Hearing Loss in Patients with Ankylosing Spondylitis: A Systematic Review and Meta-Analysis

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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 four databases (PubMed, Ovid MEDLINE, SCOPUS, Cochrane) was performed to identify studies evaluating HL in patients with AS. Meta-analysis was performed to identify overall prevalence rate and odds ratio (OR) of HL, as well as to compare mean differences in frequency-specific hearing thresholds between patients with and without AS.

Results: This meta-analysis included 14 studies and 1,083 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 in patients with AS over patients without AS (4.65 OR, 95% CI 2.73 – 7.91). Mean differences in pure tone hearing thresholds ranged from 0-5 decibel (dB) for frequencies 0.25-4kHz and from 5-15 dB for frequencies 6-16 kHz.

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. This may manifest as slight to moderate hearing loss. Results of this systematic review might justify increased attention audiologic manifestations of patients with AS.

Introduction

Systemic autoimmune disorders, such as rheumatoid arthritis (1), systemic lupus erythematosus (2), Sjogren's syndrome (3), psoriatic arthritis (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 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, 3-5, 7-9).

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 or 4) drug-induced ototoxicity from the myriad of immunomodulatory medications commonly used to treat patients with these disorders (10-12). Hearing loss and vestibular dysfunction can lead to significant impairment for these patients, and if the loss can be prevented or identified early, early intervention can prevent further further impairment.

Compared to the autoimmune conditions listed above, spondyloarthritis (SpA) have not been investigated as robustly for audiologic dysfunction. The traditional concept of SpA includes a number of disorders with common genetic, radiological and clinical features: ankylosing spondylitis (AS), psoriatic arthritis (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 non-radiographic axial SpA) from predominantly peripheral SpA. In epidemiologic studies, AS is the most common SpA. The role of genes is not in doubt in SpA, with an estimated 70-90% (13, 14) of patients with AS expressing the HLA-B27 gene. Given the absence of disease-specific autoantibodies and evidence supporting altered innate immune

response, AS can be considered more of an autoinflammatory over autoimmune condition; this however, remains to be elucidated.(15, 16) As AS is a systemic condition, patients can develop extra-articular manifestations such as anterior uveitis, heart conduction problems, or gastrointestinal inflammation (17). It has been hypothesized that hearing loss might be another extra-articular manifestation (18, 19).

The prevalence and characterization of audiologic dysfunction in patients with AS has not been well elucidated. Both conductive hearing loss (CHL) and sensorineural hearing loss (SNHL) have been reported in the literature (20, 21). As AS causes ankyloses of joints, it might cause ossicular fixation leading to CHL (19). Alternatively, immune-mediated inner ear problems could result in SNHL (19). The nature of hearing loss has not been well characterized, however in other autoimmune conditions, has been seen to affect high frequencies in particular.(22-24) This has also been demonstrated in patients with AS (21). Therefore, this systematic review aims to determine the rate of hearing loss (HL) in patients with AS. Secondarily, we aim to describe frequency-specific hearing threshold changes in patients with AS as compared to patients without AS.

Methods

Search Strategy and Study Selection

This systematic review was performed in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.(25) This review queried four databases (PubMed, Scopus, OVID Medline, Cochrane) from inception to January 23rd, 2020 for studies that assessed hearing loss in patients with one of the four spondyloarthritis (PsA, AS, IBD-associated SpA, ReA). The search strategy included a 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", "audiogram". To ensure 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 additionally included from this. EndNote (Clarivate Analytics, 99 Philadelphia, PA, USA) served as a repository for included studies.

Inclusion criteria consisted of: 1) assessment of one of four spondyloarthritis (PsA, AS, IBD-associated SpA, ReA); 2) data on incidence of hearing loss (HL) or pure-tone audiometric thresholds (PTT); 3) comparison to age-matched control, 4) exclusion of patients with 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 PTTs or incidence of hearing loss; 5) non-English language; and 6) non-human subjects. Review of studies for inclusion was conducted by two separate authors (F.Y. and P.R.); any disputes were resolved by a third author (S.A.N.).

Data Extraction and Statistical Analysis

Extracted data included author, publication year, country of publication, study design, and patient characteristics. Specific patient characteristics include sex, age, HLA-B27 status, mean duration of AS illness, illness severity characteristics, incidence and type of hearing loss, and pure-tone audiogram frequency-specific thresholds. We extracted data from both conventional hearing thresholds (0.5 - 8kHz) as well as extended high frequency (EHF) (10-16 kHz) thresholds. Severity of hearing loss 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) (26). Additional methods for hearing evaluation included speech discrimination scores (SDS), speech receptive threshold (SRT), both transient evoked otoacoustic emissions (TEOAE) and distortion produced otoacoustic emissions (DPOAE), and auditory brainstem response (ABR); additional methods to assess vestibular function using electronystagmography include oculographic testing (saccade and tracking test), positional tests for nystagmus and caloric test. Unfortunately, data regarding these parameters were not consistently reported and unable to be included in the meta-analysis.

Meta-analysis was performed to first describe the rate and risk of HL and second, to generate mean differences of frequency-specific hearing thresholds between patients with AS and patients without AS. This was executed using Cochrane Review Manager Software (Revman version 5.3, Cochrane IMS, Denmark). Pooled odds ratio (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. Meta-analysis of proportions (MedCalc-Software (v19.1), Oostende, Belgium) was conducted to determine overall prevalence. Heterogeneity of included studies was first assessed by the Q statistic, with p values less than 0.05 to be statistically significant. 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 less than 50%, a fixed statistical effect model was used. Alternatively, if I^2 was greater than 50%, a random statistical effect model was used. A *p* value of<0.05 was considered to indicate a statistically significant difference for all statistical tests.

Lastly, study of heterogeneity was evaluated using the Sterne and Egger tests (27, 28). This generated a funnel plot, which displays pooled values plotted on the horizontal axis and standard error on the vertical axis. A funnel plot can provide a graphical representation of study heterogeneity included in meta-analysis. The vertical line represents the summary estimated derived using fixed-effect meta-analysis. Two diagonal lines represent (pseudo) 95% confidence limits (effect ± 1.96 SE) around the summary effect for each standard error on the vertical axis (29). 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 (**Supplemental figure 1**).

Quality Assessment

First, the level of evidence of all included studies was ascertained using the Oxford Center for Evidence-Based Medicine criteria (30). Next, all included studies were evaluated for risk of bias according to the Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0 (31). Specifically, the ROBINS-I tool was used as this systematic review evaluated non-randomized studies (32). Two authors (FY and PR) performed a pilot assessment on three studies to check for consistency of assessment. Both then performed independent risk assessments on the remaining studies. All disagreements were resolved by the 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 is graded as “low”, “unclear”, or “high”.

Results

Search Results

Our initial search generated 388 studies, from which 327 unique studies were assessed. Of these, 62 articles underwent full-text review. In conclusion, 14 studies were included for quantitative analysis. **Figure 1** demonstrates a PRISMA diagram outlining a summary of the search process.

Summary of Included Studies

This meta-analysis included 14 studies and 1,083 patients (598 with AS vs. 485 without AS) (**Table 1**) (18, 19, 21, 33-43). Of these 14 studies, 11 studies were used to analyze the risk of HL in patients with AS (18, 19, 21, 33, 34, 36, 38, 40-43) and 9 studies were used to pool frequency-specific threshold data (19, 21, 33, 35, 37, 39-42). Only 6 studies reported CHL as well as SNHL, whereas the other 8 studies only examined SNHL in patients with AS. The overall mean age was 37.7 years (age range 16-71).

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, the studies evaluating IBD did not have patients that all had arthritic extra-intestinal involvement. The studies describing ReA were primarily case studies or series < 10 patients. Three studies evaluating PsA met inclusion criteria, however data extraction did not yield enough data points to draw meaningful conclusions from meta-analysis. Thus, all 14 included studies evaluated HL in patients with AS. As all studies were case-control studies, these were all considered as level 3 evidence according to the Oxford Center for Evidence-Based Medicine criteria (30). A risk of bias summary and graph are provided in **Supplemental figures 2 and 3**. All studies had low or unclear risk assessments in each category.

The mean duration of AS disease was 9.2 years (range 1 - 40). HLA-B27 status was reported in 5 studies (18, 19, 21, 34, 36) with a pooled rate of HLA-B27 expression of 76%. Definitions of hearing loss 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 effect on cochlear function is unclear. These include non-steroidal anti-inflammatory agents (NSAIDs), biologic agents (such as tumor necrosis factor [TNF]-alpha inhibitors), disease modifying anti-rheumatic drugs (DMARDS) (sulfasalazine [SSZ], azathioprine [AZA], methotrexate [MTX]), and corticosteroids. Pharmacologic treatment of patients with AS was described in 9 of the included studies as detailed in **Table 1.**

Hearing Loss Prevalence and Risk in Ankylosing Spondylitis

In a pooled analysis of 574 patients with AS, pooled prevalence of HL was 42.4% (95% CI 29.2 - 56.2%). By subtype, the pooled rate of SNHL in 574 patients with AS was 37.2% (95% CI 24.9 - 50.5); the pooled rate of CHL in 279 patients was 13.5 (95% CI 3.1 - 29.6) (**Table 2**). Pooled evaluation comparing 532 patients with AS and 373 patients without AS revealed significantly higher odds ratio (OR) of HL in patients with AS over patients without AS (4.65 OR, 95% CI 2.73 – 7.91) (**Figure 2**).

Pure Tone Audiometry Frequency-Specific Threshold Changes

Frequency-specific PTA data were available for meta-analysis 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 **Supplemental figures 2-5**. Significantly elevated hearing thresholds in patients with AS were seen across all frequencies. Mean differences in PTT ranged from 0-5 dB for frequencies 0.25-4kHz and from 5-15 dB for frequencies 6-16 kHz. These were generally increasing as frequencies increased except for at 16 kHz, at which mean difference was 9 dB (95% CI 5 – 15).

Only at 6-16 kHz frequencies were mean HT elevated above 25 Hz (**Table 3**). The pooled mean HTs reported by the included studies represent patients with and patients without HL. This may represent an underestimation of HT elevation, if wanting to see the differences in HT only in patients with HL.

Discussion

Spondyloarthritis, including AS, SpA, IBD-associated SpA and ReA, often have multiple extra-articular manifestations including anterior uveitis, neurological and pulmonary involvement, and cardiac conduction problems(44). Out of the 4 SpA, AS is the most common. Inner ear disease, manifesting as hearing loss and vestibular dysfunction has been proposed as an extra-articular manifestation of AS. The exact nature of HL in particular remains to be elucidated. Patients with AS were theorized to have CHL secondary to ankylosing arthritic effect on the middle ear structures (19), however SNHL has been equally recognized to occur in patients with AS. Therefore, this systematic review aims 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 demonstrate a 42.4% prevalence of HL in patients with AS. Patients with AS also have an OR of 4.65 of developing HL over 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.

Degree of Hearing Loss

Mean threshold differences at 0.25-2kHz frequencies was minimal, ranging from 0 – 5 dB. Across this frequency range, mean hearing thresholds of SpA patients did not exceed 25 dB and was 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 PTT of only SNHL patients. The clinical significance of slight HL has not been well-defined, however Le Clerc et al. demonstrated slight hearing loss to negatively impact daily life of adolescents (45). Hearing threshold impairments of 5-15 dB were seen at higher frequencies (4-8 kHz), and EHF (10-16 kHz). 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 (0.25-2kHz), high frequency hearing ≥ 4 kHz is useful for discriminating consonants in speech (44). Also, mild to moderate HL is associated with reduced subjective wellbeing, poorer verbal memory performance (46, 47). Therefore, the slight low-frequency and mild-moderate high-frequency hearing impairments seen in this population still may be troublesome and clinically significant.

CHL might be due to ossicular fixation from AS disease affecting entheses or joints of the middle ear structures (19). SNHL has been proposed to be a secondary immune-related inner-ear disease or stem from potential ototoxicity of medications. Of note, immune-related inner-ear disease as 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 (AIED), which results from direct autoimmune attack against the inner ear, presenting with bilateral progressive SNHL over weeks to months. In our included studies, some studies found SNHL associated with AS disease severity in terms of duration of disease (18, 21); however, multiple studies were unable to demonstrate correlations to disease activity scores, extra-articular involvement, or inflammatory lab markers (ESR/CRP) (18, 34, 37-39). It is unclear how HL may be related to the above disease parameters and the role of HL as a possible extra-articular manifestation warrants future investigation.

Influence of Medication

Patients with AS are commonly treated with NSAIDs, DMARDs and biologic agents. It comes to 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 whom most likely did not require any medication. In addition to this, the exact ototoxic profile of non-salicylate NSAIDs, DMARDS (MTX, SSZ, AZA) and biologic agents (TNF-alpha inhibitors) is unclear. Multiple studies have not shown a correlation with DMARDs or NSAID amount with hearing thresholds.(21, 33, 38) However, Savastano et al. (48) did find increased SNHL in those treated with TNF-alpha inhibitors with MTX over MTX alone and hypothesized this was a result of drug-induced ototoxicity. This is slightly contrary to evidence demonstrating TNF-alpha inhibitors as protecting of cochlear function (49). Regardless of this, Alatas et al. (33) investigated a cohort of AS patients who had not been on long-term medication for 3 months prior to the study period, and concluded the incidence of SNHL (28.6%) was most likely immune-related and not due to medication.

Limitations

This 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(50) or the Assessment in AS International Working Group criteria(51) to formally diagnosis AS; in addition, comparable instruments to assess range of motion and chest expansion were used to carrying out diagnostic testing. Second, based on our strict inclusion criteria, we were unable to meaningfully meta-analyze studies regarding IBD-associated PsA, 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 as only 3 of our included studies had objective and heterogeneous data regarding vestibular dysfunction (34, 38, 41). Lastly, our conclusions regarding hearing loss were also based off pure tone audiometry results, derived from a patient's perception of

hearing. Hearing loss in autoimmune diseases may fluctuate in nature, however overall, generally progressively deteriorates.(52) Although the current available literature does not support a meta-analysis of objective measures of vestibulocochlear function such as ABR or OAE, future prospective studies can investigate this to better characterize audiovestibular dysfunction in this patient population. These limitations must be considered when interpreting our results.

Future Directions

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 mechanism behind HL in this populations and potential risk factors for HL development.

Conclusions

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. This may manifest as slight to moderate hearing loss. Results of this systematic review might justify increased attention audiological manifestations of patients with AS.

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Figure Captions

Figure 1: PRISMA Diagram Showing Inclusion and Exclusion Criteria

Figure 2: Forest Plot of Studies Describing Prevalence of Hearing Loss in Patients with Seronegative Spondyloarthropathies. Odds Ratio (OR) is the described outcome

Abbreviations: Ankylosing Spondylitis (AS); Confidence Interval (CI); Inverse Variance (IV); Standard Deviation (SD)

Supplemental Figure 1: Funnel Plot of Studies Examining Prevalence of Hearing Loss in Patients with Ankylosing Spondylitis

Supplemental Figure 2: Risk of Bias Graph

Supplemental Figure 3: Risk of Bias Summary

Supplemental Figure 4: Forest Plots of Studies Showing Mean Differences in Pure Tone Audiometry Hearing Thresholds at 250 (A); 500 (B); 1000 (C); and 2000 (D) Hz, respectively. The effect measure is mean difference.

Abbreviations: Ankylosing Spondylitis (AS); Confidence Interval (CI); Inverse Variance (IV); Standard Deviation (SD)

Supplemental Figure 5: Forest Plots of Studies Showing Mean Differences in Pure Tone Audiometry Hearing Thresholds at 4 (A); 6 (B); and 8 (C) kHz respectively. The effect measure is mean difference.

Abbreviations: Ankylosing Spondylitis (AS); Confidence Interval (CI); Inverse Variance (IV); Standard Deviation (SD)

Supplemental Figure 6: Forest Plots of Studies Showing Mean Differences in Pure Tone Audiometry Hearing Thresholds at 10 (A); 12 (B); 14 (C); and 16 (D) kHz, respectively. The effect measure is mean difference.

Abbreviations: Ankylosing Spondylitis (AS); Confidence Interval (CI); Inverse Variance (IV); Standard Deviation (SD).

Table 1: Overview of Included Studies Evaluating Ankylosing Spondylitis

Study	AS Total No.	AS M No.	AS F No.	AS Cases mean age (SD) [range]	Control No.	Control M No.	Control F No.	Control mean age (SD) [range]	HLA-B27 No. (%)	Mean BSADAI Score (SD)	Mean BASFI Score (SD)	Mean Disease Duration, years (SD) [Range]	Percentage of AS Patients on Medication[1]
Adam 2008	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	48	16	2	36 (13)	52	50	2	30 (10)	94 (94)	3.5 (2.2)	2.8 (2)	8.2 (6)	Previous: 100% NSAIDS, 29% SSZ, 9% MTX
Alatas 2005	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 2011	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-alpha blocker
Bozan 2016	30	18	12	32 (8)	35	22	13	32 (6)	NR	4.4 (1.7)	NR	5.3 (5.1)	NR
Bozkurt 2014	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	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	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	32	NR	NR	NR	30	NR	NR	NR	NR	NR	NR	NR	Current: 37.5% NSAIDS, 6.3% SSZ, 9.4% NSAID + SSZ, 6.3% NSAID + SSZ + MTZ, 6.3% SSZ + steroids

Eryilmaz 2007	59	19	10	35.2 [16-65]	52	36	16	33.9 [20-60]	NR	NR	NR	9.5 [1-40]	NR
Kahveci 2012	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-alpha blocker, 29.7% TNF-alpha blocker + SSZ/NSAID/MTX; 54.1% combo of SSZ, NSAID, MTX
Kapusuz 2014	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	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	30	18	12	46.5 [25-58]	30	11	19	40 [18-57]	NR	4.53	5.87	NR	83.4% TNF-alpha blocker, 20% SSZ, 36.7% MTX, 3.3% AZA, 16.7% steroid, NSAID

*Presented as Median (Interquartile Range)

[1]Describes medications either used currently at time of study (current) or have ever been previously used (previous)

[2]DMARDs can include MTX, SSZ, AZA if not otherwise specified

Abbreviation: Ankylosing Spondylitis (AS); Azathioprine (AZA); Bath Ankylosing Spondylitis Disease Activity Index (BASDAI); Bath Ankylosing Spondylitis Functional Index (BASFI); Disease-Modifying Anti-Rheumatic Drug (DMARD); Female (F); Male (M); Number (No.); Methotrexate (MTX); Not Reported (NR); SSZ (Sulfasalazine).

Table 2: Audiovestibular Outcomes of Included Studies

Study	AS Cases No.	HL No.[1]	SNHL No.	CHL No.	Mixed No.	Assessed Hearing Outcomes	Hearing Loss Definition	Vestibular Outcome[2]
Adam 2008	45	32	32	0	0	Rate, PTT	≥25 dB at any frequency (0.25-16 kHz)	NR
Ajmani 2019	48	48	3	29	16	Rate, PTT	>20 dB in ≥2 frequencies (0.25 – 8 kHz)	NR
Alatas 2005	28	36	36	0	0	Rate, PTT, ABR	>20 dB at any threshold (0.5-4kHz)	NR
Amor 2011	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	30	NR	NR	NR	NR	Rate, PTT	NR	NR
Bozkurt 2014	50	7	5	2	0	Rate, OAE	NR	NR
Casellini 2005	22	15	13	2	0	Rate	≥20 dB at any frequency (0.25-8kHz)	NR
Dagli 2007	28	10	10	0	0	PTT, DPOAE	NR	NR
Erbek 2006	32	18	18	0	0	Rate, PTT, TEOAE	>20 dB for speech (mean 0.5, 1, 2kHz) 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	59	21	21	0	0	PTT	NR	NR
Kahveci 2012	37	26	24	2	0	Rate	NR	35% tinnitus, 3% vertigo
Kapusuz 2014	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	47	NR	NR	NR	NR	PTT, OAE	NR	NR
Yagueshita 2018	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.
Abbreviation: Abnormal (abn); Ankylosing Spondylitis (AS); Auditory brainstem response (ABR); Distortion product optoacoustic emissions (DPOAE); electronystamography (ENG); Not Reported (NR); Otoacoustic Emissions (OAE); (OCR); Speech Recognition Threshold (SRT); Speech Discrimination (SD); Pure tone Thresholds (PTT); Transient Evoked Otoacoustic Emissions (TEOAE).

Table 3: Meta-Analysis of Pure Tone Hearing Thresholds Means and Mean Differences				
Frequency (kHz)	**Patients (n)**	**PTT Mean of AS (dB) (SD)**		**Mean Difference in PTT (dB) of AS over Control (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)
Abbreviations: ankylosing spondylitis (AS); decibels (dB); pure tone thresholds (PTT).				

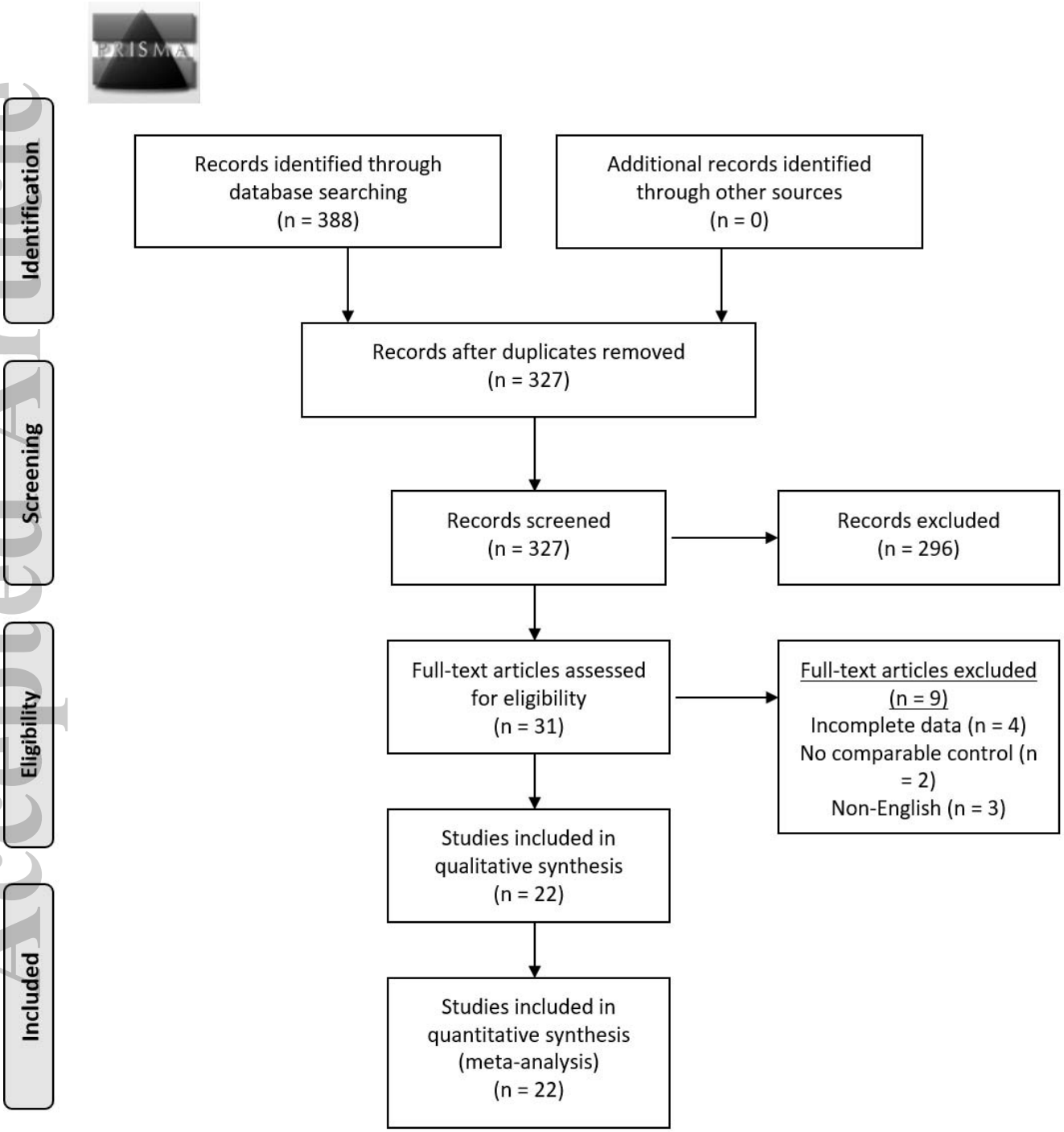

Figure 1: PRISMA Diagram Showing Inclusion and Exclusion Criteria

Study or Subgroup	AS Events	AS Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Adam 2008	32	45	12	30	12.0%	3.69 [1.39, 9.78]
Ajmani 2019	48	100	6	40	12.2%	5.23 [2.02, 13.56]
Alatas 2005	8	28	1	23	4.6%	8.80 [1.01, 76.71]
Amor 2011	29	50	8	44	12.2%	6.21 [2.40, 16.07]
Bozkurt 2014	7	50	3	34	8.2%	1.68 [0.40, 7.02]
Casellini 2005	15	22	16	31	10.4%	2.01 [0.64, 6.29]
Erbek 2006	18	32	6	30	10.5%	5.14 [1.65, 16.00]
Kahveci 2012	24	37	1	20	4.8%	35.08 [4.21, 292.56]
Kapusuz 2014	26	40	6	40	10.9%	10.52 [3.56, 31.12]
Karatas 2017	7	98	4	51	9.3%	0.90 [0.25, 3.24]
Yagueshita 2018	13	30	1	30	4.8%	22.18 [2.66, 184.80]
Total (95% CI)		**532**		**373**	**100.0%**	**4.65 [2.73, 7.91]**
Total events	227		64			

Heterogeneity: Tau² = 0.36; Chi² = 19.21, df = 10 (P = 0.04); I² = 48%
Test for overall effect: Z = 5.67 (P < 0.00001)

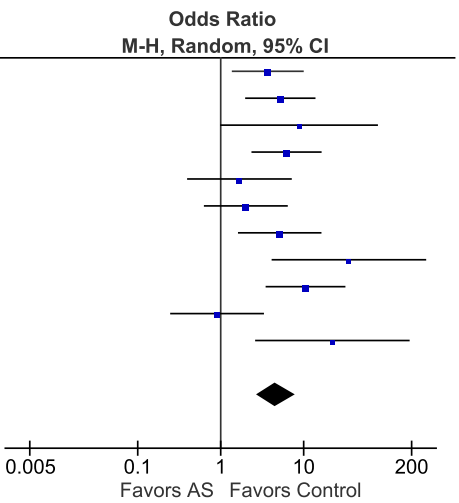

Figure 2: Forest Plot of Studies Describing Prevalence of Hearing Loss in Patients with Seronegative Spondyloarthropathies. Odds Ratio (OR) is the described outcome.

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