

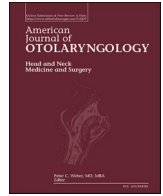


Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Contents lists available at [ScienceDirect](https://www.sciencedirect.com)

American Journal of Otolaryngology–Head and Neck Medicine and Surgery

journal homepage: www.elsevier.com/locate/amjoto

The effects of SARS-CoV-2 on hearing thresholds in COVID-19 patients with non-hospitalized mild disease[☆]

Osman Durgut^{*}, Mesut Karataş, Çağlar Çelik, Oğuzhan Dikici, Fevzi Solmaz, Sündüz Gencay

Department of Otorhinolaryngology, Health Science University, Bursa Yuksek Ihtisas Training and Research Hospital, Turkey

ARTICLE INFO

Keywords:
 COVID-19
 Hearing loss
 Pandemic
 SARS-CoV-2

ABSTRACT

Introduction: COVID-19 may have many nonspecific symptoms, such as hearing loss, tinnitus and dizziness. This study aims to investigate the effects of SARS-CoV-2 on the hearing thresholds of patients with COVID-19.
Methods: A total of 20 patients aged 20–55 years who were diagnosed with COVID-19 were included in this study. The relationship between the pure-tone thresholds of patients before and after COVID-19 was evaluated.
Results: There was no statistically significant difference between bone conduction pure-tone thresholds in all frequencies before and after COVID-19.
Conclusion: SARS-CoV-2 has no effects on the hearing thresholds in patients with non-hospitalized mild COVID-19 disease. Further studies are needed to investigate the possible effects of SARS-CoV-2 on the auditory system.

1. Introduction

In late December 2019, a group of pneumonia cases of unknown etiology was reported in Wuhan, China [1]. This life-threatening disease, called COVID-19, was caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and spread worldwide [2]. World Health Organization declared the pandemic on 11 March 2020 due to alarming spread [3]. Since then, COVID-19 has threatened people's lives. Patients with COVID-19 have nonspecific complaints of other respiratory infections. Fever, cough, fatigue and shortness of breath sore are the main symptoms [4,5]. Other symptoms include muscle ache, headache, confusion and sore throat [4,5]. There are publications reporting that half of the patients have a loss of smell and taste [6]. Nasal congestion and rhinorrhea are very rare, unlike other upper respiratory infections [4]. However, some patients with COVID-19 present with other nonspecific symptoms as hearing loss [7], tinnitus [7], dizziness [7], keratoconjunctivitis [8], cutaneous [9] and gastrointestinal findings [5]. Our knowledge of this disease is limited and we can face many clinical manifestations. As studies on the disease increase, previously unknown effects of the disease are understood day by day.

Viral infections are known to affect the audiovestibular system [10]. Although the effects of SARS-CoV-2 on the audiovestibular system are not known exactly, coronaviruses have been reported to be neuro-tropic

and neuro-invasive [11,12]. Therefore, it may have effects on the auditory system. This study aims to investigate the effects of SARS-CoV-2 on the hearing thresholds of patients with COVID-19. To our knowledge, this is the first study on this topic in the literature.

2. Methods

The present study was conducted in the ENT clinic of the tertiary education and research hospital. A total of 20 patients aged 20–55 years who were diagnosed with COVID-19 were included in this study. Patients who had a pure-tone audiometry test in our clinic in the last 12 months and subsequently had COVID-19 disease were included. Patients with a history of hearing loss, chronic ear disease and ear surgery were excluded from this study. All patients underwent otoscopic examination, pure-tone audiometry and tympanograms. SARS-CoV-2 diagnostic confirmation of all patients was performed by real-time reverse transcriptase-polymerase chain reaction (RT-PCR) technique on nasopharyngeal swab sample. All of the participants were outpatients with mild COVID-19 disease. Pre-COVID-19 pure-tone thresholds values were used as control.

Pure-tone audiometry was performed with the GSI AudioStar Pro device. Air conduction pure-tone thresholds were tested at 250 Hz, 500 Hz, 1000 Hz, 2000 Hz, 4000 Hz and 8000 Hz. Bone conduction pure-

[☆] This paper consists of original, unpublished work, has not been published or accepted for publication. It is not under consideration at another journal.

^{*} Corresponding author at: Health Science University, Bursa Yuksek Ihtisas Training and Research Hospital, Department of Otorhinolaryngology, Mimarşinan Mahallesi, Emniyet Cd. No: 35, 16310 Yıldırım/Bursa, Turkey.

E-mail address: durgutosman@yahoo.com (O. Durgut).

<https://doi.org/10.1016/j.amjoto.2021.103320>

Received 3 September 2021;

Available online 14 December 2021

0196-0709/© 2021 Elsevier Inc. All rights reserved.

tone thresholds were tested at 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz. The average pure-tone thresholds at 500 Hz, 1000 Hz and 2000 Hz were used to estimate the level of hearing impairment. Tympanometry was performed in a quiet room using the Maico MI34 device. All post-COVID-19 audiometric investigations were performed by the same audiologist.

This study was performed in accordance with the requirements of the declaration of Helsinki after obtaining approval by the Ethics Committee of the tertiary research hospital (decision number 2011-KAEK-25 2021/03-07). Informed consent was obtained from all patients.

Data analysis was performed using the SPSS software, version 23.0 (Statistical Package for the Social Sciences, Chicago, IL, USA). Paired *t*-test was used to evaluate the relationship between pure-tone thresholds before and after COVID-19. *p*-Value <0.05 was considered statistically significant.

3. Results

A total of 20 patients, seven male and 13 female, diagnosed with COVID-19 were included in this study. Hearing thresholds of 40 ears were evaluated. The mean age of the patients aged 20–55 was 36.25 ± 9.06 years. Tympanograms of all ears were type A and none of them had middle ear pathology before and after COVID-19. The time of performing pure-tone audiometry before COVID-19 was between 1 and 12 months, and after COVID-19, it was between 3 and 12 months.

Half of the patients (10 patients) included in this study presented with loss of smell and taste. Other complaints of the patients were as follows fatigue in eight patients, sore throat in five patients, cough in five patients, tinnitus in four patients, fever in four patients, headache in four patients, dizziness in three patients, joint pain in three patients, back pain in two patients, ear fullness in two patients, hearing loss in one patient. The patient, who described hearing loss during COVID-19, was evaluated six months after COVID-19. This patient had no complaints and her hearing thresholds were normal.

No statistically significant difference was found between the bone conduction pure-tone thresholds measured before and after COVID-19 at all frequencies (500 Hz, *p* = 0,482; 1000 Hz, *p* = 0,147; 2000 Hz, *p* = 0,057; 4000 Hz, *p* = 0,063). Fig. 1 shows the bone conduction pure-tone audiometric thresholds for both pre- and post-COVID-19 groups. Similarly, there was no statistically significant difference between the air conduction pure-tone thresholds between 1000 Hz and 8000 Hz frequencies before and after COVID-19 (1000 Hz, *p* = 0,069; 2000 Hz, *p* = 0,406; 4000 Hz, *p* = 0,900; 8000 Hz, *p* = 0,131). However, better hearing thresholds were determined after COVID-19 at 250 and 500 Hz frequencies in air conduction pure-tone thresholds. The mean air conduction pure-tone hearing thresholds before and after COVID-19 at a frequency of 250 Hz were 16 and 11.62, respectively (*p* = 0,000). At 500 Hz, it was 14.37 and 11.12, respectively (*p* = 0,001). Fig. 2 shows the air conduction pure-tone audiometric thresholds for both pre- and

post-COVID-19 groups. The average value of mean bone conduction thresholds at 500 Hz, 1000 Hz, 2000 Hz was 8.16 ± 5.74 and 9.37 ± 5.5 (*p* = 0,121) before and after COVID-19, respectively. The average values of the mean air conduction thresholds were 14.41 ± 5.92 and 12.37 ± 6.96 (*p* = 0,018) before and after COVID-19. Fig. 3 shows audiograms of mean thresholds at each frequency obtained before and after COVID-19.

Thirteen of the patients used only favipiravir treatment for five days, 1600 mg twice a day on the first day and 600 mg twice a day on the following days. In addition to favipiravir treatment, two patients used hydroxychloroquine treatment, 200 mg twice a day, for five days. Five patients did not receive any drug treatment. When the pre- and post-COVID-19 bone conduction hearing thresholds of 15 patients using favipiravir treatment were compared, no significant difference was found in all frequencies (500 Hz, *p* = 0,879; 1000 Hz, *p* = 0,284; 2000 Hz, *p* = 0,134; 4000 Hz, *p* = 0,120).

4. Discussion

The studies conducted during the COVID-19 pandemic show that SARS-CoV-2 infection affects the central nervous system, peripheral nervous system and muscle. Headache, decreased responsiveness, anosmia, hyposmia, hypogeusia and dysgeusia are common central nervous system symptoms of coronavirus infection. The rare cases where COVID-19 infection affects the peripheral nervous system and muscles are Guillain-Barré syndrome, Miller Fisher syndrome, polyneuritis cranialis and rhabdomyolysis. Studies suggest that the neurological findings of the SARS-CoV-2 virus have a direct neurotropic effect and a secondary effect of the virus [13,14]. Although it is still unknown how the virus affects the audiovestibular system, the literature on the subject is expanding.

In Mustafa's study, which consisted of 20 asymptomatic COVID-19 patients, it was shown that hearing was affected especially at high frequencies (4000–8000 Hz) and a significant decrease was found in transient evoked otoacoustic emission (TEOAE) thresholds. The researcher claimed that CoV-2, like other neurotropic viruses, caused viral damage in the organ of Corti and hair cells, which was shown by the effect in the otoacoustic emission results [15]. In another study, worse mean hearing thresholds were found in hospitalized COVID-19 patients at high frequencies from 1000 Hz than the control group [16]. Apart from these studies, literature data on the relationship between COVID-19 and the auditory system are mostly case reports. Sriwijitalai and Wiwanitkit reported the first reported case of sensorineural hearing loss in an elderly individual with COVID-19 in the literature [17]. In another study, otalgia, tinnitus and unilateral conductive hearing loss in a patient with COVID-19 were reported [18]. Kılıç et al. stated that the PCR test was positive in one of the five patients who came to the clinic with the diagnosis of sudden hearing loss during the COVID-19 process [19]. Karimi-Galougahi et al. also reported six cases of unilateral sensorineural hearing loss associated with COVID-19 disease [20].

In our study, in which mild COVID-19 patients who were administered outpatient treatment were evaluated, we showed that SARS-CoV-2 had no bad effect on hearing values. Unlike other studies in the literature, the patients' own audiometry values were used as control. We found better mean air conduction hearing thresholds at 250 Hz and 500 Hz frequencies after COVID-19 although a statistically significant difference was found at these frequencies. We thought that this might be because hearing thresholds were made by different audiologists at different times. The fact that there is a difference between the mean air conduction pure-tone hearing thresholds before and after COVID-19 at both frequencies (250–500 Hz) is not more than 5 dB supports our claim.

Hydroxychloroquine and favipiravir used in the treatment of COVID-19 may show potential ototoxic side effects. It has been reported in the literature that unilateral or bilateral hearing loss or tinnitus may develop due to the use of these drugs [21]. In our study, 13 of 20 patients used favipiravir alone and two used favipiravir plus hydroxychloroquine

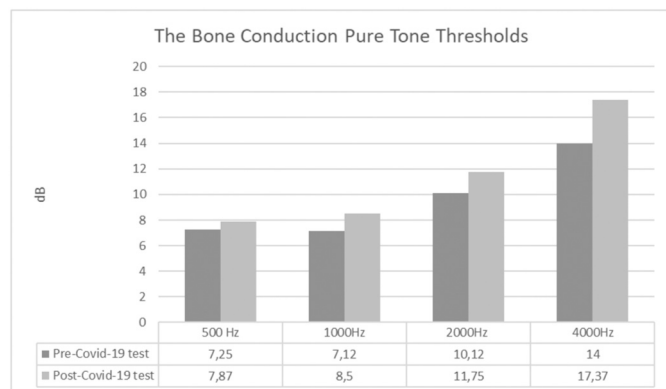


Fig. 1. The bone conduction pure-tone audiometric thresholds for both pre- and post-COVID-19 groups.

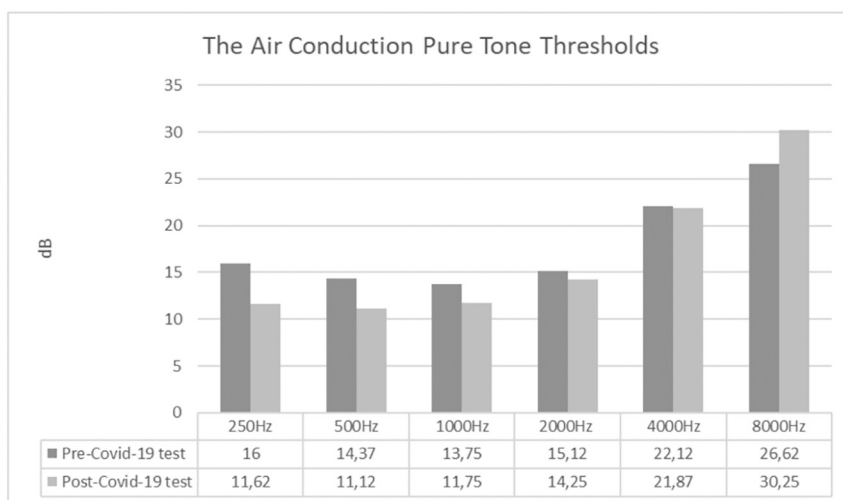


Fig. 2. The air conduction pure-tone audiometric thresholds for both pre- and post-COVID-19 groups.

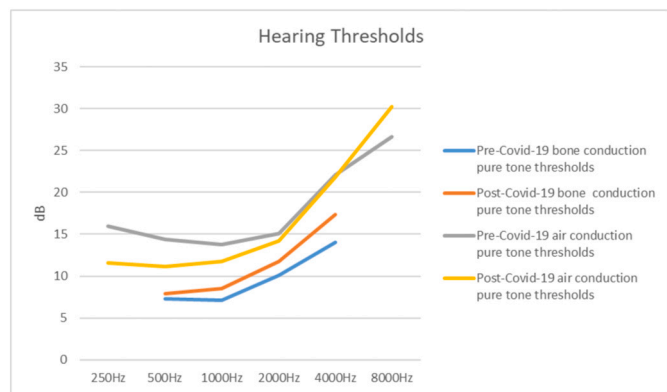


Fig. 3. The audiograms of mean thresholds at each frequency obtained before and after COVID-19.

treatment. Five patients did not use any drug treatment for COVID-19. When the pre- and post-COVID-19 hearing thresholds of 15 patients receiving favipiravir treatment were compared, no statistically significant difference was found. In conclusion, we found that the use of favipiravir had no effect on hearing thresholds in patients with mild COVID-19 disease who were not hospitalized.

This study has limitations, such as the small number of patients. Pre-COVID-19 audiometry and post-COVID-19 audiometry were not performed by the same audiologist, and the lack of standardization between pre- and post-COVID-19 audiometry times was the other limitation. Also, the absence of patients' otoacoustic emissions and speech audiometry were other limitations. However, we should note that none of the patients in this study reported a difference in their pre- and post-COVID-19 hearing levels makes these limitations partially unimportant.

In conclusion, although we did not detect the effects of SARS-CoV-2 on the hearing thresholds in patients with non-hospitalized mild COVID-19 disease, our study is a preliminary one. Further studies are needed to investigate the possible effects of SARS-CoV-2 on the auditory system.

Funding

There are no funding sources.

CRedit authorship contribution statement

Osman Durgut: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data curation, Writing - Original draft, Supervision, Project administration.

Mesut Karataş: Investigation, Data curation, Resources, Writing - review & editing.

Çağlar Çelik: Investigation, Data curation, Resources, Writing - review & editing.

Oğuzhan Dikici: Writing - review & editing, Supervision, Project administration.

Fevzi Solmaz: Supervision, Project administration.

Sündüz Gencay: Supervision, Project administration.

Declaration of competing interest

Osman Durgut, M.D. declares that he has no conflicts of interest.

Mesut Karataş, M.D. declares that he has no conflicts of interest.

Çağlar Çelik, M.D. declares that he has no conflicts of interest.

Oğuzhan Dikici, M.D. declares that he has no conflicts of interest.

Fevzi Solmaz, M.D. declares that he has no conflicts of interest.

Sündüz Gencay, M.D. declares that he has no conflicts of interest.

References

- [1] Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med* 2020;382:727–33.
- [2] Zhai P, Ding Y, Wu X, Long J, Zhong Y, Liet Y. The epidemiology, diagnosis and treatment of COVID-19. *Int J Antimicrob Agents* 2020;55:105955.
- [3] WHO Director-General's opening remarks at the media briefing on COVID-19. <https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19-11-march-2020>; 11 March 2020.
- [4] Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020;395:507–13.
- [5] Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA* 2020;323:1061–9.
- [6] Klopfenstein T, Kadiane-Oussou NJ, Toko L, Royer PY, Lepiller Q, Gendrin V, et al. Features of anosmia in COVID-19. *Med Mal Infect* 2020;50:436–9.
- [7] Almufarrij I, Ulus K, Munro KJ. Does coronavirus affect the audio-vestibular system? A rapid systematic review. *Int J Audiol* 2020;59:487–91.
- [8] Cheema M, Aghazadeh H, Nazarali S, Ting A, Hodges J, McFarlane A, et al. Keratoconjunctivitis as the initial medical presentation of the novel coronavirus disease 2019 (COVID-19). *Can J Ophthalmol* 2020;55:e125–9.
- [9] de Medeiros VLS, Silva LFT. Follow-up of skin lesions during the evolution of COVID-19: a case report. *Arch Dermatol Res* 2020;313:603–6.
- [10] Cohen BE, Durstenfeld A, Roehm PC. Viral causes of hearing loss: a review for hearing health professionals. *Trends Hear* 2014;18. 2331216514541361.

- [11] Natoli S, Oliveira V, Calabresi P, Maia LF, Pisani A. Does SARS-CoV-2 invade the brain? Translational lessons from animal models. *Eur J Neurol* 2020;27:1764–73.
- [12] Desforges M, Le Coupanec A, Dubeau P, Bourgouin A, Lajoie L, Dube M, et al. Human coronaviruses and other respiratory viruses: underestimated opportunistic pathogens of the central nervous system? *Viruses* 2019;12:14.
- [13] Román GC, Spencer PS, Reis J, Buguet A, Faris MEA, Katrak SM, et al. The neurology of COVID-19 revisited: a proposal from the Environmental Neurology Specialty Group of the World Federation of Neurology to implement international neurological registries. *J Neurol Sci* 2020;414:116884.
- [14] Niazkar HR, Zibae B, Nasimi A, Bahri N. The neurological manifestations of COVID-19: a review article. *Neurol Sci* 2020;41:1667–71.
- [15] Mustafa MWM. Audiological profile of asymptomatic Covid-19 PCR-positive cases. *Am J Otolaryngol* 2020;41(3):102483.
- [16] Alves de Sousa F, Pinto Costa R, Xara S, Pinto AN, Sousa CAE. SARS-CoV-2 and hearing: an audiometric analysis of COVID-19 hospitalized patients. *J Otol* 2021; 16:158–64.
- [17] Sriwijitalai W, Wiwanitkit V. Hearing loss and COVID-19: a note. *Am J Otolaryngol* 2020;41(3):102473.
- [18] V Fidan New type of corona virus induced acute otitis media in adult. *Am J Otolaryngol*. 41(3):102487.
- [19] Kilic O, Kalcioğlu MT, Cag Y, Tuysuz O, Pektas E, Caskurlu H, et al. 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. *Int J Infect Dis* 2020;97:208–11.
- [20] Karimi-Galougahi M, Naeini AS, Raad N, Mikaniki N, Ghorbani J. Vertigo and hearing loss during the COVID-19 pandemic - is there an association? *Acta Otorhinolaryngol Ital* 2020;40:463–5.
- [21] Ciorba A, Corazzi V, Skarżyński PH, Skarżyńska MB, Bianchini C, Pelucchi S, et al. Don't forget ototoxicity during the SARS-CoV-2 (Covid-19) pandemic! *Int J Immunopathol Pharmacol* 2020;34. 2058738420941754.