Review Article

Audio-Vestibular Manifestations in COVID-19; A Systematic Review and Meta-analysis

https://doi.org/10.47210/bjohns.2022.v30i2.755

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ABSTRACT

Introduction

Audio-Vestibular (AV) presentation as a consequence of COVID-19 is a less ventured zone. The aim of the study was systematically review the literature (both studies and case reports) published up to August 2021, in order to provide evidence on audio-vestibular symptoms in SARS-CoV-2, COVID-19 patients. Systematic review and meta-analysis was performed for assessment of prevalence of AV symptoms among COVID-19 patients.

Materials and Methods

A search of existing literature using key words and MeSH (Medical Subject Headings) terms was done. The methods were developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. 36 qualitative studies were narratively synthesized. Meta-analysis was performed on 18 quantitative studies

Results

Hearing loss was most commonly reported AV manifestation among case series / case reports. In the quantitative studies, the pooled estimate of Hearing loss, Dizziness and Tinnitus was 4.558%, 4.226% and 5.513% respectively. Other reported AV symptoms included ear ache, aural fullness and facial paresis.

Conclusion

Prevalence of AV symptoms in COVID-19 differs from that of the published literature. This prevalence of hearing loss is less than that reported amongst the world population. Structured community-based studies with homogeneous working definitions have to be conducted to assess the true prevalence.

Keywords

COVID-19; SARS-CoV-2; Dizziness; Vertigo; Hearing Loss; Tinnitus

SARS-CoV-2 are seventh among Coronaviruses.[1] Symptoms are commonly due to multisystem involvement, predominantly respiratory.[2] SARS CoV-2 has a neurotropic nature and can involve temporal lobe, brain stem and temporal bone. Among the otolaryngology related symptoms, anosmia and dysgeusia has been widely reported.[3] Audio-Vestibular (AV) symptoms as a consequence of nasopharyngitis and neurological involvement of inner ear by the neurotropic virus is possible.[4] But these symptoms have been addressed by very few researchers, although not unreported. This study is aimed to compile the reported data in the form of a Systematic Review (SR) and Meta-Analysis to assess the prevalence of AV symptoms among the COVID-19 patients worldwide and to search for any causal association between them.

Materials and Methods

In August 2021, a Systematic review and Meta-Analysis had been performed to search for association between

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SARS-CoV-2 infection and AV symptoms. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) protocol was followed in the review process. A search of PubMed, Embase (OVID), Science direct, and Wiley Online Library was completed by the authors using structured search strategy. Search vocabulary included Key words and MeSH terms like "Coronavirus infection", "COVID-19", "SARS- CoV-2", "Hearing Loss", "Audiology", "Deafness'', "Vertigo", "Dizziness", "Imbalance", "Tinnitus". Boolean query like (COVID-19 OR SARS-CoV-2) AND (Hearing Loss OR Audiology* OR Vertigo OR Dizziness OR Tinnitus) and various combinations of the search vocabulary were used. PubMed search terms that we determined were then adapted for other search engines. Additional articles were hand searched from references of articles already populated in our searched library.

Eligibility criteria :

Studies that had evaluated the incidence, prevalence and association of AV symptoms with SARS-CoV-2 disease as diagnosed by respective researchers (RTPCR Positive, RAT positive and/or Radiological Diagnosis). Original research (prospective or retrospective cohort studies, observational studies, case series or case reports) in the English language were extracted.

Exclusion criteria :

Studies or case reports with non-established cases of SARS CoV-2 infection, inadequate information on AV symptoms, Meta-analysis, Systematic Literature Reviews and studies published in languages other than English were excluded from the study.

Search Strategy, Data Management and Data Analysis:

Three investigators independently reviewed titles and abstracts of all studies identified by the search strategy and tabulated them in Excel Sheet. Those fulfilling the inclusion criteria underwent full text review. Figure 1 Flow Diagram summarizing the screening process. The Data were extracted in a pre-designed extraction sheet. From the main grand spreadsheet, two daughter charts were prepared. First one contained the data from the articles with quantitative analysis (Prospective or Retrospective Cohort study, Case Control and Observational studies). Second one comprised data extracted from the Case series, Case reports and short communication pertaining to particular patient data. Data dictionary was prepared alongside to code the tabulated data. Author, year of publication, study design, sample size, age range, gender ratio, mean age, no of cases with hearing loss, conductive hearing Loss cases, sensorineural hearing loss cases, number of cases with vertigo, number of cases with tinnitus, number of cases with earache, other symptoms if any, number of patients with ototoxic drug usage if any, remarks if any. Data were put accordingly in Microsoft Excel 2010. AV symptoms in qualitative studies were narratively synthesized. For the studies included in quantitative synthesis we performed multiple meta-analyses to pool the prevalence of each of the AV symptoms reported. The estimates and 95% confidence interval (CI) for each study were calculated.

The pooled estimates and 95% CI were aggregated using the inverse-variance method (DerSimonian and Laird 1986[6]) following the recommendations of the Cochrane Handbook (Higgins and Green 2008[7]). In case of high statistical heterogeneity (I^2 Ã 61%), a random-effect model was used. Egger's and Begg's tests were done to assess publication bias if any. Missing data were inferred from other available data. All analyses were performed using MedCalc® software.

Results

Study Searching and Selection:

Total 1081 records were identified initially. After removing 706 duplicate records and 22 records due to non-fulfilling the criteria, 353 records were selected for screening. Among these 175 records were excluded due to lack of AV symptoms in the study population. Rest 178 studies were screened for full text review and data retrieval. In 41 records data could not be retrieved. Remaining 137 records were screened thoroughly and 69 cases were excluded as there was no confirmatory laboratory

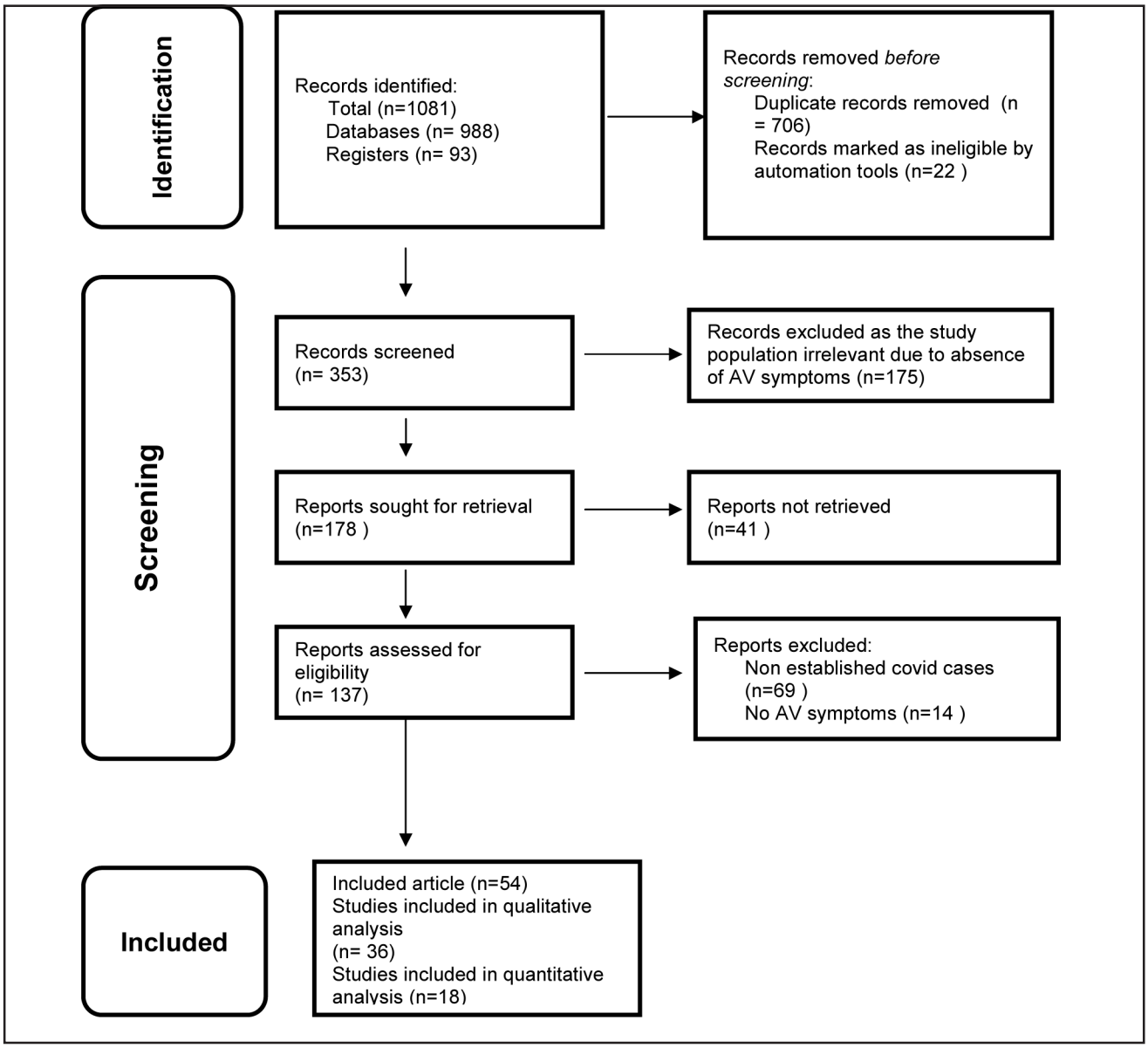

Fig.1. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only.[5]

evidences for COVID-19 infection. 14 cases were further excluded due to lack of AV symptoms. 54 records were finally selected for the study and divided in two categories. 36 studies (Case reports, Case Series, short communications, letter to editor) included in qualitative analysis for systematic review and rest 18 studies (prospective or retrospective cohort studies, observational studies) were included for meta-analysis.

Systematic Review of qualitative studies (n=36):

AV symptoms were reported in 36 qualitative studies (Case report- 24, Case Series- 4, Letter to Editor- 8) involving 54 patients.[8-43] Two third of the studies were reported in 2020, while rest were reported in 2021. Majority were female (n=30). Patients belonged to the age group of 13-88 yrs., with mean± SD were 45.02±

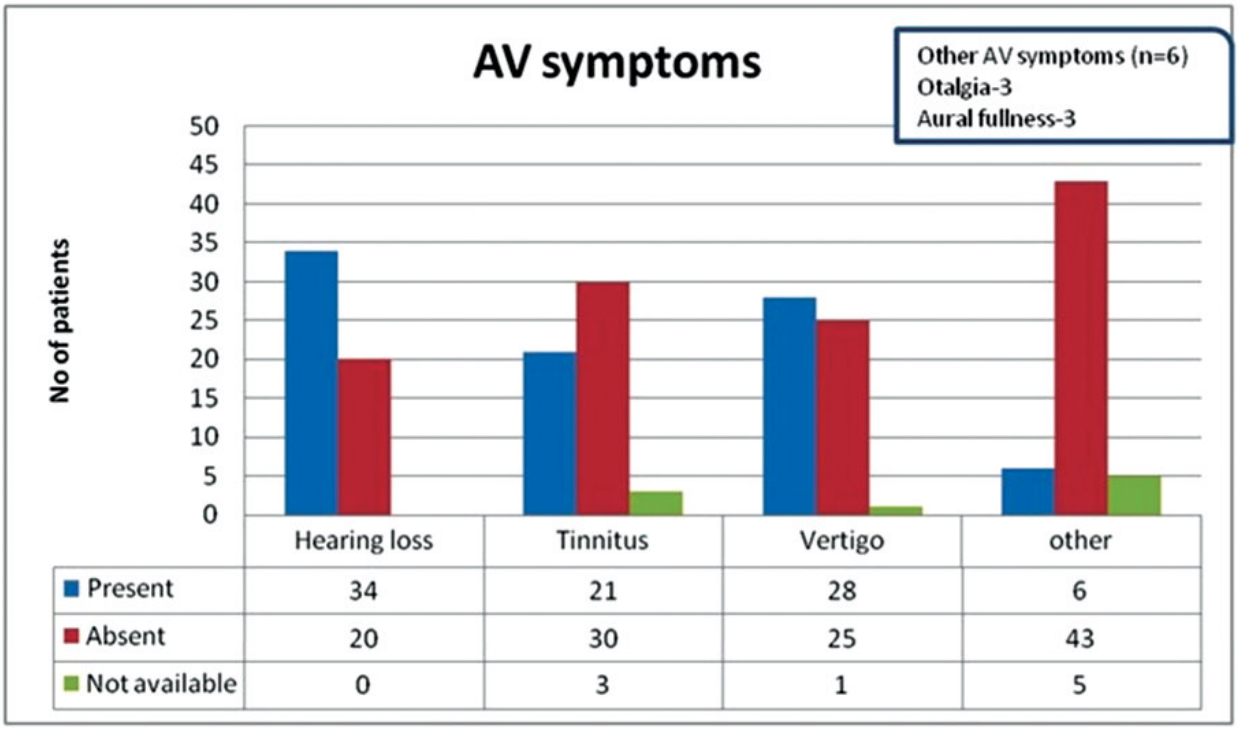

Fig. 2. Audio-Vestibular Symptoms in COVID-19 Patients

18.08 yrs. Figure 2 shows the distribution of AV symptoms among these patients. Hearing loss (HL) was the commonest symptoms reported, followed by vertigo and tinnitus.

Otoscopy was performed on 26 patients, out of which 92% were found to be normal.

Hearing Loss:

Total 34 patients were reported to have hearing loss. Laterality of hearing loss was reported in 31 cases. Majority of the patients (84%) had unilateral hearing loss (Left-12, Right-14). Severity of hearing loss was reported in 30 cases, (mild- 9. moderate-6 and severe-15). Type of hearing loss was mentioned in 31 cases (sensorineural-29, conductive-1, mixed-1). Tympanometry was performed in only seven studies (7 patients, 14 ears), among which 11 ears showed normal (Type A) tympanogram and in only 3 ears, tympanogram were of type B (low compliance). Only one researcher used Oto-Acoustic Emission (OAE) as screening tool for hearing assessment and found refer result.[31]

Dizziness and Tinnitus:

In the qualitative studies dizziness was present in 28 out of 54 cases (51.8%). Out of this in one case dizziness was not investigated.

Tinnitus was reported in 38.8% of the patients in the qualitative studies. Information regarding usage of any ototoxic drug was given only to 10 patients. Only three patients received drugs with ototoxic potentials, while rest seven did not receive any such drugs.

Multiple AV Symptoms:

More than one AV symptoms were present among 19 patients. All the three symptoms (hearing loss, tinnitus and dizziness) are present in only 5 patients. But usage of terms like 'dizziness' or 'imbalance' were non-specific,

which may be due to any short of weakness (common after COVID infection) or any other neurological reason.

Other symptoms related to AV system:

3 patients were reported to have earache, 3 had aural fullness and 2 patients had facial paresis. There were 3 patients who had multiple symptoms other than hearing loss, tinnitus or vertigo. As a whole total 6 patients were reported to have other AV symptoms.

Meta-analysis of the Quantitative Studies (n=18):

AV symptoms were investigated in 18 studies with quantitative analysis involving 4319 COVID-19 patients.[44-61] Eleven of them were Prospective cohort studies, three were retrospective studies and two each were Cross-sectional studies and Case-control studies respectively. Patients were from age range of 18-88 years, with mean age of 41.46 years. Females were the majority (54.6%).

Hearing Loss:

Hearing loss was present in 201 patients, accounting for 4.86% of the patients surveyed. Type of hearing loss was mentioned in 127 cases, out of which 96.8% had sensorineural hearing loss and rest had conductive type of hearing loss. Figure 3 depicts the forest plot for the prevalence of hearing loss. The pooled estimate was 4.558 (95% CI: 1.443-9.300). The estimate was aggregated using both the fixed and random-effect meta-analyses, but only the random effect was reported because of the high heterogeneity of the studies (I^2 = 97.19%).

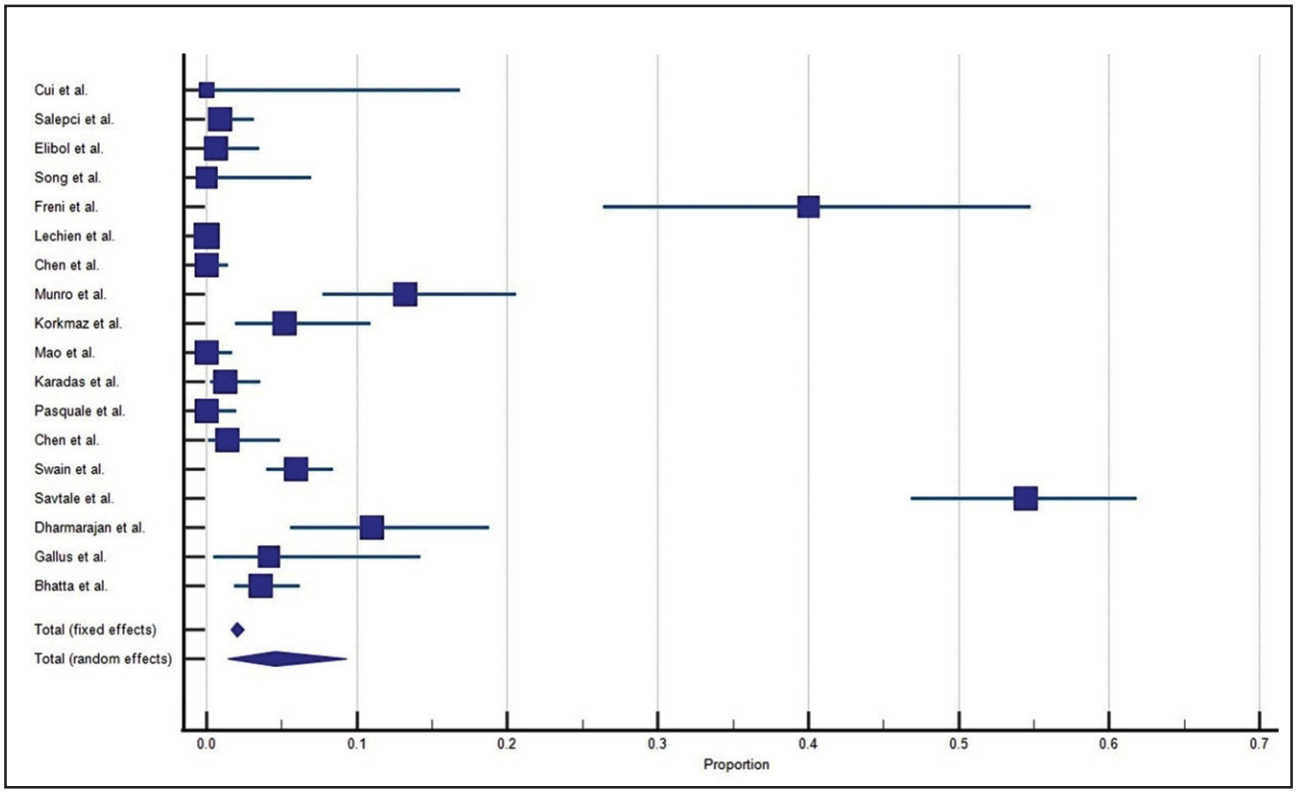

Fig. 3. Forest plot for the prevalence of Hearing Loss

Vertigo / Dizziness:

Vertigo was present in 164 patients, accounting for 4.11% of the patients surveyed. Figure 4 depicts the forest plot for the prevalence of vertigo. The pooled estimate was 4.226 (95% CI: 1.912-7.395). Random effect was taken into consideration because of the high heterogeneity of the studies ($I^2 = 94.49\%$).

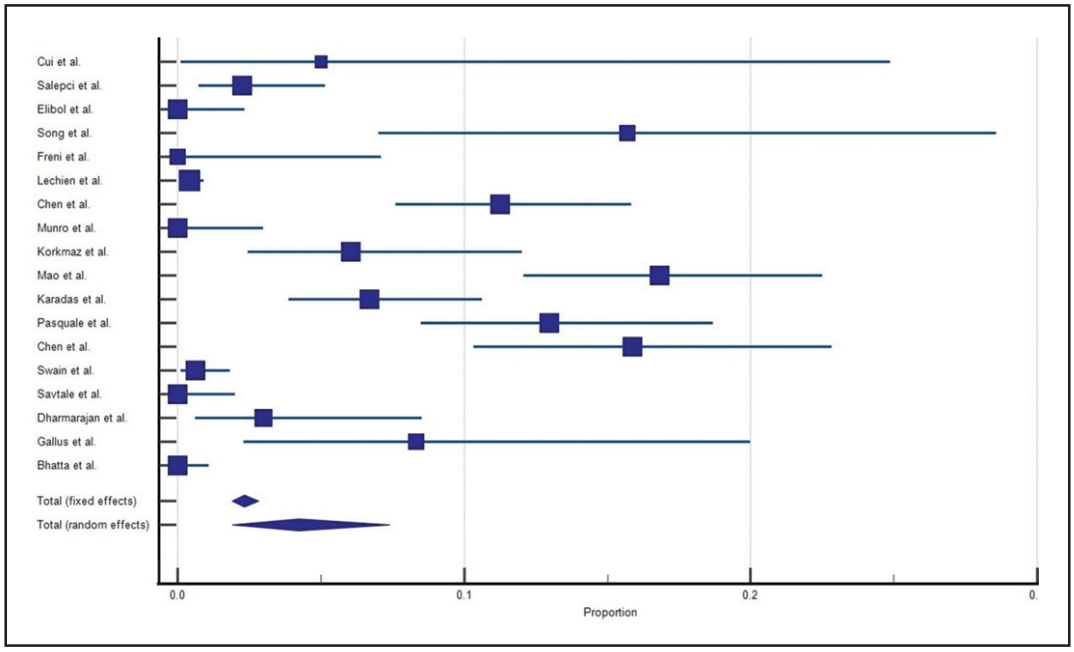

Fig. 4. Forest plot for the prevalence of Vertigo

Tinnitus:

Tinnitus was found to be present in 239 patients, accounting for 5.53% of the patient surveyed. Figure 5 depicts the forest plot for the prevalence of tinnitus. The pooled estimate was 5.513 (95% CI: 1.643-11.468). Random effect was reported because of the high heterogeneity of the studies ($I^2 = 97.87\%$). Earache was present in 36 patients, accounting for 1.19% of the patients surveyed. Figure 3 depicts the forest plot for the prevalence of Earache. The pooled estimate was 0.998 (95% CI: 0.298-2.104). Here also, the random effect was taken into consideration because of the high heterogeneity of the studies ($I^2 = 85.89\%$).

Discussion

Association of the SARS-CoV-2 and AV system is less ventured as it is overshadowed by more severe lung affection or "cytokine storm" in most of the published literature. However, there are both qualitative and quantitative studies to find out any association between SARS-CoV-2 and AV morbidity. In our analysis, we have investigated for AV symptoms associated with SARS-CoV-2 among 18 quantitative and 36 qualitative studies and tallied our findings with all pre-existing meta-analysis and systematic reviews.

Hearing Loss (HL) was most frequently encountered AV symptom reported in the qualitative studies (62.9% of the AV symptoms). It was mostly sensorineural type (93.5%), unilateral (76.4%) and severe (50%). Amongst the quantitative studies, HL was the second most common symptom reported, preceded by tinnitus and followed by vertigo. Prevalence of pooled estimates among quantitative studies for HL was 4.558%, which correlates with the studies we considered. Type of HL was mentioned in 127 cases, out of which 96.8% had

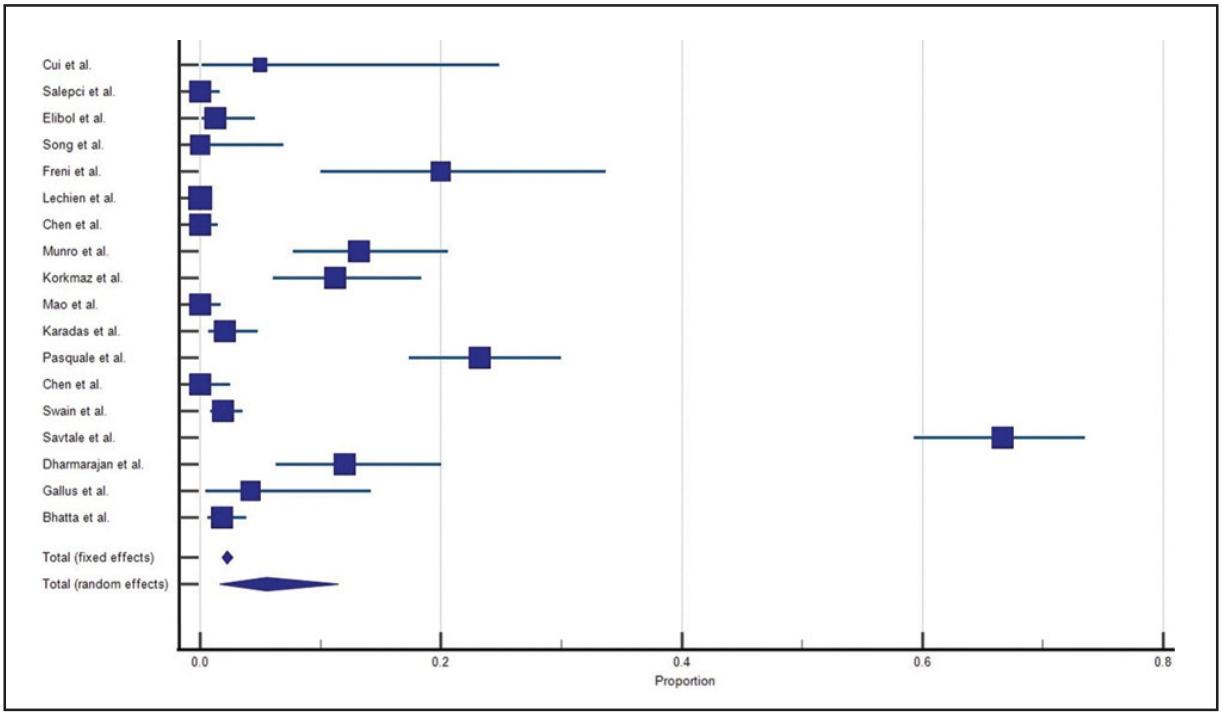

Fig. 5. Forest plot for the prevalence of Tinnitus

sensorineural HL and this reflects most of the literature we have reviewed. Due to high heterogeneity and low level of evidence, the finding of the results needs a judgment from a critical viewpoint. Freni et al.,[48] in their study, found estimated hearing loss to be too high (40%). The higher value obtained might be due to the tool they have used to search for hearing loss. They used Hearing Handicap Inventory for Adults (HHIA) by Newman et al, which is highly subjective. In another study by Savtale et al.,[58] which was based only on clinical interview from COVID 19 + patients, the prevalence was even higher (54%). When subjected to tuning fork tests, the presence of mild to moderate Sensorineural hearing loss (SNHL) was only elicited in 12% among them.

Our analysis also corroborates well with the meta-analysis conducted by Jafri et. al.[62] They have found the prevalence to be 3.1%. In a Systematic review by Almufarrij et al.[63] the pooled estimate of hearing loss prevalence based primarily on retrospective recall of symptoms, was 7.6%. (CI: 2.5–15.1) The value might be a bit higher as it was purely based on symptomatology and has a recall bias.

The HL, thus occurring due to SARS-CoV-2, may be due to direct effect on the organ of corti, stria vascularis. In such cases it is transmitted from blood to labyrinth (stria vascularis), from CSF to inner ear and/or due to involvement of neural structures by ACE-2 receptors in the brain stem or temporal lobe, affecting components of the auditory pathway. It might be due to cross reactivity to certain antigens. This explains the high prevalence of SNHL among the affected patients. Literature has thrown very little light on the causation of conductive or mixed HL in the rest of the COVID-19 positive patients affected with HL. COVID nasopharyngitis, Eustachian tube dysfunction and serous otitis media may be the attributing factors. The worldwide prevalence of "disabling" hearing loss requiring rehabilitation is over 5%,[64] and for the Indian population the scenario is even worse with 6.3% requiring rehabilitation for hearing.[65] The true prevalence of hearing loss, albeit a higher one is still unknown, hidden underneath in the "submerged portion of the iceberg".

HL prevalence found in our analysis is less than that reported among the general population worldwide. So as per present evidence, COVID-19 cannot be directly attributed to be a cause of increased prevalence of HL in the population. But there was one fact that was worth mentioning. 11 cases of sudden sensorineural hearing loss were reported among 31 reported cases of hearing loss (more than a third) found in qualitative studies. From this fact, Sudden Sensorineural hearing loss can be considered as the most common mode of onset of hearing loss as observed among SARS-CoV-2 infected patients.

Dizziness/Vertigo is a broad term which can be sub classified into – vertigo, disequilibrium, pre-syncope & light-headedness. But these terms have been used interchangeably in the reviewed literature. The qualitative studies incorporated in our analysis, were conducted over 54 patients and 28 patients had some kind of dizziness as an AV symptom**.** In the quantitative studies the pooled estimate of prevalence of dizziness is 4.226%. Chen et.al.[56] in their retrospective study has found dizziness in 20% of their study population. This is due to sole reliance on the history and not eliciting the cause of dizziness by relevant ENT examination and/or investigation. Moreover, dizziness in itself can be due to causes without the vestibular system being involved. In another study conducted by Song et.al.[47], dizziness prevalence was found to be 15.6%. Further remark on the case of dizziness and attributing it to peripheral vestibular origin was not highlighted. Viola et al.[55] in their study found out dizziness prevalence around 14% and of them 5.9% to be acute vertigo attacks. This high value can be attributed to numerous different causes of dizziness relating to COVID -19. Neuronal tissue damage by SARS-CoV-2 on the central nervous system (CNS) and inner ear by infection and inflammation can be an important causative factor. Dyselectrolytemia, dehydration, psychological effect due to stress, pre-existing cardiovascular disorders can also be the attributing factors. True vertigo is only evidenced in a very limited number of cases. Furthermore, the examination (otoscopy and neuro-otological examination for balance and equilibrium) and investigations pertaining to the vestibular system were not being documented. Another study by Gallus R et.al.[60] found in their study the dizziness prevalence to be 8.3%, which is nearer to the pooled estimate in our analysis. Thorough ENT histories including recent onset AV symptoms, examinations as well as tests like Video Head Impulse Test (vHIT) were performed in their study in addition to routine audiometric tests.

In a systematic review and meta-analysis by Jafri et al.,[62] the pooled estimate of dizziness was 12.20%. In another systematic review conducted by Almufarrij et al.[63] the pooled estimate was 7.2%, for rotatory vertigo. The values of different analyses might differ due to the different studies authors have incorporated, lack of proper working definition of dizziness/vertigo, non-documentation of relevant investigation for dizziness and low level of evidence among the studies. Only a few studies aimed to reflect the true vertigo in SARS-CoV-2 patients, whereas, a majority of share found association of non-specific dizziness with COVID-19. Some studies also searched for the audiological symptoms exclusively overlooking vestibular symptoms. Therefore, currently there is a requirement of more research to highlight the role of SARS-CoV-2 in vestibular pathology.

"Tinnitus is a symptom that is defined as any sound perceived by the patient when no external source of the sound exists."[63] Tinnitus as an AV symptom was reported in 21 patients (among 54) in the qualitative studies. Pooled estimate of tinnitus in our analysis is 5.513%, highest among all AV symptoms in quantitative studies. The result reflected the findings of most of the studies we have incorporated. In a study, conducted by Viola. et al.[55] prevalence of tinnitus among the COVID-19 patients was 23.2%. Such a high prevalence rate is attributed to the methodology used for the purpose of the study. It is primarily because the patients were diagnosed to have tinnitus based on questionnaire and Visual Analogue Scale (VAS) only. Secondly, the patients suffering from severe SARS-CoV-2 infection were excluded from the study. This eliminated the protective effect of oxygen therapy, on cochleo-vestibular microcirculation; if any. In another study by Savtale et.al.[58], 66.6% of the patients had some kind of tinnitus of recent onset, and 54.44%, had hearing

loss. This higher value may be attributed to more thorough history taking & audio vestibular examination. Although investigations such as PTA, TEOAE for further confirmation of ongoing cochlear pathology were not elicited. Additionally, the study was a tertiary care based cross-sectional study which might not be reflecting the true prevalence of tinnitus among patients suffering from SARS-CoV-2 specially the milder and asymptomatic ones. Jafri et al.[62] in their Systematic review and meta-analysis on six articles concluded the tinnitus prevalence to be 4.5%, which corroborates with our analysis. Almufarrij et. al.[63] in their systematic review (SR), found the pooled estimate of prevalence to be 14.8%. The synthesis in this SR has a larger database including 24 quantitative studies and 56 qualitative studies in comparison to our meta-analysis. Furthermore, their review team had included studies by Davis et al.,[67] Micarelli et al,[68] Daikhes et al.,[69] and Kamal et. al.,[70] where it was not properly mentioned that the tinnitus was of recent onset or a pre-existing one.

Earache can arise due to aural pathology or as referred pain arising by the nearby anatomical structures like tonsil, pharynx etc. 3 patients complained of earache in the qualitative studies. The pooled estimate of earache in patients of SARS-COV-2 among quantitative studies was 0.998%. Most of the studies, including Lechien et al.,[49] Munro et al.[51], korkmaz et al.,[52] have found no association of otalgia with COVID-19 among their patients. Freni et al.[48] found the prevalence of new onset earache in their studies to be 30%. This data has been collected by using an online questionnaire based on IFOS questionnaire (International Federations of Oto-rhino-laryngological Society's questionnaire) and no clinical ENT examination was performed. Therefore, the subjectivity of the symptoms was not being investigated in an objective manner. Thus the etiology for the otalgia was not being considered.

Aural fullness can be due to multiple etiology. Only the qualitative studies have searched for this symptom. Only 3 patients complained of this symptom. Chern et al.[8] in their case report have found the presence of aural fullness along with SNHL and vestibular symptoms and MRI revealed the presence of intra-labyrinthine hemorrhage secondary to infection with SARS-CoV-2. The presence of hemorrhage may be attributed to the causation of aural fullness.

Facial paresis was reported in 2 patients among qualitative studies including one pregnant lady,[21] and another 62 yr old lady.[18] In both these patients there was associated sensorineural hearing loss without any otorrhoea, vesicles and significant otoscopic finding. This may be attributed to the neurotropic character of the virus due to abundance of ACE-2 receptors in the temporal lobe and brainstem as well as the Organ of Corti.

Conclusion

AV symptoms manifested in COVID 19 had been less investigated. Systematic review and meta-analysis of relevant qualitative and quantitative studies has put forward hearing loss, dizziness and tinnitus to be the common manifestations. Other uncommon manifestations are earache, aural fullness and facial paresis. This study doesn't report an increased prevalence of AV symptoms that can be directly attributed to COVID-19. Although the findings alert the clinicians regarding the existing possibility of such presentation, common as well as rare like sudden sensorineural hearing loss and facial paresis in some cases. Structured community based studies with homogeneous working definitions have to be conducted to assess the true prevalence.

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