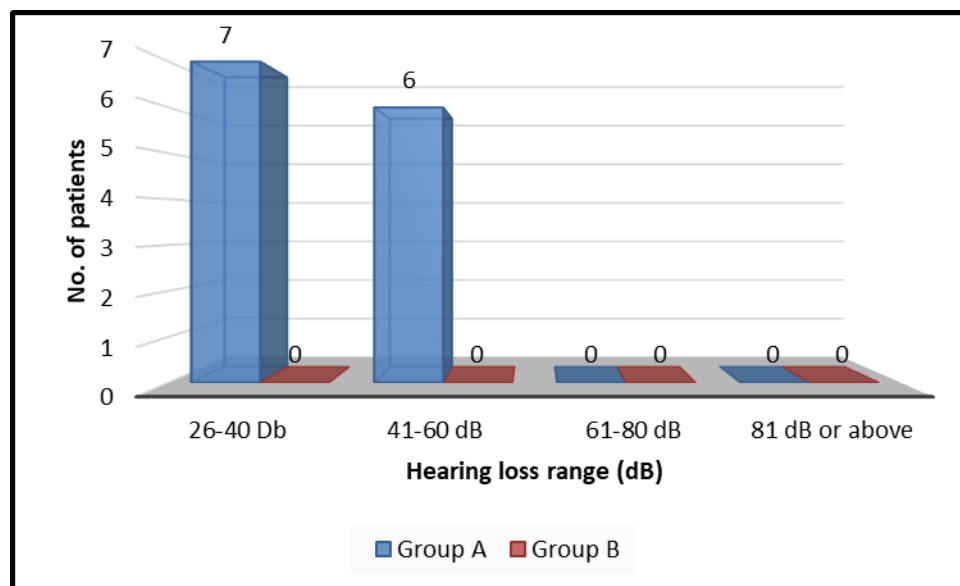
Based on the pure tone audiogram, hearing loss was classified as mild (26-40 dB), moderate (41-60dB), severe (61-80dB), profound (≥ 81 dB) according to **World Health Organisation (WHO)** classification of hearing loss.⁸

Though only 07 (20%) patients presented with complaint of hearing loss, pure tone audiometry revealed hearing loss in 13 (37.14%) patients.

Table-6: Comparison of hearing loss in group A & group B in accordance to WHO classification.

Grade of impairment	Hearing loss range (dB HL)	Total number of patients (%)	
		Group A	Group B
Slight impairment	26-40 Db	7 (53.84 %)	00
Moderate impairment	41-60 dB	6 (46.15 %)	00
Severe impairment	61-80 dB	00	00
Profound impairment	81 dB or above	00	00
TOTAL	-	13 (37.14 %)	00

In group A, out of 35 patients, 13 (37.14 %) patients had hearing loss out of which 07 (53.84 %) patients were having hearing loss in the range 26-40 dB and 06 (46.15 %) patients were having hearing loss in the range 41-60 dB while in group B, hearing was within normal limit (Table-6 & graph 3).



Graph 3: Bar diagram showing hearing loss according to WHO classification among both study groups

Tinnitus Assessment

In group A, Out of total 35 patients, 11 (31.43%) patients had tinnitus and among them 07 patients belong to Grade-1 tinnitus & 04 patients belong to Grade-2 tinnitus according to Tinnitus Handicap Inventory grading system.⁹ In group B, none of the enrolled cases had a history of tinnitus (Table 7).

Table 7: Tinnitus Handicap Inventory grading and Score

Grades of THI	THI score	Number of Patients (group A)	Number of Patients (group B)
Grade 1	0-16	7	0
Grade 2	18-36	4	0
Grade 3	38-56	0	0
Grade 4	58-76	0	0
Grade 5	78-100	0	0
TOTAL		11 (31.43%)	00

IV. Discussion

Coronaviruses are divided into 4 essential subgroups: alpha, beta, gamma, and delta. Coronaviruses as infective agents in humans has been recognized since 1960. In humans, the 4 prevalent corona viruses (229E, OC43, NL63, and HKU1) typically cause common respiratory symptoms. Usually they are known to cause mild infection but Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infections resulted in large scale epidemics, with mortality rates of 10% for SARS-CoV and 37% for MERS-CoV.^{1,2,10} Similarly SARS-CoV-2 proved to be a highly infectious virus.

With a incubation period ranging from 2 to 14 days, SARS-CoV-2 usually manifests with fever, dry cough, fatigue and sore throat, loss of smell and taste accompanied by headache, nausea, vomiting. The symptoms of COVID-19 range from mild, moderate to serious illness among the affected individuals.^{10,11}

Viral infections have been implicated in hearing loss which can result either from direct or indirect injury to the inner ear. Cytomegalovirus, herpes simplex, rubella, hepatitis, mumps & varicella zoster viruses

have been reported to cause hearing loss. The earlier reported corona virus causing pandemics were SARS CoV, MERS CoV were not associated with hearing loss but hearing loss has been reported to be associated with SARS CoV-2 infections. SARS COV-2 is thought to cause hearing loss like most other viral infections. Various theories explaining the hearing loss includes immune mediated damage, ischemic theory, inflammation of the auditory pathway and involvement of Angiotensin Converting Enzyme (ACE-2) receptors in the neurons of the glial cells.^{7,12,13} Three possible mechanisms are proposed to cause hearing loss in viral infections neuritis: caused by viral involvement of the cochlear nerves, cochleitis: due to viral involvement of the cochlea and perilymphatic tissues and stress response: resulting from cross reactions of the inner ear antigen to viral infection.¹⁴

Numerous case reports have been published in which SARS - COV-2 patients were reported to present only with hearing impairment. The predominant type of hearing loss associated with COVID- 19 infection was sensorineural type hearing loss. Later a few studies were reported exploring the relation of SARS - COV-2 with hearing loss. We have taken a prospective study at PGIMS Rohtak for evaluation of relation between SARS-COV- 2 and hearing loss.

Seventy patients of either sex in age group of 18-45 years were enrolled in the study after obtaining their consent. The patients were divided into two groups. Group A comprised of thirty five rRT-PCR proven patients (after the patients were rRT-PCR negative) and group B comprised of thirty five healthy adults (with no history of COVID-9 infection). All patients selected in group A had a history of rRT- PCR proven COVID-19 infection in the past , while group-B had no previous history of rRT – PCR proven COVID-19 infection. Case inclusion in the group A is similar to that of Ozturk B et al.¹⁵ Participants in Ozturk B et al study were also diagnosed with COVID -19 by PCR at least one month prior to inclusion in the study. All patients had mild COVID -19 diseases in the past.

Cases in both group A and group B with history of pre -COVID hearing loss, history of noise exposure, ear discharge, ear surgery, and diabetes were excluded from the study. This is in accordance to other studies by Ozturk B et al¹⁵ and Durgut O et al.¹⁶

In the case group (Group A) there were 19 male and 16 female patients while in the control B (Group B) there were 12 male and 23 female volunteer. Case selection in our study is similar to the study of Ozturk B et al.¹⁵

In the present study age of participants in both case group & control group was between 18 and 45 years, to minimize the possible effects of aging on the auditory system. This is in accordance to the study of Ozturk B et al.¹⁵

In Group A maximum patients 21(60%) belonged to age group 31- 45 and rest 14(40%) were between 18 - 30 years .While in group B all volunteer belonged to age group 18-30 years. Otoscopic examination was performed on all participants both to group A & group B.

In group A : In rRT PCR group (Group A) the otological reason for seeking medical care was seen in only 19 out of 35 patients. Seven (07) patient presented with chief complaints of hearing loss, one patient with feeling of vertigo, while maximum i.e. eleven (11) patients had tinnitus as the chief presenting complaint. The remaining 16 patients had other chief complaints including ear heaviness, ear pain, headache, fatigue and GERD etc. No case in control group had any otological or any other complaint.

The presenting complaints suggest that post COVID-19 infection, there may be otological & others complaints for which patient may seek medical advice. This suggests that COVID-19 cases after resolution of acute episode may still pose problems for the patients. These features suggest that patients should remain on follow up for possible long COVID syndrome.

The presenting complaints in our case study are similar to the studies of others. Ozturk B et al¹⁵ in their study reported that in there series of 30 post COVID – 19 patients, two case complained of hearing loss during COVID-19 episode and 5 patients (16.7%) after recovery from acute COVID - 19 episode. 11 (33.3%) patients presented with tinnitus, one (3.3%) with ear pain and one (3.3%) with fullness of ear.

Dharmarajan S et al¹⁷ in their study of 100 post- COVID patients reported that 31 out of 100 patients had ear symptoms, with 12 (39%) out of 31 patients had chief complaints of tinnitus.

Freni F et al¹⁸ in their study of 50 post COVID-19 patients reported that post COVID - 19 resolution, only 40% (20) cases reported the appearance or worsening of hearing loss, while tinnitus was seen in 20% (10) cases.

In our study most patients had bilateral involvement of ears. Out of 7 cases who presented with hearing loss 05 (71.43%) cases had complaints related to both ears while only 02 cases had complaint of unilateral hearing loss. Similarly out of 11 patients presenting with tinnitus, 08 (72.73%) patients had complaint related to both ear while only 03 cases had unilateral complaint of tinnitus. No otological complaints were seen in volunteer group (group-B).

Otoscopic examination was done on all participants in the present study. In group A, 34 (97%) patients had normal tympanic membrane and one (3%) had retracted tympanic membrane while in group-B, all

volunteers had a normal appearing tympanic membrane, while in both group A & B, external auditory canal (EAC) was normal in all cases. Our findings are in accordance to the findings of study of Dharmarajan S et al.¹⁷ The author reported normal external auditory canal in all cases and normal Tympanic membrane in 95% of cases with only 4% of cases showing retraction of tympanic membrane and 1% had a dull tympanic membrane.

Hearing loss was the chief presenting complaint in 7 (20%) cases in the group-A however on pure tone audiometry 13 (37.14%) cases had hearing loss. This is accordance to study of Dharmarajan S et al¹⁷, the authors reported that 11 (11%) cases had hearing loss as presenting complaint but on PTA 53% cases were found to have sensorineural hearing loss, implying that the incidence of hearing loss on PTA was higher and the patients may not be aware of underlying hearing loss. This may be because only the higher frequencies are involved. Dusan M et al¹⁹ in their study to evaluate incidence of hearing loss in COVID-19 patients found hearing loss in 30 (40.5%) out of a total of 74 patients.

In our study out of a total of 13 (37.14%) cases with hearing loss, 7 cases (53.84%) had mild hearing impairment and 6 cases (46.15%) had moderate hearing impairment (41-60 dB). A significant trend noted in the study was the frequency specific involvement. In our study the hearing loss was more significantly affected the higher frequency and more so in 8 KHz. Similar findings were reported by Ozturk B et al.¹⁵ Mustafa MW et al²⁰ in their study of 20 asymptomatic COVID19 patients also reported that hearing was specially affected in the high frequency (4 KHz & 8 KHz).

Dharmarajan S et al¹⁷ also reported a high frequency hearing loss in their series of 100 COVID-19 patients. Rhman SA et al²¹ reported that post COVID-19 patients had sensorineural type of hearing loss in particularly involving frequency of 8 KHz. The hearing loss pattern in our study was thus in accordance to that reported by other authors. The hearing loss was primarily of SNHL and mainly affecting the higher frequencies 4 KHz & 8 KHz with loss at 8 KHz >4 KHz.

The period of audiological assessment varied from three to eight months post COVID-19 recovery. This is in accordance to other studies. Dusan M et al¹⁹ also enrolled patients post COVID-19 recovery. In the study Ozturk B et al¹⁵ participants were diagnosed with rRT-PCR at least one month before enrolment in the study. In the study by Durgut O et al¹⁶ the period of performing PTA varied from 3 to 12 months post COVID19 recovery. These findings are suggestive of possibility that hearing loss in post COVID-19 recovery phase can persist for a longer time and not all patients are aware of the underlying hearing loss. It may be due to the fact that SNHL caused in the post COVID phase precisely affects the higher frequencies.

Tinnitus is typically referred to as the perception of sound in the absence of an acoustic stimulus or that is generated by ear, structure in the ear and is commonly defined as ringing in one or both ears.²² Tinnitus has been linked to stress & related disorders. Individual's emotional states appear to be an important factor in mediating the effects of tinnitus loudness with anxiety, de-motivation and depression being possible mediation in tinnitus related distress. An increased incidence of post COVID-19 tinnitus was a noted as the presenting complaint in our study which is in accordance to the study of Ozturk B et al¹⁵ and Dharmarajan S et al.¹⁷

In our study a total of 11 (31.43%) patients out of 35 presented with complaints of tinnitus. Ozturk B et al¹⁵ in their study of 30 post-COVID patients reported 8 cases with persistent tinnitus. Durgut O et al¹⁶ in their study of 20 cases reported 4 cases with tinnitus. While Dharmarajan S et al¹⁷ reported tinnitus in 31 (31%) out of 100 post -COVID cases. Our findings of tinnitus in post-COVID patients are thus in accordance to other studies.

All patients were assessed regarding tinnitus using Tinnitus Handicap Inventory (THI).⁹ It is a 25 item self report measure to determine perceived tinnitus handicap severity. The THI comprises of 25 items, grouped into three sub scales: functional, emotions and catastrophic. The THI is scored from 0-100 where higher score indicates more Tinnitus Handicap Severity. The THI score of 0-16 (grade-I) indicates slight or no handicap, THI score of 18-36 (grade-II) indicates Mild Handicap, THI score of 38-56 (grade-III) is associated with moderate Handicap, THI score of 58-76 indicates severe handicap while, a THI score of 78-100 (grade -V) indicates catastrophic handicap.

Out of the total of 35 cases in the present study, 11 had tinnitus, with 7 cases having grade-1 tinnitus and 4 cases falling grade-2. Patient in grade-1 does not interfere with sleep or daily activities and patient with mild (grade-2) tinnitus required counselling. All patients were advised to continue on follow up beyond the period of study.

One case in our study presented with history of vertigo. However on examination positional test, Romberg test, spontaneous nystagmus and other tests were negative. Galougahi MK et al²³ also reported one case of vertigo in their case series of 6 cases. SARS-CoV-2 neurotropism may make it possible to inflict a wide spectrum of neuropathic effects, potentially including effects on neural network governing hearing and possible.

COVID-19 can damage the auditory system in various ways already discussed. It is possible that SARS CoV-2 may causes damage to the outer hair cells in cochlea, especially at higher frequencies. Ozturk B et al¹⁵ used Auditory Brainstem Response (ABR) test to evaluate the effects of COVID-19 on the brain stem. The authors reported prolongation in I, III and V absolute latencies in the test group suggesting the possibilities of

cochlear damage at higher frequencies rather than neural pathology and or brainstem damage. On the pure tone audiometry the authors found that only frequencies 4K Hz & 8K Hz deteriorated significantly in individuals with COVID-19. This is in concurrence with our study. Similarly Mustafa MW et al²⁰ also reported involvement of higher frequency 4k & 8k Hz. The authors also reported significant decrease in transient evoked otoacoustic emission (TEOAE) thresholds. These findings suggest that like other neurotropic viruses, SARS CoV-2 causes damage in the organ of Corti & hair cells. TEOAEs can pick up subtle deterioration in the outer hair cell function. Thus, suggesting the possibilities that this deterioration could be attributed to the damaging effects of viral infection on the outer hair cells.

Dharmarajan S et al¹⁷ reported on MRI findings in a case of COVID-19 case with hearing loss & tinnitus. The authors report that MRI brain showed a pronounced contrast enhancement in right cochlea & decreased fluid signal in the base, indicating an inflammatory process in cochlea.

Thus the deteriorating effects of SARS CoV-2 on cochlear function is also suggested in addition to the possibility of effect on brainstem & hearing centre due to presence of ACE-2 receptors in brain, medulla oblongata due to inflammatory response through cytokines release.

V. Conclusion

Hence, COVID-19 infection could have deteriorating effects on the cochlear hair cells function despite being asymptomatic. It primarily causes SNHL and mainly affects higher frequencies. Recovered COVID-19 patients should be inquired & assessed for possible otological involvement.

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