

# Comparative study of tinnitus and cardiorespiratory fitness among people post COVID-19

## Estudo comparativo de zumbido e aptidão cardiorrespiratória entre pessoas pós-COVID-19

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### ABSTRACT

**Purpose:** To verify the relation between tinnitus and cardiorespiratory fitness among people after COVID-19. **Methods:** Cross-sectional study with a sample of people post Covid-19 who responded to the Visual-Analog Scale for tinnitus and standardized questionnaire containing data on hospitalization and tinnitus. To evaluate cardiorespiratory fitness, it used the clinical assessment and Bruce test to measure oxygen consumption directly (via gas analyzer, using peak oxygen consumption - VO<sub>2</sub>peak). **Results:** In total, 192 participants were assessed, with a mean age of 47.8 ± 12.6 years. The prevalence of self-reported tinnitus was 27.1% (n = 52). Of these 52 patients with tinnitus, 27 people started with the symptom during or after the diagnosis of COVID-19. There was a significant difference for the absolute VO<sub>2</sub>peak and the groups with and without tinnitus (p = 0.035): the tinnitus group showed the lowest values, the effect size was small. There was no correlation between the scores of the Visual-Analog Scale for tinnitus and the absolute and relative VO<sub>2</sub>peak (p > 0.05). **Conclusion:** There was a statistically significant difference between tinnitus complaints and the VO<sub>2</sub>peak among people post COVID-19, with the tinnitus group having a lower absolute VO<sub>2</sub>peak than the non-tinnitus group. In tinnitus patients, we also found lower absolute and relative VO<sub>2</sub>peak for women, in addition to lower relative VO<sub>2</sub>peak for hypertensive and obese patients.

**Keywords:** Tinnitus; Cardiorespiratory fitness; COVID-19; Visual Analog Scale; Oxygen

### RESUMO

**Objetivo:** Verificar a relação entre zumbido e aptidão cardiorrespiratória em pessoas após COVID-19. **Métodos:** estudo transversal com amostra de pessoas pós-COVID-19 que responderam à Escala Visual Analógica para zumbido e questionário padronizado contendo dados sobre internação e zumbido. Para avaliar a aptidão cardiorrespiratória, utilizou-se a avaliação clínica e o Teste de Bruce para mensurar o consumo de oxigênio diretamente (via analisador de gases, com utilização do consumo pico de oxigênio - VO<sub>2</sub>pico). **Resultados:** Participaram 192 pessoas, com média de idade de 47,8 ± 12,6 anos. A prevalência de zumbido autorreferido foi de 27,1% (n = 52). Dos 52 pacientes com zumbido, 27 iniciaram com o sintoma durante ou após o diagnóstico de COVID-19. Houve diferença significativa para o VO<sub>2</sub>pico absoluto entre os grupos com e sem zumbido (p = 0,035), sendo que o grupo com zumbido apresentou os menores valores; o tamanho do efeito foi pequeno. Não houve correlação entre os escores da Escala Visual Analógica para o zumbido e os valores de VO<sub>2</sub>pico absoluto e relativo (p > 0,05). **Conclusão:** Houve diferença estatisticamente significativa entre as queixas de zumbido e o VO<sub>2</sub>pico nas pessoas após a COVID-19, sendo que o grupo com zumbido apresentou o VO<sub>2</sub>pico absoluto menor do que o grupo sem zumbido. Nos pacientes com zumbido, também foi encontrado VO<sub>2</sub>pico absoluto e relativo menor para as mulheres, além do VO<sub>2</sub>pico relativo menor para os hipertensos e obesos.

**Palavras-chave:** Zumbido; Aptidão cardiorrespiratória; COVID-19; Escala Visual Analógica; Oxigênio

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## INTRODUCTION

COVID-19 had a great epidemiological impact on people's mortality and morbidity in all continents<sup>(1)</sup>. The World Health Organization (WHO) has already defined well the classic COVID-19 symptoms. However, other ones still need to be clarified, including changes secondary to the acute viral infection such as hearing, smell, and taste disorders<sup>(1)</sup>. Post-COVID-19 patients have reported tinnitus, which can be characterized as an auditory symptom identified as subjective noise that interferes with the quality of life. Nevertheless, it has been seldom investigated<sup>(2)</sup>. A multicentric study encompassing 15 hospitals in different regions of Italy used a 10-item closed-ended online questionnaire to identify tinnitus and balance disorders in COVID-19 patients between May 5 and June 10, 2020. It was administered to 185 patients who had been diagnosed with COVID-19 more than 30 days and less than 60 days before. Their answers on the presence and characteristics of tinnitus and other complaints were recorded in an Excel spreadsheet. Altogether, 43 (23.2%) of those patients reported tinnitus. The authors concluded that subjective otoneurological symptoms such as tinnitus can affect post-COVID-19 patients and that further studies are needed to investigate the prevalence and physiopathological mechanisms underlying these subjective symptoms<sup>(2)</sup>.

It has been suggested that cardiorespiratory fitness can help identify individuals at greater risk of severe COVID-19 disease<sup>(3,4)</sup>. Such fitness is one of the most significant variables to monitor health, to which the gold standard is the maximum or peak oxygen consumption ( $VO_{2max}$  or  $VO_{2peak}$ ), directly analyzing gas exchanges. This is equivalent to the maximum capacity to transport and use oxygen during high-intensity physical activity<sup>(5-8)</sup>. Hence,  $VO_{2max}$  demonstrates one's maximum capacity to absorb, transport, and consume oxygen. Structured exercise programs can keep the levels of physical activity and prevent unfitness<sup>(8)</sup>.  $VO_{2peak}$  has the potential to be a relevant clinical screening tool during the COVID-19 outbreak<sup>(8)</sup>. Hence, the respiratory infection caused by COVID-19 may trigger tinnitus because it interferes with the person's capacity to absorb, transport, and consume oxygen, likely affecting the inner ear.

It is believed that population studies on the prevalence and associated factors involving the various COVID-19 symptoms can help construct knowledge about symptoms secondary to the disease and its continuity in recovered patients, in both mild and severe forms. They also help include such secondary symptoms among predictive protection or aggravation factors regarding the various forms of the disease. To our knowledge, no study has examined cardiorespiratory fitness in patients with tinnitus or associated cardiorespiratory effectiveness with tinnitus in post-COVID-19 patients. Hence, this study aimed to verify the relationship between tinnitus sensation, assessed with a visual analog scale (VAS), and cardiorespiratory fitness, measured with  $VO_{2peak}$ , in post-COVID-19 patients.

## METHODS

This cross-sectional study is part of broader research named "Post-COVID-19 Project". The Human Research Ethics

Committee of the *Centro Universitário de Maringá* (UniCesumar) approved the project (CAAE 18270919.1.0000.5539). Before beginning the study, all patients were informed about its objectives and procedures and signed an informed consent form (ICF).

The inclusion criteria for this study were as follows: being 19 to 65 years old; having been positively diagnosed with COVID-19 via qualitative molecular test (RT-PCR), presenting the test result and/or hospital discharge after COVID-19 treatment; having contracted COVID-19 between March 1 and July 1, 2021; having received the first dose of the COVID-19 vaccine; and having a medical report allowing them to undergo cardiorespiratory fitness tests.

Based on the exclusion criteria, the study did not accept patients with debilitating neurological diseases or mobility difficulties (needing a walking stick or wheelchair), without a medical report allowing them to undergo the Bruce Test, or who did not agree to sign an ICF<sup>(9,10)</sup>.

Data were collected between August and December 2021 by trained assessors of the multi-professional team at the institution's Interdisciplinary Laboratory for Health Promotion Intervention (LIIPS), guided by physicians, physical therapists, speech-language-hearing therapists, nutritionists, and physical educators. Patients were recruited via referral from the municipal hospital, after their discharge<sup>(10)</sup>.

On their first visit to the research laboratory, participants were clinically assessed (arterial pressure, glycemia, oxygen saturation, physical assessment with anthropometry, body composition with electrical bioimpedance, and cardiorespiratory effort test) and answered a standardized questionnaire with 90 open-ended and closed-ended items, encompassing data on medical history, preexisting diseases (self-reported hypertension and diabetes, obesity, hyperthyroidism or hypothyroidism, and hypocholesterolemia or hypercholesterolemia), need for hospitalization, length and type of hospital stay, symptomatology (tinnitus, dizziness, vertigo, aural fullness, hearing loss, headache, anosmia, ageusia) during and/or after COVID-19, and duration of symptoms after hospital discharge. Patients also underwent hearing assessments on their second visit and blood tests on the third one. This study used data collected on their first visit to the research laboratory.

The questionnaire asked them specifically about having tinnitus sensation at the time of the assessment. They were also asked about laterality (which ear was affected, or both), symptom type and duration, and its relationship with COVID-19 to verify whether it was previous or posterior to it, or whether it appeared during the COVID-19 infection. VAS was applied to those who reported tinnitus to assess their degree of annoyance or discomfort. Each patient was asked to score their tinnitus from 0 to 10 on an appropriate ruler<sup>(11)</sup>.

Then, their body composition was assessed, and their anthropometric measures were taken, measuring their body weight and height, and calculating and classifying the body mass index (BMI). Patients whose BMI ranged from 18.00 to 24.99 kg/m<sup>2</sup> were classified as normal weight; from 25.00 to 29.99 kg/m<sup>2</sup>, as overweight; and 30.00 or more kg/m<sup>2</sup> as obese<sup>(12)</sup>.

Lastly, the Bruce Test was used to measure oxygen consumption<sup>(8)</sup> with a metabolic gas analyzer (VO2000®). Gas exchanges during the Bruce Test were directly analyzed with VO2000 metabolic gas analyzer (Medgraphics®, Saint Paul, USA), using the participants'  $VO_{2peak}$  as an analysis variable.

SPSS software for Windows was used to analyze data with a 95% confidence interval (CI), setting the significance at a p-value < 0.05. The descriptive analysis of the data was performed with absolute and relative frequencies, means, standard deviations, and, when appropriate, medians and interquartile ranges. The Shapiro-Wilk and Kolmogorov-Smirnov tests did not find normality in the data; hence, nonparametric statistical analysis was performed with the Mann-Whitney and Kruskal-Wallis tests, Spearman correlation, and the chi-square test.

The Mann-Whitney test was used to compare the groups with and without tinnitus, sex, previous tinnitus, need for hospitalization, hypertension, diabetes, and VO<sub>2</sub> peak values. The effect size for the Mann-Whitney test was calculated using the Equation 1<sup>(13)</sup>:

$$r = \frac{Z}{\sqrt{n}} \quad (1)$$

in which “n” is the number of observations.

The Kruskal-Wallis test was used to compare the group per age range, BMI category, and VO<sub>2</sub> peak values in the analysis of the tinnitus group. The effect size was calculated with the estimated epsilon-square ( $E_{r^2}$ ), using the Equation 2:

$$E_{r^2} = \frac{H}{\frac{(n^2 - 1)}{(n + 1)}} \quad (2)$$

in which “ $E_{r^2}$ ” is the coefficient, whose value ranges from 0 (indicating no relationship) to 1 (indicating a perfect relationship); “H” is the value obtained with Kruskal-Wallis, and “n” is the number of observations<sup>(14)</sup>. The effect sizes followed Cohen’s 1988 classification<sup>(15)</sup>. The Spearman correlation used the VAS scores and VO<sub>2</sub> pico values.

The chi-square test was used to verify the association between the categorical variables. The “Phi” effect size, represented by the Greek letter “φ”, was calculated for the 2x2 tables, and “Cramer’s V”, represented by the letter “V”, was calculated for the 2x3 tables. Both effect sizes were calculated in SPSS, used in the analyses.

## RESULTS

The analyses encompassed 192 participants, of whom 51.6% (n = 99) were males, with a mean age of 47.8 ± 12.6 years. Of these patients, 27.1% (n = 52) reported tinnitus and 14.1% (n = 27) reported tinnitus onset during or after the COVID-19 diagnosis. The mean VAS score of patients with complaints of tinnitus was 6.2 ± 2.5 points (Table 1).

There was a significant difference in absolute VO<sub>2</sub> peak between the groups with and without tinnitus (p = 0.035; r = 0.15); the group with tinnitus had the lower values, and the effect size was small. No significant difference was found for relative VO<sub>2</sub> peak (p > 0.05). Tinnitus VAS scores did not correlate with the assessed VO<sub>2</sub> values (p > 0.05) (Table 2 and Table 3).

**Table 1.** Descriptive data of the sample (n = 192)

| CATEGORICAL VARIABLES                     | n     | %                  |
|---|-------|--------------------|
| SEX                                       |       |                    |
| Males                                     | 99    | 51.6               |
| Females                                   | 93    | 48.4               |
| AGE RANGES                                |       |                    |
| 18-44 years                               | 77    | 40.1               |
| 45-64 years                               | 101   | 52.6               |
| 65-80 years                               | 14    | 7.3                |
| NEED FOR HOSPITALIZATION                  |       |                    |
| No  | 65    | 34                 |
| Yes                                       | 126   | 66                 |
| BMI CATEGORY                              |       |                    |
| Normal weight                             | 22    | 10.5               |
| Overweight                                | 75    | 39.5               |
| Obesity                                   | 95    | 50                 |
| HYPERTENSION                              |       |                    |
| No  | 139   | 72.4               |
| Yes                                       | 53    | 27.6               |
| DIABETES                                  |       |                    |
| No  | 169   | 88                 |
| Yes                                       | 23    | 12                 |
| TINNITUS                                  |       |                    |
| No  | 140   | 72.9               |
| Yes                                       | 52    | 27.1               |
| TIME BEFORE TINNITUS                      |       |                    |
| N/A                                       | 140   | 72.9               |
| Before the COVID diagnosis                | 25    | 13                 |
| During or after the COVID diagnosis       | 27    | 14.1               |
| TINNITUS – EAR                            |       |                    |
| N/A                                       | 143   | 74.5               |
| Right                                     | 8     | 4.2                |
| Left                                      | 15    | 7.8                |
| Bilateral                                 | 26    | 13.5               |
| TINNITUS PERSISTED AFTER DISCHARGE        |       |                    |
| N/A                                       | 145   | 75.5               |
| No  | 11    | 5.7                |
| Yes                                       | 36    | 18.8               |
| TIME OF TINNITUS PERSISTENCE              |       |                    |
| N/A                                       | 150   | 78.1               |
| < 2 months                                | 10    | 5.2                |
| 2 – 4 months                              | 2     | 1                  |
| 4 – 6 months                              | 3     | 1.6                |
| > 6 months                                | 27    | 14.1               |
| CONTINUOUS VARIABLES                      | Mean  | Standard deviation |
| Age (years)                               | 47.8  | 12.6               |
| Height (cm)                               | 165.4 | 16.4               |
| Body weight (kg)                          | 86.2  | 19.5               |
| BMI                                       | 30.8  | 6.6                |
| General ward stay (days)                  | 6.3   | 7.4                |
| ICU stay (days)                           | 5.5   | 13.1               |
| Absolute VO <sub>2</sub> peak (L/min)     | 2     | 0.7                |
| Relative VO <sub>2</sub> peak (ml/kg/min) | 23.4  | 8.1                |
| VAS – tinnitus                            | 6.2   | 2.5                |

**Subtitle:** n = number of participants; % = percentage; N/A = not applicable; < = less than; > = more than; cm = centimeter; kg = kilogram; ICU = intensive care unit; BMI = body mass index; VO<sub>2</sub> peak = peak oxygen consumption; L/min = liters of oxygen per minute; ml/kg/min = milliliters of oxygen per kilogram per minute; VAS = visual analog scale

Participants with tinnitus were analyzed in subgroups. Significant differences with a moderate effect size were found between the sexes regarding absolute ( $p = 0.001$ ;  $r = 0.62$ ) and relative  $VO_{2peak}$  ( $p = 0.001$ ;  $r = 0.56$ ). Women had lower values than men. There was a difference with a small effect size for relative  $VO_{2peak}$  in those who reported hypertension ( $p = 0.048$ ;  $r = 0.28$ ); hypertensives had lower values.

Differences were also found in relative  $VO_{2peak}$  for those whose BMI was classified as obesity ( $p = 0.039$ ;  $E_r^2 = 0.13$ ), with a small effect size (Table 4).

The comparative analysis between participants who reported tinnitus previous to the infection and those who reported it during or after the infection found no differences or associations between them for any of the variables ( $p > 0.05$ ) (Table 5).

**Table 2.** Comparative analysis of the cardiorespiratory fitness in people with and without tinnitus after the infection ( $n = 192$ )

| Cardiorespiratory fitness         | Without tinnitus              | With tinnitus    | p-value                     |
|-----------------------------------|-------------------------------|------------------|-----------------------------|
|                                   | ( $n = 140$ )                 | ( $n = 52$ )     | effect size ( $r$ )         |
| Absolute $VO_{2peak}$ (L/min)     | 2.01 [1.46-2.62] <sup>a</sup> | 1.63 [1.37-2.21] | $p = 0.035^*$<br>$r = 0.15$ |
| Relative $VO_{2peak}$ (ml/kg/min) | 23.2 [17.1-28.6]              | 20.5 [16.3-25.8] | $p = 0.176$<br>$r = 0.10$   |

<sup>a</sup>statistically significant; <sup>a</sup>median and interquartile range [25%-75%]

**Subtitle:**  $n$  = number of participants;  $VO_{2peak}$  = peak oxygen consumption; L/min = liters of oxygen per minute; ml/kg/min = milliliters of oxygen per kilogram per minute;  $r$  = effect size calculated for the Mann-Whitney test

**Table 3.** Correlation between the tinnitus discomfort scale and the cardiorespiratory fitness in people after the infection ( $n = 52$ )

| VAS – TINNITUS | Absolute $VO_{2peak}$ | Relative $VO_{2peak}$ |
|----------------|-----------------------|-----------------------|
|                | $r_s$ ; p-value       | $r_s$ ; p-value       |
|                | -0.091; 0.572         | -0.144; 0.369         |

$r_s$  Spearman correlation

**Subtitle:**  $n$  = number of participants; VAS = visual analog scale;  $VO_{2peak}$  = peak oxygen consumption

**Table 4.** Analysis of tinnitus subgroups ( $n = 52$ )

| Variables                       | Absolute $VO_{2peak}$         | p-value          | Relative $VO_{2peak}$ | p-value           |
|---------------------------------|-------------------------------|------------------|-----------------------|-------------------|
|                                 |                               | Effect size      |                       | Effect size       |
| <b>SEX</b>                      |                               |                  |                       |                   |
| Males                           | 2.19 [1.84-2.91] <sup>a</sup> | $p = 0.001^{**}$ | 25.52 [21.36-31.84]   | $p = 0.001^{*†}$  |
| Females                         | 1.41 [1.04-1.62]              | $r = 0.62$       | 16.94 [13.48-21.15]   | $r = 0.56$        |
| <b>AGE RANGE</b>                |                               |                  |                       |                   |
| 18-44 years                     | 1.65 [1.17-2.81]              | $p = 0.867^{††}$ | 21.36 [14.62-38.40]   | $p = 0.564^{††}$  |
| 45-64 years                     | 1.62 [1.39-2.10]              | $E_r^2 = 0.01$   | 19.98 [16.71-25.64]   | $E_r^2 = 0.02$    |
| 65-80 years                     | 1.61 [1.09-1.96]              |                  | 20.93 [13.57-23.89]   |                   |
| <b>TINNITUS</b>                 |                               |                  |                       |                   |
| Before the infection            | 1.63 [1.17-2.22]              | $p = 0.831^{†}$  | 20.67 [14.78-28.24]   | $p = 0.892^{†}$   |
| During or after the infection   | 1.66 [1.38-2.24]              | $r = 0.01$       | 20.27 [16.84-25.65]   | $r = 0.01$        |
| <b>NEED FOR HOSPITALIZATION</b> |                               |                  |                       |                   |
| No                              | 1.65 [1.40-2.01]              | $p = 0.834^{†}$  | 22.08 [16.88-29.05]   | $p = 0.478^{†}$   |
| Yes                             | 1.62 [1.32-2.40]              | $r = 0.02$       | 19.26 [15.62-25.77]   | $r = 0.10$        |
| <b>HYPERTENSION</b>             |                               |                  |                       |                   |
| No                              | 1.79 [1.40-2.74]              | $p = 0.122^{†}$  | 23.09 [18.26-27.46]   | $p = 0.048^{*†}$  |
| Yes                             | 1.52 [1.05-2.03]              | $r = 0.21$       | 17.93 [13.73-23.74]   | $r = 0.28$        |
| <b>DIABETES</b>                 |                               |                  |                       |                   |
| No                              | 1.69 [1.39-2.26]              | $p = 0.652^{†}$  | 21.25 [15.85-25.98]   | $p = 0.896^{†}$   |
| Yes                             | 1.55 [1.16-2.21]              | $r = 0.06$       | 18.86 [16.56-27.41]   | $r = 0.02$        |
| <b>BMI CATEGORY</b>             |                               |                  |                       |                   |
| Normal weight (18-24.99)        | 1.76 [1.47-2.63]              | $p = 0.846^{††}$ | 27.43 [20.90-38.23]   | $p = 0.039^{*††}$ |
| Overweight (25-29.99)           | 1.61 [1.25-2.40]              | $E_r^2 = 0.01$   | 23.05 [18.78-29.87]   | $E_r^2 = 0.13$    |
| Obesity (30 or more)            | 1.62 [1.39-2.19]              |                  | 18.55 [13.48-24.13]   |                   |

<sup>a</sup>median and interquartile range [25%-75%]; \*statistically significant; † = Mann-Whitney test values; †† = Kruskal-Wallis test values

**Subtitle:**  $n$  = number of participants;  $VO_{2peak}$  = peak oxygen consumption;  $r$  = effect size calculated for the Mann-Whitney test;  $E_r^2$  = effect size calculated for the Kruskal-Wallis test; BMI = body mass index

**Table 5.** Comparative analysis between participants who reported tinnitus before the infection and those who reported it during or after the infection (n = 52)

| Continuous variables                      | Tinnitus before the infection (n = 25) | Tinnitus during or after the infection (n = 27) | p-value               |
|---|--|---|-----------------------|
|   |  |   | (Mann-Whitney)        |
| Age (years)                               | 54 [43.5 – 62.5] <sup>a</sup>          | 53 [45 – 58]                                    | p = 0.769<br>r = 0.01 |
| Weight (kg)                               | 81 [71.9 – 90.2]                       | 79.7 [69 – 91.6]                                | p = 0.721<br>r = 0.01 |
| Height (cm)                               | 165.5 [151.5 – 171.2]                  | 157 [154 – 172]                                 | p = 0.934<br>r = 0.01 |
| BMI                                       | 30.4 [26.4 – 36.8]                     | 31.6 [27.6 – 33.6]                              | p = 0.920<br>r = 0.01 |
| VAS – Tinnitus                            | 7 [5 – 8]                              | 5 [4 – 8]                                       | p = 0.153<br>r = 0.02 |
| Absolute VO <sub>2</sub> peak (l/min)     | 1.63 [1.2 – 2.2]                       | 1.6 [1.4 – 2.2]                                 | p = 0.831<br>r = 0.01 |
| Relative VO <sub>2</sub> peak (ml/kg/min) | 20.6 [14.7 – 28.2]                     | 20.2 [16.8 – 25.6]                              | p = 0.892<br>r = 0.01 |
| Categorical variables                     | Tinnitus before the infection – n (%)  | Tinnitus during or after the infection – n (%)  | p-value               |
|   |  |   | (chi-square)          |
| Sex                                       |  |   |                       |
| Males                                     | 13 (56.5)                              | 10 (43.5)                                       | p = 0.402             |
| Females                                   | 12 (41.4)                              | 17 (58.6)                                       | φ = 0.151             |
| Age range                                 |  |   |                       |
| 18 – 44 years                             | 7 (53.8)                               | 6 (46.2)  | p = 0.758             |
| 45 – 64 years                             | 15 (44.1)                              | 19 (55.9)                                       | V = 0.114             |
| 65 – 80 years                             | 3 (60.0)                               | 2 (40.0)  |                       |
| Need for hospitalization                  |  |   |                       |
| No  | 10 (50.0)                              | 10 (50.0)                                       | p = 1.00              |
| Yes                                       | 15 (46.9)                              | 17 (53.1)                                       | φ = 0.030             |
| Hypertension                              |  |   |                       |
| No  | 15 (48.4)                              | 16 (51.6)                                       | p = 1.00              |
| Yes                                       | 10 (47.6)                              | 11 (52.4)                                       | φ = 0.008             |
| Diabetes                                  |  |   |                       |
| No  | 22 (48.9)                              | 23 (51.1)                                       | p = 1.00              |
| Yes                                       | 3 (42.9)                               | 4 (57.1)  | φ = 0.41              |
| BMI category                              |  |   |                       |
| Normal weight<br>(18-24.99)               | 3 (75.0)                               | 1 (25.0)  | p = 0.643             |
| Overweight<br>(25-29.99)                  | 9 (45.0)                               | 11 (55.0)                                       | V = 0.156             |
| Obesity<br>(30 or more)                   | 13 (46.4)                              | 15 (53.6)                                       |                       |

<sup>a</sup>(median and interquartile range [25%-75%])

**Subtitle:** n = number of participants; VAS = visual analog scale; VO<sub>2</sub>peak = peak oxygen consumption; l/min = liters of oxygen per minute; ml/kg/min = milliliters of oxygen per kilogram per minute; r = effect size calculated for the Mann-Whitney test; φ = Phi – effect size for the chi-square test, 2x2 table; V = Cramer's V – effect size for the chi-square test, 2x3 table; BMI = body mass index

## DISCUSSION

The study aimed to verify the relationship between tinnitus sensation and cardiorespiratory fitness in people who had COVID-19. Its main findings indicated no correlation between tinnitus sensation (assessed with VAS) and cardiorespiratory fitness (assessed with VO<sub>2</sub>peak). However, there was a significant difference between tinnitus complaints and cardiorespiratory fitness among post-COVID-19 patients – the group with tinnitus had lower VO<sub>2</sub>peak than the group without tinnitus.

The self-reported prevalence of tinnitus was 27.1% (n = 52), of whom 27 patients began having the sensation during or after the

COVID-19 diagnosis. Moreover, among those with tinnitus, women had lower absolute and relative VO<sub>2</sub>peak, and hypertensive and obese participants had lower relative VO<sub>2</sub>peak. This demonstrates that the respiratory capacity can greatly influence the onset or continuity of tinnitus in post-COVID-19 patients, with an intrinsic relationship with sex and comorbidities, such as hypertension and obesity.

Because data in the literature is scarce, further studies should be carried out in healthy post-COVID-19 adults that have not been hospitalized and in people with different sensory conditions to obtain more in-depth knowledge of tinnitus. Accordingly, a statistically significant difference was found between post-COVID-19 tinnitus and cardiorespiratory fitness, with lower absolute VO<sub>2</sub>peak values in this population.

Nevertheless, these findings must be cautiously interpreted, as no difference was found for relative  $\text{VO}_2\text{peak}$ . Hence, further studies should also be conducted in post-COVID-19 adults and older adults.

The literature in the area has reported the impact of cardiorespiratory fitness, other factors related to comorbidities, and lifestyle on the aggravation of COVID-19 symptoms. A recent study associated lifestyle and socioeconomic factors with the risk of severe COVID-19 – greater cardiorespiratory fitness decreased the risk associated with obesity and arterial hypertension and mediated the risk associated with various socioeconomic factors. This response emphasizes the importance of interventions to maintain or increase cardiorespiratory fitness in the general population to strengthen their immunity and minimize the possibility of severe COVID-19, especially in high-risk individuals<sup>(16)</sup>. Various studies suggest that SARS-CoV-2-induced immune deregulation and hyperinflammatory response are more involved in disease severity than the virus itself<sup>(17-19)</sup>. Immune deregulation due to COVID-19 is characterized by delayed and impaired interferon response, lymphocyte exhaustion, and cytokine storm, with diffuse damages to the pulmonary tissue and posterior thrombotic phenomena leading to low cardiorespiratory fitness<sup>(17-19)</sup>. Moreover, cardiovascular disease is inversely and independently associated with long-term cardiorespiratory fitness and the risk of incident heart failure<sup>(16)</sup>. Thus, the protective effect of cardiorespiratory fitness on the risk of heart failure requires further assessment.

The prevalence of self-reported tinnitus in this study was 27.1%. This high prevalence was probably due to COVID-19 infection and its sequelae, as 14.1% of the patients with tinnitus reported that its sensation began during or after the COVID-19 diagnosis. Studies show that immune deregulation with increased proinflammatory cytokines has been observed in patients with tinnitus, especially those exposed to occupational noise. This suggests an association between IL-1 $\alpha$  gene polymorphism and susceptibility to tinnitus in individuals with no history of occupational noise, as well as an association between IL6 gene polymorphisms in the region -174G/C and susceptibility to tinnitus<sup>(20,21)</sup>.

Cytokine storms – i.e., exaggerated immune responses - are often found in viral infections and are closely related to COVID-19 progression and associated complications and mortality. It was verified that such storms can help elucidate risk factors and reduce COVID-19-related health complications<sup>(17-19)</sup>, along with the factors related to tinnitus.

The present study also found, among individuals with tinnitus, that women had lower absolute and relative  $\text{VO}_2\text{peak}$ . This result was expected, as demonstrated in another study in healthy men and women ( $n = 60$ ); it found that throughout mature adulthood (42-88 years), women have less  $\text{O}_2$  transport capacity. The systolic volume, cardiac output,  $\text{VO}_2\text{peak}$ , and blood volume in the cited study were determined with established methods, including transthoracic echocardiogram and central arterial pressure, and  $\text{O}_2$  measure. Measurements were retaken in men after taking their blood and  $\text{O}_2$  transport. The capacity corresponding to women's levels decreased. Before the blood was normalized, the  $\text{O}_2$  and blood volume load capacity was markedly smaller in women than in men ( $p < 0.001$ )<sup>(22)</sup>.

The strengths of this study are the cohort of people with COVID-19 with data variations regarding a diversity of lifestyle factors, assessed with precise information on length of hospital stay and standardized methods, such as the Bruce Test.

The limitations of the study include self-reported data on tinnitus complaints, which are subject to memory bias. Another limitation was the impossibility to generalize the results and contextual factors because of the cross-sectional design, which does not enable to determine a cause-effect relationship, possibly interfering with the results. Nonetheless, this study presents interesting and unprecedented results on the relationship between tinnitus and cardiorespiratory fitness in post-COVID-19 patients, which can be used as a support to clinical practice and a broader look at procedures to minimize or heal tinnitus in this population, also considering their respiratory capacity and continuity of tinnitus complaints after COVID-19.

Furthermore, the results of this study – which demonstrate a mean VAS score of  $6.2 \pm 2.5$  points regarding tinnitus intensity – reinforce the importance of further research on the consequences of tinnitus on the quality of life of people with long COVID-19. It was also demonstrated that further studies with more robust designs should address individuals with tinnitus beginning during or after COVID-19 to acquire more in-depth knowledge on tinnitus in this population, as well as its peculiarities, characteristics, and factors associated with its progress, helping clarify gaps, provide support to clinical practice, and implement health promotion programs with strategies to reduce possible symptoms and comorbidities due to COVID-19.

These findings help raise awareness of the need for strategies to recover health conditions through physical activity and a healthy diet. These are essential to people with tinnitus who survived COVID-19, particularly those who remain symptomatic. Hence, cardiorespiratory variables must be monitored to verify possible COVID-19 sequelae in people with persistent tinnitus after long COVID-19.

## CONCLUSION

The prevalence of self-reported tinnitus was 27.1% ( $n = 52$ ), of whom 27 began having the sensation during or after the COVID-19 diagnosis. No correlation was found between tinnitus sensation (assessed with VAS) and cardiorespiratory fitness (measured with  $\text{VO}_2\text{peak}$ ) in people who had COVID-19. Also, there were no differences or associations in the study variables between those who reported tinnitus previous and not previous to the infection. However, there was a statistically significant difference between tinnitus complaints and  $\text{VO}_2\text{peak}$  in post-COVID-19 patients – the group with tinnitus had lower absolute  $\text{VO}_2\text{peak}$  than the group without tinnitus. Among the patients with tinnitus, women had lower absolute and relative  $\text{VO}_2\text{peak}$ , and hypertensive and obese participants had lower relative  $\text{VO}_2\text{peak}$ .

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