Systematic review and meta-analysis of extended high-frequency audiometry in tinnitus patients

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Background: This study aimed to systematically evaluate the detection effect of extended high-frequency audiometry (EHFA) in tinnitus patients and provide a theoretical basis for the clinical diagnosis of tinnitus.

Methods: We conducted a computer-based search for randomized controlled trial (RCT) literature on extended audiometry in tinnitus patients using the PubMed, Web of Science, China National Knowledge Infrastructure (CNKI), and Elsevier Science Direct databases. The search dates ranged from the database establishment date to February 2020. Risk of bias in the included literature was evaluated using the RCT bias risk assessment standard provided in the Handbook for Systematic Reviews for Interventions (version 5.0.2, 2008, Chapter 9). Finally, Review Manager 5.3 software was used to conduct a meta-analysis of the included literature.

Results: The retrieved literature was systematically screened. A total of 10 RCTs were included in the meta-analysis, which involved a total of 1,389 tinnitus patients. The results of the meta-analysis showed that at the frequencies of 14 kHz and 16 kHz, there was visible difference in detection rate of hearing threshold (DR-HT) between the 2 groups [odds ratio (OR) =0.21, 95% confidential interval (CI): 0.14–0.32, Z=7.29, P<0.00001] and (OR =0.14, 95% CI: 0.07–0.27, Z=5.96, P<0.00001) respectively. When the frequency was 18 kHz, there was a significant statistical difference in DR-HT between the 2 groups (OR =0.13, 95% CI: 0.07–0.24, Z=6.50, P<0.00001), and at 20 kHz, the statistically significant difference in DR-HT between the 2 groups was high (OR =0.17, 95% CI: 0.12–0.23, Z=10.38, P<0.00001).

Discussion: EHFA had a critical effect on tinnitus patients. The meta-analysis provided evidence for early hearing loss in tinnitus patients. EHFA played a crucial role in the clinical diagnosis of tinnitus patients.

Keywords: Meta-analysis; tinnitus; extended high-frequency audiometry (EHFA); detection rate of hearing threshold

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Introduction

Tinnitus is a condition in which a sound in the head or ear is experienced subjectively but there is no corresponding external sound source. Tinnitus, which usually increases with age (1). Tinnitus can be caused by an underlying condition or disease, or it may result from exposure to external sound waves. Based on the cause, tinnitus can be

classified into external ear tinnitus, middle ear tinnitus, inner ear tinnitus, neurological tinnitus, central tinnitus, tinnitus caused by the external auditory system, tinnitus caused by salicylic acid, and trauma-associated tinnitus. The pathogenesis of tinnitus is usually related to the posterior cochlear nerve, the sensory system, hormones, and central neurotransmitters (2). The base of the cochlea turns to

the basement membrane to experience high-frequency sound, so hearing loss often starts from high-frequency and gradually develops to middle and low-frequency. At present, the diagnosis of tinnitus is mainly carried out from four aspects: nature, etiology, lesion location and quantification. When the tinnitus test is used for diagnosis, it is often considered that the tinnitus is mostly a single tone, and the loudness is often within the 5dB hearing threshold (3). Studies have confirmed that the regular pure tone audiometry frequency of some tinnitus patients is within the normal range (4). But this cannot prove that the cochlear function of tinnitus patients has not been damaged.

At present, pure tone audiometry (PTA) is the most commonly used clinical hearing assessment method. The human auditory system can perceive sounds with a frequency of 20–20,000 Hz, and the range of conventional pure tone audiometry is only 125–8,000 Hz, while the extended high frequency audiometry (EHFA) can measure the hearing threshold of the human auditory system 10–20 kHz, so it can reflect the early stage of the cochlea damage (5). Therefore, EHFA is an important means for early evaluation of hearing impairment, is conducive to the early diagnosis and treatment of tinnitus patients, and is of great significance in clinical audiology (6).

Although there have been some clinical studies involving the diagnosis of tinnitus using the high-frequency portion of the hearing range, the quality of the literature is uneven and there is a lack of unified testing standards. For this reason, we performed a meta-analysis of randomized controlled trials (RCTs) involving EHFA in patients with tinnitus and evaluated the effect of EHFA by expanding the detection rate of hearing threshold (DR-HT) for tinnitus. The objective of this study was to provide a theoretical basis for the clinical diagnosis of tinnitus. We present the following article in accordance with the PRISMA reporting checklist (available at <https://dx.doi.org/10.21037/apm-21-3060>).

Methods

Article inclusion and exclusion criteria

The inclusion criteria were as follows: articles with an experimental group comprising patients clinically diagnosed with tinnitus and a control group involving people with normal hearing, as tested by pure tone audiometry (PTA), and no history of disease that could cause deafness; articles involving an RCT; articles published in English from a foreign or English database; articles in which the

experimental and control groups were tested by EHFA or EHFA combined with conventional PTA; and articles with comparable baseline data for the experimental and control groups.

The exclusion criteria were as follows: articles which involved a non-RCT study, such as retrospective research; articles whose research objects were animals, and; unpublished literature, non-English literature, and literature with incomplete data.

Article search

We used 4 databases to search for RCT literature on EHFA in tinnitus patients: PubMed, Web of Science, China National Knowledge Infrastructure (CNKI), and Elsevier Science Direct. The search dates ranged from the database establishment date to February 2020. Literature search keywords consisted of subject words and free words, including “tinnitus”, “extended high-frequency”, “pure tone audiometry”, “extended high-frequency audiometry”, “PTA”, “EHF”, and “EHFA”, and were connected with “and” or “or”. The literature search was done independently by 2 researchers.

Article screening

Once the literature search was complete, the articles were screened independently by 2 researchers. The article bibliographies were first imported into NoteExpress 3.2.0 software to establish a database. After excluding duplicate documents, the 2 researchers manually screened the remaining articles. During manual screening, the researchers read the title and abstract of the articles and deleted those that did not meet the requirements. The researchers then read the full text of the remaining articles and using the inclusion and exclusion criteria, determined whether they could be included in the meta-analysis. If there was any disagreement between the 2 researchers, it was resolved through discussion. If they were unable to reach a consensus, a third party arbitrated.

Data extraction

Data extraction, including basic article information, research objects, intervention measures, outcome indicators, and other data, was carried out by the 2 researchers. Once the extraction was complete, a cross-examination was conducted. If there was disagreement, it was resolved

through discussion. If the 2 researchers were unable to reach a consensus, a third party arbitrated. The content extracted from the articles included the following items: the title, first author, and publication date of the article; the age, gender, sample size, and baseline comparability of the research subjects; research intervention measures and control measures; and, research outcome indicators and research data.

Quality evaluation of articles

RCT bias risk assessment criteria provided in the Cochrane Handbook for Systematic Reviews for Interventions (version 5.0.2, 2008, Chapter 9) were adopted to assess the bias risk of the included articles. The assessment tool evaluated whether the study involved a randomized sequence, whether assignments were concealed, whether subjects were blinded, whether outcome assessors were blinded, whether the research data was complete, whether there was selective reporting, and whether there were other biases.

Statistical analysis

Review Manager 5.3 software was used to conduct a meta-analysis of the included articles and draw forest diagrams and funnel diagrams for the research indicators. As all the variables involved 2 categories, risk ratio (RR) was undertaken to describe the effect size, and a 95% confidence interval (95% CI) was calculated. The main methods of sensitivity analysis include: changing the inclusion criteria (especially for controversial studies), excluding low-quality studies, and using different statistical methods/models to analyze the same data. This study excluded low-quality articles for sensitivity analysis. Heterogeneity of the included articles was evaluated with I^2 . If $I^2 > 50\%$ and the source of the heterogeneity could not be explained, a random-effects model (REM) was adopted for analysis of the combined effect size, and if $I^2 < 50\%$, a fixed-effects model (FEM) was applied. The combined effect size adopted U test and 95% CI. The U test result was expressed as P value, and $P < 0.05$ indicated that the difference was statistically significant.

Results

Results of article search

Preliminary searches of the databases resulted in a total of

792 related articles, including 162 from PubMed, 269 from Web of Science, 202 from CNKI, and 159 from Elsevier Science Direct. After duplicate documents were eliminated using NoteExpress 3.2.0 software, 588 articles remained. Once the titles and abstracts were read and screened according to the inclusion criteria, there were 91 remaining articles. The 2 researchers read each of the remaining articles carefully, 14 articles that meet the requirements were included. After reading the full text, 3 articles with “too many people fall off” and 1 article with “research indicators were not clear” were further excluded. Finally, 10 articles were ultimately included in the meta-analysis (7-16). The publication dates varied from 2003 to 2020. The 10 articles contained a total of 1,236 subjects and 2,361 ears, which included 620 subjects and 1,184 ears in the experimental group and 616 subjects and 1,177 ears in the control group. The baseline data of the study subjects were comparable. A flow chart illustrating the article search is shown in *Figure 1*, and the basic characteristics of the included articles are provided in *Table 1*.

Bias risk assessment

After risk of bias in the 10 articles was evaluated using the Cochrane Handbook for Systematic Reviews for Interventions (version 5.0.2), charts were drawn using Review Manager 5.3 software (as shown in *Figures 2,3*). The evaluation items for risk of bias included: randomized sequencing: 5 articles (9,10,12,14,15) did not mention which randomization method was used, so they were defined as having an unclear risk of bias; assignment concealment: 10 articles (7-16) did not mention whether assignments were concealed, suggesting that they had an unclear risk of bias; subjects blinded: 1 article (13) mentioned that “subjects signed informed consents”, suggesting a high risk of bias, and the remaining 9 articles (7-12,14-16) did not report whether the subjects were blinded, so the risk of bias in these cases was unclear; 10 articles (7-16) did not mention whether outcome assessors were blinded, indicating that the risk of bias was unclear; data completeness: the outcome data of all 10 articles (7-16) were complete, indicating a low risk of bias; selective reporting: there was no selective reporting among the 10 articles (7-16), suggesting a low risk of bias; other risks of bias: for 3 articles (13,14,16) it was impossible to judge whether there were other biases, suggesting an unclear risk of bias, and for 5 articles (7-11), the number of subjects in the experimental and control groups was inconsistent, suggesting a high risk of bias.

Figure 1 Flow chart for the article search.

DR-HT at 8 kHz

A total of 6 documents (7,10,12-14,16) reported on DR-HT at 8 kHz, which included 679 subjects and 1,263 ears (374 subjects and 704 ears in the experimental group, 305 cases and 559 ears in the control group). There was a certain degree of heterogeneity among the included studies ($I^2=97\%$ and $P<0.00001$), and REM was used for analysis. The results are shown in *Figure 4* [risk ratio (RR) =0.97, 95% CI: 0.88–1.06, $Z=0.72$, $P=0.47$] and suggest that there was no statistical difference between the experimental and control groups in DR-HT at 8 kHz.

DR-HT at 10 kHz

A total of 8 articles (7,9-14,16) reported on DR-HT at 10 kHz, which included 948 subjects and 1,795 ears (490 subjects and 934 ears in the experimental group, and 458 cases and 861 ears in the control group). There was a certain degree of heterogeneity among the included studies ($I^2=97\%$ and $P<0.00001$). The results of REM analysis are shown in *Figure 5* (RR =0.98, 95% CI: 0.93–1.03, $Z=0.97$, $P=0.33$) and suggest that the experimental

and control groups were not significantly different in DR-HT at 10 kHz.

DR-HT at 12 kHz

There were 7 documents (7,9-11,13,14,16) reporting on DR-HT at 12 kHz, which included 768 subjects and 1,435 ears (400 subjects and 754 ears in the experimental group, and 368 cases and 681 ears in the control group). The heterogeneity among the included studies was visible ($I^2=97\%$ and $P<0.00001$), and REM was adopted for analysis. The results in *Figure 6* (RR =0.88, 95% CI: 0.77–1.01, $Z=1.85$, $P=0.06$) indicate that there was no statistically significant difference between the 2 groups in DR-HT at 12 kHz.

DR-HT at 14 kHz

A total of 7 documents (7-9,11,13,14,16) reported on DR-HT at 14 kHz, which included 645 subjects and 1,322 ears (323 subjects and 658 ears in the experimental group and 322 cases and 664 ears in the control group). The heterogeneity among the included studies was small ($I^2=49\%$

Table 1 Basic characteristics of the included articles

First author	Year of publication	Group	Number of subjects	Number of ears	Countermeasures
Luo HJ (7)	2003	Experimental	35	60	EHFA
		Control	30	60	EHFA
Wang C (8)	2005	Experimental	35	60	EHFA + PTA
		Control	30	60	EHFA + PTA
Zhai CS (9)	2010	Experimental	78	154	EHFA + PTA
		Control	73	142	EHFA + PTA
Tang J (10)	2011	Experimental	77	138	EHFA
		Control	46	59	EHFA
Li DM (11)	2014	Experimental	38	76	EHFA + PTA
		Control	80	160	EHFA + PTA
Li GF (12)	2016	Experimental	90	180	EHFA + PTA
		Control	90	180	EHFA + PTA
Ma F (13)	2018	Experimental	134	268	EHFA
		Control	101	202	EHFA
Gong JM (14)	2019	Experimental	18	18	EHFA + PTA
		Control	18	18	EHFA + PTA
Ding LP (15)	2020	Experimental	188	376	EHFA
		Control	188	376	EHFA
Zhang XH (16)	2020	Experimental	20	40	EHFA
		Control	20	40	EHFA

EHFA, extended high-frequency audiometry; PTA, pure tone audiometry.

Figure 2 Bar graph for bias assessment of the included articles.

and $P=0.08$), so FEM was applied for analysis. The results (Figure 7, OR =0.21, 95% CI: 0.14–0.32, $Z=7.29$, and $P<0.00001$) indicate that there was a statistically significant difference in DR-HT between the 2 groups at 14 kHz.

DR-HT at 16 kHz

Ten articles (7-16) reported on DR-HT at 16 kHz, which included 1,389 subjects and 2,667 ears (713 subjects and

1,370 ears in the experimental group, and 676 subjects and 1,297 ears in control group). There was heterogeneity among the included studies ($I^2=73\%$ and $P<0.0001$), so REM was applied for analysis. The results are shown

in *Figure 8* [odds ratio (OR) =0.14, 95% CI: 0.07–0.27, $Z=5.96$, $P<0.00001$] and reveal an obvious difference in DR-HT at 16 kHz between the 2 groups.

DR-HT at 18 kHz

Seven articles (7,8,11,13–16) reported on DR-HT at 18 kHz, which included 935 subjects and 1,814 ears (468 subjects and 898 ears in the experimental group, and 467 cases and 916 ears in the control group). There was heterogeneity among the included studies ($I^2=68\%$ and $P=0.004$). The REM analysis results are shown in *Figure 9* (OR =0.13, 95% CI: 0.07–0.24, $Z=6.50$, $P<0.00001$) and indicate that the experimental group showed an observable difference compared to the control group in DR-HT at 18 kHz.

DR-HT at 20 kHz

A total of 7 articles (7,8,11,13–16) reported on DR-HT at 20 kHz, which included 935 subjects and 1,814 ears (468 subjects and 898 ears in the experimental group, and 467 cases and 916 ears in the control group). The heterogeneity among the included studies was small ($I^2=28\%$ and $P=0.22$). The FEM analysis results are shown in *Figure 10* (OR =0.17, 95% CI: 0.12–0.23, $Z=10.38$, $P<0.00001$) suggest that there was a statistically significant difference in DR-HT at 20 kHz between the 2 groups.

Analysis of publication bias

Publication bias was evaluated using Review Manager 5.3 software, and the results are shown in *Figure 11*. The DR-HTs at 8, 10, 14, 18, and 20 kHz were distributed within the CI, and the publication bias was low. The DR-HT funnel charts at 12 and 16 kHz had some scattered

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Ding 2020	?	?	?	?	+	+	+
Gong 2019	?	?	?	?	+	+	?
Li 2014	+	?	?	?	+	+	+
Li 2016	?	?	?	?	+	+	+
Luo 2003	+	?	?	?	+	+	+
Ma 2018	+	?	?	?	+	+	?
Tang 2011	?	?	?	?	+	+	+
Wang 2005	+	?	?	?	+	+	+
Zhai 2010	?	?	?	?	+	+	+
Zhang 2020	+	?	?	?	+	+	?

Figure 3 Risk assessment of the included articles.

Figure 4 Forest diagram of detection rate of hearing threshold (DR-HT) at 8 kHz.

Figure 5 Forest diagram of detection rate of hearing threshold (DR-HT) at 10 kHz.

Figure 6 Forest diagram of detection rate of hearing threshold (DR-HT) at 12 kHz.

Figure 7 Forest diagram of detection rate of hearing threshold (DR-HT) at 14 kHz.

points outside the CI, indicating that there was some publication bias.

Discussion

The incidence of tinnitus gradually increases with age

and can cause upset, insomnia, and anxiety in patients. At present, there is no clinically effective drug for the treatment of tinnitus, and as the mechanism of tinnitus is unclear, early diagnosis is the basis for treatment (17). One of the characteristics of tinnitus is early high-frequency hearing impairment. Compared with conventional PTA,

Figure 8 Forest diagram of detection rate of hearing threshold (DR-HT) at 16 kHz.

Figure 9 Forest diagram of detection rate of hearing threshold (DR-HT) at 18 kHz.

Figure 10 Forest diagram of detection rate of hearing threshold (DR-HT) at 20 kHz.

EHFA can detect hearing impairment earlier (18).

The results of our meta-analysis showed that at 8–12 kHz, the DR-HT of the experimental group was lower than that of the control group, but there was no strong statistical

difference between the 2 groups. At 14–20 kHz, there was a statistically obvious difference in DR-HT between the 2 groups. As the frequency increased, the lower the DR-HT, indicating that degeneration of the auditory system

Figure 11 Funnel diagrams of detection rate of hearing threshold (DR-HT) at different frequencies.

in tinnitus patients starts with high frequencies and then moves to medium and low frequencies.

For the diagnosis of tinnitus, it is recommended that the

doctor ask for a comprehensive medical history, improve the examination methods of the otolaryngology department, and detailed audiological examination methods. The severity

of tinnitus can be graded through interviews, or the degree of tinnitus can be assessed by designing a tinnitus self-rating scale. This is conducive to doctors' targeted design of treatment methods. For the treatment of tinnitus, it can be eliminated by medication, dietary supplements, cochlear implants, transcranial electrical stimulation, vagus nerve stimulation, and acupuncture treatment (19-21). However, there is currently no way to completely cure subjective tinnitus. Therefore, treatments can help patients adapt to tinnitus and reduce the impact of tinnitus on daily life, such as sound therapy, hearing aids, and psychotherapy (22,23).

At present, the cognition of tinnitus remains in a state of unknown cause and incurable. Moreover, the curative effect evaluation standard of tinnitus has not yet reached a uniform at home and abroad. Therefore, in future research, we hope to achieve new breakthroughs in the diagnosis and treatment of difficult diseases such as tinnitus through the perspective of traditional Chinese medicine.

Conclusions

Our meta-analysis of EHFA in tinnitus patients included 10 articles, which involved a total of 1,236 subjects and 2,361 ears. The results of the meta-analysis showed that there was no obvious statistical difference in DR-HT between tinnitus patients and healthy subjects at 8–12 kHz. At a frequency of 14–20 kHz, the DR-HT of tinnitus patients differed greatly from that of the normal population. As the frequency increased, DR-HT decreased. EHFA was effective in detecting tinnitus patients at high frequencies. Results of the meta-analysis in this study provided evidence for early hearing loss in tinnitus patients and a theoretical basis for the application of EHFA to the early clinical diagnosis of tinnitus patients.

This study had some limitations. The amount of included literature was low, resulting in a small sample size, and the high-frequency audiometry threshold of each frequency was not analyzed and evaluated. Therefore, in future work, more high-quality, large-sample experiments are needed for supplementary verification.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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