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Hearing Loss in Patients With Ankylosing Spondylitis: A Systematic Review and Metaanalysis

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ABSTRACT. ***Objective***. To determine the prevalence of hearing loss (HL) in patients with ankylosing spondylitis (AS) and to describe frequency-specific hearing threshold changes in this patient population compared to patients without AS.

Methods. A systematic review querying 4 databases (PubMed, OVID Medline, Scopus, Cochrane) was performed to identify studies evaluating HL in patients with AS. Metaanalysis was performed to identify overall prevalence rate and OR of HL, as well as to compare mean differences in frequency-specific hearing thresholds between patients with and without AS.

Results. Our metaanalysis included 14 studies and 1083 patients (598 with AS vs 485 without AS). The pooled prevalence of HL in patients with AS was 42.4% (95% CI 29.2–56.2). Patients with AS had a significantly higher OR of HL than patients without AS (OR 4.65, 95% CI 2.73–7.91). Mean differences in pure-tone hearing thresholds ranged from 0–5 decibels (dB) for frequencies of 0.25–4 kHz, and from 5–15 dB for frequencies of 6–16 kHz.

Conclusion. Patients with AS have higher odds of having HL than patients without AS. The AS population also presents with significantly impaired hearing thresholds across all conventional and extended pure-tone frequencies. This may manifest as slight to moderate HL. Results of this systematic review might justify increased attention to audiologic manifestations of patients with AS.

Key Indexing Terms: ankylosing spondylitis, hearing loss, high-frequency hearing loss, spondyloarthritis

Systemic autoimmune disorders, such as rheumatoid arthritis[1], systemic lupus erythematosus[2], Sjögren syndrome[3], psoriatic arthritis (PsA)[4], and systemic sclerosis[5], have been associated with audiovestibular dysfunction. This is commonly referred to as immune-mediated inner ear disease (IMIED), which embodies a constellation of clinical presentations[6]. Hearing loss (HL) is present in the majority of cases and is often sensorineural in nature. Vestibular dysfunction can be present in up to 50% of cases and can present with symptoms such as vertigo, tinnitus, aural fullness, or disequilibrium[1,3,4,5,7,8,9].

Multiple hypotheses exist regarding the pathogenesis of these phenomena, including (1) vasculitis of stria vascularis, (2) immune complex deposition or other hypersensitive reaction affecting the inner ear, (3) autoinflammation resulting from a dysregulated innate immune system; and (4) drug-induced ototoxicity from the myriad of immunomodulatory medications commonly used to treat patients with these disorders[4,10,11]. HL and vestibular dysfunction can lead to significant impairment for these patients, so if the loss can be prevented or identified early, intervention can help to prevent further impairment.

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Compared to the autoimmune conditions listed above, spondyloarthritis (SpA) has not been investigated as robustly for audiological dysfunction. The traditional concept of SpA includes a number of disorders with common genetic, radiological, and clinical features: ankylosing spondylitis (AS), PsA, inflammatory bowel disease (IBD), associated SpA, reactive arthritis (ReA), and undifferentiated SpA. These were originally termed "seronegative SpA" because patients with these conditions typically have a negative rheumatoid factor. The modern concept of SpA distinguishes predominantly axial SpA (including AS and nonradiographic axial SpA) from predominantly peripheral SpA. In epidemiological studies, AS is the most common SpA. The role of genes is not in doubt in SpA, with an estimated 70–90%[12,13] of patients with AS expressing the *HLA-B27* gene. Given the absence of disease-specific autoantibodies and evidence supporting an altered innate immune response, AS can be considered more of an autoinflammatory condition than an autoimmune condition; however, this remains to be further elucidated[14,15]. Since AS is a systemic condition, patients can develop extraarticular manifestations, such as anterior uveitis, heart conduction problems, or gastrointestinal inflammation[16]. It has been hypothesized that HL might be another extraarticular manifestation[17,18].

The prevalence and characterization of audiological dysfunction in patients with AS has not been well elucidated. Both conductive HL (CHL) and sensorineural HL (SNHL) have been reported in the literature[19,20]. Since AS causes ankyloses of joints, it might cause ossicular fixation leading to CHL[18]. Alternatively, IMIED could result in SNHL[18]. The nature of HL

in patients with AS has not been well characterized; however, in other autoimmune conditions, HL has been found to affect high frequencies in particular[21,22,23]. This has also been demonstrated in patients with AS[20]. Therefore, our systematic review aims to determine the rate of HL in patients with AS. Secondarily, we aim to describe frequency-specific hearing threshold changes in patients with AS compared to patients without AS.

MATERIALS AND METHODS

Search strategy and study selection. Our systematic review was performed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines[24]. This review queried 4 databases (PubMed, Scopus, OVID Medline, Cochrane) from their inceptions to January 23, 2020, for studies that assessed HL in patients with 1 of 4 types of SpA (PsA, AS, IBD-associated SpA, ReA). The search strategy included the following combination of subject headings and search terms: "spondyloarthropathy," "spondyloarthritis," "seronegative," "inflammatory bowel disease" or "Crohn's" or "ulcerative colitis," "ankylosing spondylitis," "reactive arthritis," "psoriatic arthritis," "hearing loss," "hearing," "inner ear," "cochlea," "audiometry," and "audiogram." To ensure the completeness of our search, we performed a manual review of the bibliographies of the included studies to identify additional relevant studies. However, no studies were included from this additional step. EndNote (Clarivate Analytics) served as a repository for included studies.

Inclusion criteria consisted of (1) assessment of 1 of 4 SpA types (PsA, AS, IBD-associated SpA, ReA); (2) data on incidence of HL or pure-tone audiometric thresholds (PTT); (3) comparison to age-matched controls; and (4) patients with no prior otologic pathology, ototoxic drug use, or otologic surgery. Exclusion criteria consisted of (1) letters, reviews, case reports, or case series < 10 patients; (2) studies without an age-matched control population; (3) incomplete data regarding PTT or incidence of HL; (4) non-English language; and (5) nonhuman subjects. Review of studies for inclusion was conducted by 2 separate authors (FY and PR), and any disputes were resolved by a third author (SAN).

Data extraction and statistical analysis. Extracted data included author, publication year, country of publication, study design, and patient characteristics. Specific patient characteristics included sex, age, HLA-B27 status, mean duration of AS illness, illness severity characteristics, incidence and type of HL, and pure-tone audiogram frequency-specific thresholds. We extracted data from both conventional hearing thresholds (0.5–8 kHz) as well as extended high frequency (EHF; 10–16 kHz) thresholds. Severity of HL was differentiated into "slight" [16–25 decibel (dB)], "mild" (25–40 dB), "moderate" (40–70 dB), and "severe" (70-90 dB) categories, according to the American Speech-Language-Hearing Association (ASHA)[25]. Additional methods for hearing evaluation included speech discrimination scores, speech recognition threshold, transient-evoked otoacoustic emissions, distortion-product otoacoustic emissions, and auditory brainstem response. Additional methods to assess vestibular function using electronystagmography include oculographic testing (saccade and tracking tests), positional tests for nystagmus, and the caloric reflex test. Unfortunately, data regarding these variables were not consistently reported and were unable to be included in the metaanalysis.

Metaanalysis was performed to describe the rate and risk of HL, and to generate mean differences for frequency-specific hearing thresholds between patients with AS and patients without AS. This was executed using Cochrane Review Manager Software (RevMan v5.3, Cochrane IMS). Pooled OR were generated using a Mantel-Haenszel model, and pooled mean differences for frequency-specific pure-tone thresholds (PTT) were generated using an inverse variance analysis model. Metaanalysis of proportions (MedCalc v19.1, MedCalc Software) was conducted to determine overall prevalence. Heterogeneity of included studies was first assessed using the Q statistic. Heterogeneity was also evaluated using the I^2 statistic. Lower I^2 values indicated lower heterogeneity, and vice versa with higher I^2 values. If I^2 was < 50%, a fixed statistical effect model was used. Alternatively, if I^2 was > 50%, a random statistical effect model was used. A value of $P < 0.05$ was considered to indicate a statistically significant difference for all statistical tests.

Last, study heterogeneity was evaluated using the Sterne and Egger tests[26,27]. This generated a funnel plot, which displays pooled values plotted on the horizontal axis and standard error (SE) on the vertical axis. A funnel plot can provide a graphical representation of study heterogeneity included in metaanalyses. The vertical line represents the summary estimated, derived using fixed effects metaanalysis. Two diagonal lines represent (pseudo) 95% confidence limits (effect ± 1.96 SE) around the summary effect for each SE on the vertical axis[28]. These show the expected distribution of studies in the absence of heterogeneity or of selection bias. In the absence of heterogeneity, 95% of the studies should lie within the funnel defined by these diagonal lines. Publication bias results in asymmetry of the funnel plot. For summarized rate of HL in patients with AS, only 1 study fell outside the funnel plot, indicating overall little heterogeneity (Supplementary Figure 1, available from authors on request).

Quality assessment. First, the level of evidence of all included studies was ascertained using the Oxford Center for Evidence-Based Medicine (OCEBM) criteria[29]. Next, all included studies were evaluated for risk of bias according to the Cochrane Handbook for Systematic Reviews of Interventions (v5.1.0)[30]. Specifically, the ROBINS-I tool was used because our systematic review evaluated nonrandomized studies[31]. Two authors (FY and PR) performed a pilot assessment on 3 studies to check for consistency of assessment. Both then performed independent risk assessments on the remaining studies. All disagreements were resolved by way of discussion with a third author (SAN). Risk of bias items included the following: bias due to confounding, bias in selection of participants into the study, bias in classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measurement of outcomes, and bias in selection of reported result. The risk of bias for each aspect was graded as "low," "unclear," or "high."

RESULTS

Search results. Our initial search generated 388 studies, from which 327 unique studies were assessed. Of these, 31 articles underwent full-text review. Ultimately, 14 studies were included for quantitative analysis. Figure 1 shows a PRISMA diagram outlining a summary of the search process.

Summary of included studies. Our metaanalysis included 14 studies and 1083 patients (598 with AS vs 485 without AS; Table 1)[17,18,20,32–42]. Of these 14 studies, 11 studies were used to analyze the risk of HL in patients with AS[17,18,20,32,33,35,37,39–42] and 9 studies were used to pool frequency-specific threshold data[18,20,32,34,36,38,39,40,41]. Only 6 studies reported CHL as well as SNHL, whereas the other 8 studies only examined SNHL in patients with AS (Table 2). The overall mean age of patients with AS was 37.7 years (range 16–71 yrs).

Our search included 4 forms of SpA (PsA, AS, IBD-associated SpA, and ReA); however, we were unable to include any studies evaluating IBD-associated SpA, ReA, or PsA because of strict inclusion criteria as well as paucity of data regarding these disease states. Specifically, none of the studies evaluating IBD had 100% of the patients have arthritic extraintestinal involvement. The studies describing ReA were primarily case studies or cohorts < 10 patients. Three studies evaluating PsA met inclusion criteria; however, data extraction did not yield enough datapoints to draw meaningful conclusions from the metaanalysis. Thus, all

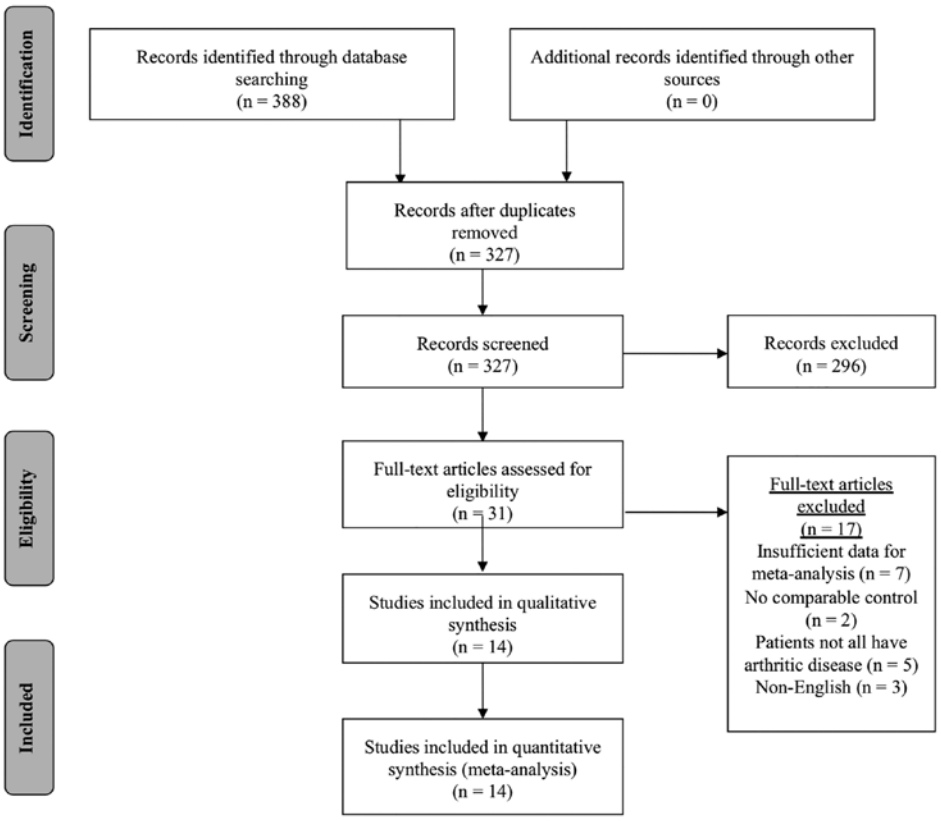

Figure 1. PRISMA diagram showing inclusion and exclusion criteria. PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses.

14 included studies evaluated HL in patients with AS. Since all studies were case-control studies, they were all considered as level 3 evidence, in accordance with the OCEBM criteria[29]. A risk of bias summary and graph are provided in Supplementary Figures 2 and 3 (available from authors on request). All studies had low or unclear risk assessments in each category.

The mean duration of AS disease was 9.2 years (range 1–40 yrs). HLA-B27 status was reported in 5 studies[17,18,20,33,35] with a pooled rate of HLA-B27 expression of 76% (Table 1). Definitions of HL slightly varied among our included studies, as listed in Table 2.

Although all included studies excluded patients who had a history of ototoxic drug use (including salicylates), most patients were treated with various medications for which the effects on cochlear function were unclear. These include nonsteroidal antiinflammatory drugs (NSAID), biologic agents [such as tumor necrosis factor (TNF)-α inhibitors], disease-modifying antirheumatic drugs [DMARD; sulfasalazine (SSZ), azathioprine (AZA), methotrexate (MTX)], and corticosteroids. Pharmacological treatment of patients with AS was described in 9 of the included studies, as detailed in Table 1.

HL prevalence and risk in AS. In a pooled analysis of 598 patients with AS, pooled prevalence of HL was 42.4% (95% CI 29.2–56.2%). Of the 12 studies that differentiated hearing loss by subtype, the pooled rate of SNHL was 32.5% (95% CI 29.6-36.5%). Pooled evaluation comparing 532 patients with AS and 373 patients without AS revealed significantly higher OR of HL in patients with AS than in patients without AS (OR 4.65, 95% CI 2.73–7.91; Figure 2).

Pure-tone audiometry frequency-specific threshold changes. Frequency-specific pure-tone audiometry data were available for metaanalysis at 0.25, 0.5, 1, 2, 4, 6, 8, 10, 12, 14, and 16 kHz (Table 3). Forest plots for mean differences of frequency-specific mean hearing thresholds are available in Supplementary Figures 2–5 (available from authors on request). Significantly elevated hearing thresholds in patients with AS were seen across all frequencies. Mean differences in PTT ranged from 0–5 dB for frequencies of 0.25–4 kHz and from 5–15 dB for frequencies of 6–16 kHz. The mean differences generally increased as frequencies increased, with the exception of frequencies at 16 kHz, at which the mean difference was 10 dB (95% CI 5 – 15).

Only at 6–16 kHz frequencies were mean HT elevated > 25 kHz (Table 3). The pooled mean HT reported by the included studies represented patients with and patients without HL. This may have led to an underestimation of HT elevation, if studies examined only the differences in HT in patients with HL.

DISCUSSION

Spondyloarthropathies—including AS, SpA, IBD-associated SpA, and ReA—often has multiple extraarticular manifestations including anterior uveitis, neurological and pulmonary involvement, and cardiac conduction problems[43]. Out of the

Table 1. Overview of included studies evaluating ankylosing spondylitis (AS).

Study Author, Year	AS Total, n	AS M, n	AS F, n	AS Mean Age, Years (SD) [Range]	Controls	Controls, M, n	Controls, F, n	Control Mean Age, Years (SD) [Range]	HLA-B27, n, %	Mean BASDAI Score (SD)	Mean BASFI Score (SD)	Mean Disease Duration, Years (SD) [Range]	Percentage of AS Patients on Medication[a]
Adam 2008[20]	45	23	22	39.6 (9.1) [19–63]	30	15	15	NR	30 (67)	NR	NR	10.6 (8.1) [1–30]	Current: 100% NSAID and/or DMARD
Ajmani 2019[18]	100	96	4	32 (12)	40	NR	NR	NR	94 (94)	3.5 (2.2)	2.8 (2)	8.2 (6)	Previous: 100% NSAID, 29% SSZ, 9% MTX
Alatas 2005[32]	28	20	8	38 [19–50]	23	13	10	35 [20–50]	NR	NR	5.8 (3)	12.0 (8.4)	No use of regular and long-term medication
Amor-Dorado 2011[33]	50	40	10	52.5 (15.3)	44	33	11	50.7 (17.3)	37 (74)	2.8 (1.9)	2.5 (2.0)	18.7 (13.6)	Previous: 100% NSAID, 28% TNF-α blocker
Bozan 2016[34]	30	18	12	32 (8)	35	22	13	32 (6)	NR	4.4 (1.7)	NR	5.3 (5.1)	NR
Bozkurt 2014[17]	50	40	10	32.2 (8.3) [18–55]	34	22	12	35.6 (8.2) [20–50]	27 (54)	3.5 (2.0)	3.2 (2.7)	5.2 [0–22]	NR
Casellini 2005[35]	22	21	1	45.5 [38–54]*	31	13	18	53 [30–65]*	15 (83)	5.14*	5.3*	20 [12.5–26.3]*	Previous: 100% NSAID use; 9.1% MTX; 50% SSZ
Dagli 2007[36]	28	25	3	34.3 [23–60]	25	17	8	28.4 [20–38]	NR	NR	NR	11.6 [2–40]	Current: 96.4% SSZ ± MTX; 3.6% NSAID use
Erbek 2006[37]	32	NR	NR	NR	30	NR	NR	NR	NR	NR	NR	NR	Current: 37.5% NSAID, 6.3% SSZ, 9.4% NSAID + SSZ, 6.3% NSAID + SSZ + MTZ, 6.3% SSZ + steroids
Eryilmaz 2007[38]	59	49	10	35.2 [16–65]	52	36	16	33.9 [20–60]	NR	NR	NR	9.5 [1–40]	NR
Kahveci 2012[39]	37	28	9	41.16 [20–71]	20	15	5	41.15 [21–68]	NR	3.32	NR	9.3 [1.5–32]	Previous: 13.5% TNF-α blocker, 29.7% TNF-α blocker + SSZ/NSAID/MTX; 54.1% combo of SSZ, NSAID, MTX
Kapusuz Gencer 2014[40]	40	37	3	30.2 [20–50]	40	35	5	32.5 [22–50]	NR	3.5 (2.1)	4 (3.1)	6 (4.2) [1–22]	NR
Karatas 2017[41]	47	27	20	44.57 [20–69]	51	25	26	40.84 [17–67]	NR	3.82 (1.99)	NR	11.68 [5–40]	NR
Yagueshita 2018[42]	30	18	12	46.5 [25–58]	30	11	19	40 [18–57]	NR	4.53	5.87	NR	83.4% TNF-α blocker, 20% SSZ, 36.7% MTX, 3.3% AZA, 16.7% steroid, NSAID

* Values are median (IQR). [a] Describes medications either used currently at time of study (current) or have ever been previously used (previous); [2]DMARD can include MTX, SSZ, AZA if not otherwise specified. AZA: azathioprine; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; DMARD: disease-modifying antirheumatic drug; F: female; M: male; MTX: methotrexate; NR: not reported; NSAID: nonsteroidal antiinflammatory drug; SSZ: sulfasalazine; TNF-α: tumor necrosis factor-α.

Table 2. Audiovestibular outcomes of included studies.

Study	AS Cases, n	HL, n[1]	SNHL, n	CHL, n	Mixed, n	Assessed Hearing Outcomes	HL Definition	Vestibular Outcome[2]
Adam 2008[20]	45	32	32	0	0	Rate, PTT	≥ 25 dB at any frequency (0.25–16 kHz)	NR
Ajmani 2019[18]	100	48	3	29	16	Rate, PTT	> 20 dB in ≥ 2 frequencies (0.25–8 kHz)	NR
Alatas 2005[32]	28	8	8	0	0	Rate, PTT, ABR	> 20 dB at any threshold (0.5–4 kHz)	NR
Amor-Dorado 2011[33]	50	29	29	0	0	Rate, PTT	≥ 25 dB in ≥ 2 frequencies (0.5–8 kHz)	14% tinnitus, 14% vertigo, 12% dizziness, 16% disequilibrium, 18% abn oculographic test, 10% abn OCR, 28% nystagmus, 26% abn caloric test
Bozan 2016[34]	30	NR	NR	NR	NR	PTT	NR	NR
Bozkurt 2014[17]	50	7	5	2	0	Rate, OAE	NR	NR
Casellini 2005[35]	22	15	13	2	0	Rate	≥ 20 dB at any frequency (0.25–8 kHz)	NR
Dagli 2007[36]	28	10	10	0	0	Rate, PTT, DPOAE	NR	NR
Erbek 2006[37]	32	18	18	0	0	Rate, PTT, TEOAE	> 20 dB for speech (mean 0.5, 1, 2 kHz) or high (mean 4, 6, 8 kHz) frequencies	25% abn oculographic, 6% abn optokinetic, 9% abn caloric test; 34% any abn ENG (25% central, 9% peripheral)
Eryilmaz 2007[38]	59	21	21	0	0	Rate, PTT	NR	NR
Kahveci 2012[39]	37	26	24	2	0	Rate	NR	35% tinnitus, 3% vertigo
Kapusuz Gencer 2014[40]	40	7	7	0	0	Rate, PTT, SRT	NR	18% abn oculographic, 5% abn caloric, 43% abn Dix-Hallpike test; 66% any abn ENG (18% central, 40% peripheral, 8% mixed)
Karatas 2017[41]	47	NR	NR	NR	NR	PTT, OAE	NR	NR
Yagueshita 2018[42]	30	13	13	0	3	Rate, PTT	NR	NR

[1]Hearing loss cases may exceed number of patients, as right and left hearing may be assessed separately. [2]Oculographic tests refers to saccade and tracking tests. Tinnitus and vertigo were subjectively defined. Abn: abnormal; AS: ankylosing spondylitis; ABR: auditory brainstem response; CHL: conductive hearing loss; dB: decibels; DPOAE: distortion product optoacoustic emissions; ENG: electronystamography; HL: hearing loss; NR: not reported; OAE: otoacoustic emissions; OCR: oculocephalic response; SNHL: sensorineural hearing loss; SRT: speech recognition threshold; PTT: pure-tone thresholds; TEOAE: transient-evoked otoacoustic emissions.

4 SpA types, AS is the most common. Inner ear disease, manifesting as HL and vestibular dysfunction, has been proposed as an extraarticular manifestation of AS, although the exact nature of HL in particular has yet to be elucidated. Patients with AS were theorized to have CHL secondary to ankylosing arthritic effect on the middle ear structures[18]; however, SNHL has been equally recognized to occur in patients with AS. Therefore, our systematic review aimed to evaluate audiologic dysfunction by first determining the prevalence of HL. Second, we aimed to better characterize HL by assessing frequency-specific pure-tone audiometric threshold changes. The results of this study demonstrated a 42.4% prevalence of HL in patients with AS. Patients with AS were also found to have an OR of 4.65 of developing HL compared to patients without AS (95% CI 2.73–7.91). This is accompanied by significant decreases in hearing thresholds across all frequencies, with clinically relevant differences seen at higher frequencies.

Mean threshold differences at 0.25–2 kHz frequencies were minimal, ranging from 0 to 5 dB. Across this frequency range, mean hearing thresholds of patients with SpA did not exceed 25 dB and were indicative of, at the most, slight HL (11–25 dB). Granted, averages of hearing thresholds included both patients with and without SNHL and may be an underrepresentation of the PTT of patients with SNHL. The clinical significance of slight HL has not been well defined; however, Le Clercq, *et al* demonstrated that slight HL negatively affects daily life in adolescents[44]. Hearing threshold impairments of 5–15 dB were seen at higher frequencies (4–8 kHz) and EHF (10–16 kHz).

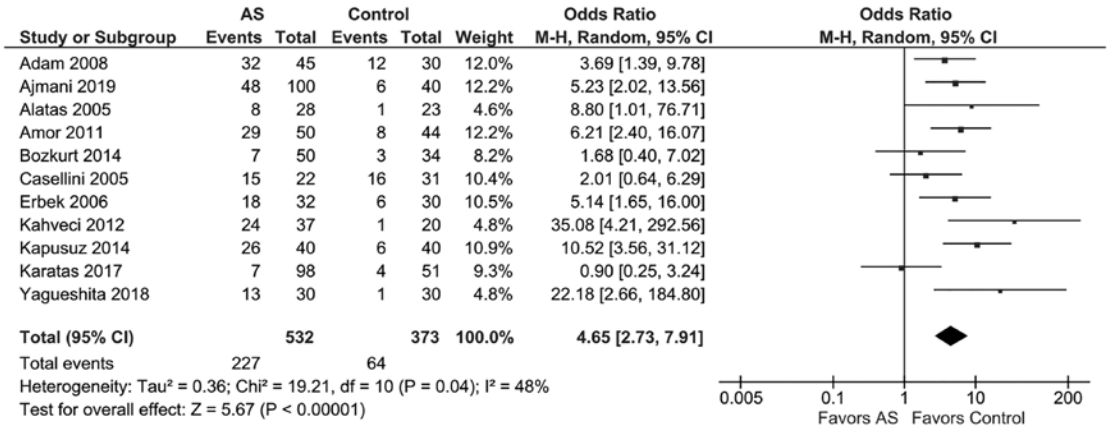

Figure 2. Forest plot of studies describing prevalence of hearing loss in patients with seronegative spondyloarthropathies. OR is the described outcome. AS: ankylosing spondylitis; df: degrees of freedom; IV: inverse variance; M-H: Mantel-Haenszel test.

Table 3. Metaanalysis of pure-tone thresholds (PTT) means and mean differences.

Frequency, kHz	Patients, n	AS, dB Mean	AS, dB SD	Mean Difference in PTT of AS Over Controls, dB (95% CI)
0.25	917	17.5	9.7	4.1 (2.7–5.5)
0.5	917	15.3	9.6	3.7 (2.9–4.5)
1	917	13.4	10.0	2.9 (2.1–3.7)
2	917	13.8	11.2	3.4 (2.4–4.3)
4	1215	23.2	16.2	7.3 (5.2–9.4)
6	728	26.0	15.8	9.2 (5.6–12.8)
8	727	29.3	17.8	8.6 (5.0–12.2)
10	205	30.8	21.8	13.4 (8.6–18.2)
12	205	36.8	23.0	12.5 (6.8–18.1)
14	205	44.6	22.5	14.5 (8.5–20.4)
16	205	45.0	16.3	9.8 (5.0–14.7)

AS: ankylosing spondylitis; dB: decibels.

Mild (26–40 dB) to moderate (41–55 dB) HL were seen at frequencies > 6 kHz. Although speech recognition is commonly deciphered at low frequencies (0.25–2 kHz), high-frequency hearing > 4 kHz is useful for discriminating consonants in speech[43]. Additionally, mild to moderate HL is associated with reduced subjective well-being and poorer verbal memory performance[45,46]. Therefore, the slight low-frequency and mild–moderate high-frequency hearing impairments seen in this population may still be troublesome and clinically significant.

CHL may be due to ossicular fixation from AS affecting entheses or joints of the middle ear structures[19]. SNHL has been theorized to be a secondary immune-related inner ear disease, or to stem from potential ototoxicity of medications. Notably, immune-related inner ear disease may be a potential cause of hearing impairment with an insidious onset, proposed to result from vasculitis, chronic inflammation, or immune complex deposition/indirect hypersensitivity reaction. This is an entity separate from autoimmune inner ear disease, which results from a direct autoimmune attack against the inner ear, presenting with bilateral progressive SNHL over weeks to months. Within our included studies, some studies found SNHL to be associated with AS disease severity in terms of duration of disease[17,20]; however, multiple studies were unable to demonstrate correlations to disease activity scores, extraarticular involvement, or inflammatory lab markers (erythrocyte sedimentation rate/C-reactive protein)[17,33,36,37,38]. It is unclear how HL may be related to the above disease variables, and the role of HL as a possible extraarticular manifestation warrants future investigation.

Patients with AS are commonly treated with NSAID, DMARD, and biologic agents. It comes as no surprise that most patients in the included studies were on some form of therapy. Medication may serve as a confounding factor, as patients with AS were compared to patients without AS who most likely did not require any medication. In addition to this, the exact ototoxic profile of nonsalicylate NSAID, DMARD (MTX, SSZ, AZA), and biologic agents (TNF-α inhibitors) is unclear. Multiple studies have not shown a correlation between DMARD or NSAID amount and hearing thresholds.[20,32,37] However, Savastano, *et al*[47] did find increased SNHL in those treated with TNF-α inhibitors with MTX over MTX alone, and hypothesized that this was a result of drug-induced ototoxicity. This is slightly contrary to evidence demonstrating TNF-α inhibitors as protecting cochlear function[48]. Regardless, Alatas, *et al*[32] investigated a cohort of patients with AS who had not been on long-term medication for 3 months prior to the study period, and concluded that the incidence of SNHL (28.6%) was most likely immune-related and not due to medication.

Our study is not without limitations. First, there exists heterogeneity between all included studies. This includes variations in sample sizes, study population demographics, severity and duration of disease, and treatment. We note that all included AS cases were uniformly diagnosed using either the Modified New York Diagnostic criteria[49] or the Assessment in Ankylosing Spondylitis International Working Group criteria[50] to formally diagnose AS. In addition, comparable instruments to assess range of motion and chest expansion were used to carry out diagnostic testing. Second, based on our strict inclusion criteria, we were unable to meaningfully metaanalyze studies regarding IBD-associated SpA, ReA, or PsA disease entities, and restricted

our analysis to AS only. Third, we were unable to meaningfully analyze vestibular dysfunction in this patient population because only 3 of our included studies had objective and heterogeneous data regarding vestibular dysfunction[33,37,40]. Last, our conclusions regarding HL were based on pure-tone audiometry results, derived from a patient's perception of hearing. HL in autoimmune diseases may fluctuate in nature; however, overall, it generally deteriorates progressively[51]. Although the current available literature does not support a metaanalysis of objective measures of vestibulocochlear function, such as auditory brainstem response or otoacoustic emissions tests, future prospective studies can investigate this to better characterize audiovestibular dysfunction in this patient population. These limitations must be considered when interpreting our results.

In conclusion, patients with AS have higher odds of having HL over patients without AS. This population also presents with significantly impaired hearing thresholds across all conventional and extended pure-tone frequencies, which may manifest as slight to moderate HL. Results of this systematic review might justify increased attention to audiological manifestations of patients with AS. Our study provides an estimation of HL prevalence in patients with AS; however, we were unable to ascertain how HL was related to disease course or the etiology behind the HL itself. Building upon this, future prospective studies are warranted to ascertain the mechanisms behind HL in this population, as well as potential risk factors for HL development.

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