PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Retrospective Cohort Study on Risk of Hearing Loss in Patients with Rheumatoid Arthritis Using Claims Data
AUTHORS	Huang, Chung-Ming; Chen, Hsuan-Ju; Huang, Po-Hao; Tsay, Gregory J; Lan, Joung-Liang; Sung, Fung-Chang

VERSION 1 – REVIEW

REVIEWER	Marcia Midori Shinzato Universidade Federal da Grande Dourados Mato Grosso do Sul- Brazil
REVIEW RETURNED	26-Jun-2017

GENERAL COMMENTS	Thanks for the authors for this interesting sudy, as rheumatologist we suggested 1) A more current definition of rheumatoid arthritis in the introduction using more up-to-date references. 2) In material and methods, I would like to know how hearinh loss was defined (by audiometry, by ENT physian).

REVIEWER	Amir Emamifar Department of Rheumatology, OUH, Svendborg hospital, Svendborg, Denmark
REVIEW RETURNED	03-Jul-2017

GENERAL COMMENTS	thank you for the effort you made, however there are some concerns regarding the manuscript: 1. Please discuss your selection of comorbidities. The authors should consider presence of other comorbid autoimmune diseases. Why did the authors considers hyperthyroidism and not hypothyroidism? 2. respecting Table 1: Please discuss why there are no significant differences in the prevalence of most comorbidities, since there are strong data that these comorbidities e.g. DM are more prevalent in RA patients. 3. What treatment did patients received during this period? 4. Do consider to extract data for disease activity to boost your results. 5. please clarify how HL was diagnosed in the patients. 6. consider to update reference list. some of them are old. 7. should consider to add the following reference: Emamifar A, Bjoerndal K, Hansen IMJ. Is Hearing Impairment Associated with Rheumatoid Arthritis? A Review.

	The Open Rheumatology Journal. 2016;10:26-32. doi:10.2174/1874312901610010026. 8. the authors should consider to improve the discussion part. the discussion part is not informative. in addition, consider to discuss the IHD as a risk factor for HL with more details.

REVIEWER	Kuo, Chang-Fu Chang Gung Memorial Hospital, Taiwam
REVIEW RETURNED	10-Jul-2017

GENERAL COMMENTS	This study examined the association between RA and hearing loss. My comments include. 1. The case identification and controls were both based on NHI database in Taiwan. However, the calendar years of identification was not the same. The RA case was identified between 2000-2006 and controls from 2000. There probably has some bias related to time. Please comment on possible bias related to different calendar year used. 2. Do the authors have data about medication? 3. The authors need to explain how they decide to include the current variables. 4. The authors suggests the association between autoimmune diseases and hearing loss. However, this study only focused on RA and multiple factors, including disease, medication, may have influenced the risk for hearing loss. Therefore, I suggest not to overstretch their conclusions. 5. Since the authors have matched for age and sex, is it necessary to include age and sex in the model? Table 2 and Table 3 listed different variables, in table 2 the authors lumped all comorbidities into one categories and in Table 3, they spread out. Please explain.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Marcia Midori Shinzato
Universidade Federal da Grande Dourados, Mato Grosso do Sul- Brazil
Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

Thanks for the authors for this interesting study, as rheumatologist we suggested
1) A more current definition of rheumatoid arthritis in the introduction using more up-to-date references.
Reply: Thanks for your specific comment, we had cited up-to-date references (1st,5th, 7th and 9th references) in the section of introduction.

2) In material and methods, I would like to know how hearing loss was defined (by audiometry, by ENT physician).
Reply: Thanks for your thoughtful comment. In this study, the diagnoses of hearing loss were based on the ICD-9 codes, as determined by qualified clinical physicians (not always ENT physician) for the strictly audited reimbursement process. All insurance claims are scrutinized and coded by medical reimbursement specialists and peer reviewed according to the standard criteria for diagnoses in the study. Moreover, incorrect diagnoses or coding mistakes result in considerable penalties for the physicians.

The reliability and validity of the NHI research database for epidemiologic studies have been reported previously (reference 16: Cheng CL et al.). Therefore, the diagnoses and coding in this study should be highly reliable. In general, hearing loss is diagnosed by ENT physician or other clinical physician based on audiometry findings. We have specified in the revision: “In general, HL was diagnosed based on the audiometry test.” (Please see text: page 8 paragraph 3 line 2-3.)

References:
Cheng CL, Kao YH, Lin SJ, Lee CH, Lai ML. Validation of the national health insurance research database with ischemic stroke cases in Taiwan. Pharmacoepidemiol Drug Saf. 2011;20:236–42.

Reviewer: 2
Amir Emamifar
Department of Rheumatology, OUH, Svendborg hospital, Svendborg, Denmark
Please state any competing interests or state ‘None declared’: none declared

Please leave your comments for the authors below

Dear authors,

Thank you for the effort you made, however there are some concerns regarding the manuscript:

1. Please discuss your selection of comorbidities. The authors should consider presence of other comorbid autoimmune diseases. Why did the authors considers hyperthyroidism and not hypothyroidism?
Reply: Thanks for your specific comment. Because evidence shows that patients with RA are prevalent with comorbid diseases, such as IHD [24-26], stroke [27], hypertension [28,29], diabetes [30-32], dyslipidemia [27,33], CKD [34,35] and thyroid disease [36-38]. We have addressed the selection of comorbidities in the Discussion section. We have added hypothyroidism and autoimmune diseases (including psoriasis, SLE, systemic sclerosis, Sjogren syndrome, dermatomyositis, polymyositis, and vasculitis) in the list of comorbidities. (Table 1-3). RA may be related to both hyper- and hypo-thyroidism (text: references 36-38).

2. respecting Table 1: Please discuss why there are no significant differences in the prevalence of most comorbidities, since there are strong data that these comorbidities e.g. DM are more prevalent in RA patients.
Reply: Thank you for the comment. The study population is prevalent with younger in both age matched cohorts (Table 1). Therefore, most comorbidities were not significantly different between 2 cohorts . But, these comorbidities are associated with HL risk, stronger for the RA cohort than controls (Table 3). In the revision, we stated: “Evidences have shown that patients with RA are prevalent with comorbidities, such as IHD [24-26], stroke [27], hypertension [28,29], diabetes [30-32], dyslipidemia [27,33], CKD [34,35] and thyroid disease [36-38]. In this study, however, the study populations in both cohorts were young. The baseline prevalence rates of most comorbidities between the 2 cohorts were not significantly different, except that CKD and autoimmune diseases were more prevalent in patients with RA than in controls without RA at the baseline. It is clear that most of the comorbidities are associated with further increased incidence of HL, greater for the RA cohort than for the non-RA cohort, except hypothyroidism, and autoimmune diseases (Table 3). (Please see page 15.)

3. What treatment did patients received during this period?
Reply: Thank you for the inspirational comment. We further analyzed data on medications available from the insurance, including NSAIDs, prednisolone, DMARDs (including hydroxychloroquine, sulfasalazine, methotrexate, and leflunomide), and TNF (including etanercept and adalimumab) for patients with RA (page 10 lines 2-9). We have included findings (Table 4) in the revised manuscript and the interpretation on page 11 last 2 lines and page 12 lines 1-5.

4. Do consider to extract data for disease activity to boost your results.
Reply: Because the disease activity and DAS-28 were not available from the Taiwan National Health Insurance Research Database (NHIRD). It's the limitation of this study. The suggestion inspire us to consider using our own clinic data as another study because DAS28 data are available at our hospital.

5. please clarify how HL was diagnosed in the patients.
Reply: Thank you for your thoughtful comment. In this study, the diagnoses of hearing loss were based on the ICD-9 codes, as determined by qualified clinical physicians (not always ENT physician) for the strictly audited reimbursement process. All insurance claims are scrutinized and coded by medical reimbursement specialists and peer reviewed according to the standard criteria for diagnoses in the study. Moreover, incorrect diagnoses or coding mistakes result in considerable penalties for the physicians. The reliability and validity of the NHI research database for epidemiologic investigations have been reported previously (reference: Cheng CL et al.). Therefore, the diagnoses and coding in this study should be highly reliable. In general, hearing loss is diagnosed by ENT physician or other clinical physician based on audiometry findings. We have specified in the revision: "In general, HL was diagnosed based on the audiometry test." (Please see text: page 8 paragraph 3 line 2-3.)

6. consider to update reference list. some of them are old.
Reply: Thanks for the suggestion. We have cited near 20 articles in the reference list in addition.

7. should consider to add the following reference:
Emamifar A, Bjoerndal K, Hansen IMJ. Is Hearing Impairment Associated with Rheumatoid Arthritis? A Review. The Open Rheumatology Journal. 2016;10:26-32. doi:10.2174/1874312901610010026.
Reply: Thanks for the suggestion. We have cited the paper (the 5th reference).

8. the authors should consider to improve the discussion part. the discussion part is not informative. in addition, consider to discuss the IHD as a risk factor for HL with more details.
Reply: Thanks for the suggestion. We have elaborated more information in the Discussion part (Please see paragraphs 3,4 and 6. Paragraphs 3 and 4 elaborate the contribution of comorbidities in HL, including IHD in paragraph 4. Paragraph 6 discussed the treatment effectiveness of RA therapy in reducing HL risk.).
Your comment #3 giving us an opportunity to improve this study. We consider the findings improve the informative issue. Thanks.

Reviewer: 3
Kuo, Chang-Fu
Chang Gung Memorial Hospital, Taiwam
Please state any competing interests or state ‘None declared’: I have no competing interest.

Please leave your comments for the authors below

This study examined the association between RA and hearing loss. My comments include.
1. The case identification and controls were both based on NHI database in Taiwan. However, the calendar years of identification was not the same. The RA case was identified between 2000-2006 and controls from 2000. There probably has some bias related to time. Please comment on possible bias related to different calendar year used.
Reply: Thank you for the comment. There might be misunderstanding about the data files we used. We use the Longitudinal Health Insurance Database of 2000 (LHID2000) based on the insured population with registration in 2000, a subset of NHIRD. The RA cases were identified from the records of 2000-2006. The controls were randomly selected from the same LHID2000 data set, using random selection methods, but frequency matched by sex, age the diagnosis (index) year of the RA patients. Because controls were matched by index year, thus controls were also identified from 2000-2006. (Please see text: page 8 paragraph 2 lines 1-3.)

2. Do the authors have data about medication?
Reply: Thanks for the inspirational comment. Yes, information on medications such as NSAIDs, prednisolone, DMARDs (including hydroxychloroquine, sulfasalazine, methotrexate, and leflunomide), and TNF (including etanercept and adalimumab) were available and we have evaluated the treatment effectiveness of these medications in the revised manuscript (Method section: Please see page 10 paragraph 1). Please see Table 4 for the findings. These medications are associated with reduced risk of HL. We are pleased for having conducted this part of additional data analysis. We have included findings (Table 4, please see last page in this reply) in the revised manuscript; please see the interpretation on page 11 last 2 lines and page 12 lines 1-5:
“Table 4 shows that medications were associated with reduced incident HL for RA patients. Near 99% of RA patients used NSAIDs and users had a HL incidence of 2.98 per 1000 person-years, with an aHR of 0.12 (95% CI = 0.07-0.20) compared with non-users who had an incidence of 30.1 per 1000 person-years for HL. RA patients on medications of TNF (n = 2706) had the lowest HL incidence of 1.17 per 1000 person-years with an aHR of 0.40 (95% CI = 0.27-0.59), compared with non-users who had an incidence of 3.45 per 1000 person-years.”

3. The authors need to explain how they decide to include the current variables.
Reply: Thanks for reminding. We have elaborate the concern in the Discussion section Paragraph 3:
“Evidences have shown that patients with RA are prevalent with comorbidities, such as IHD [24-26], stroke [27], hypertension [28,29], diabetes [30-32], dyslipidemia [27,33], CKD [34,35] and thyroid disease [36-38]. In this study, however, the study populations in both cohorts were young. The baseline prevalence rates of most comorbidities between the 2 cohorts were not significantly different, except that CKD and autoimmune diseases were more prevalent in patients with RA than in controls without RA at the baseline (Table 1). It is clear that most of the comorbidities are associated with further increased incidence of HL, greater for the RA cohort than for the non-RA cohort, except hypothyroidism, and autoimmune diseases (Table 3).”

4. The authors suggests the association between autoimmune diseases and hearing loss. However, this study only focused on RA and multiple factors, including disease, medication, may have influenced the risk for hearing loss. Therefore, I suggest not to overstretch their conclusions.
Reply: Thanks for reminding us of the potential overstretch issue. We have revised the manuscript for the study cautiously to avoid overstretch. We appreciate very much for your comment #2 suggestion. The further data analysis about the medication is very helpful for this study.

5. Since the authors have matched for age and sex, is it necessary to include age and sex in the model? Table 2 and Table 3 listed different variables, in table 2 the authors lumped all comorbidities into one categories and in Table 3, they spread out. Please explain.
Reply: Thank you for your comment and suggestion.
1. Comorbidities may vary between males and females. We therefore included both sex and age group in the multivariate models.
2. We have re-analyzed Table 2 and have variables spread.

VERSION 2 – REVIEW

REVIEWER	Marcia Midori Shinzato Universidade Federal da Grande Dourados, Brazil
REVIEW RETURNED	17-Sep-2017

GENERAL COMMENTS	Thanks to the authors for this interesting population-based study that helped clarify the relationship between hearing loss and rheumatoid arthritis. However, I think that a better definition of HL and the types of HL (sensorineural, conductive or mixed; high, mid or low frequency) have to be described or if these datas are not available they have to be discussed as another limitation of the study.

REVIEWER	Amir Emamifar 1. OUH, Svendborg Hospital 2. University of Southern Denmark, Faculty of Health Sciences
REVIEW RETURNED	15-Sep-2017

GENERAL COMMENTS	Thank you authors for the revised version of the manuscript. please consider the following comments: 1. in the abstract please revise the following sentence: " adequate medications .....with RA diagnosed" or remove it. 2. Please add statistical significance level to table 2,3,4 for all variables. 3. in Table 4, do consider to perform analysis for each drug separately specially for DMARDs and TNF groups. 4. please discuss why autoimmune comorbid diseases are associated with lower incidence of Hearing loss. autoimmunity is a possible pathology due to destruction of the cochlear hair cells by deposition of immune complex.

REVIEWER	Kuo, Chang-Fu Chang Gung Memorial Hospital, Taiwan
REVIEW RETURNED	17-Sep-2017

GENERAL COMMENTS	The authors revised the article satisfactorily. I have no more comment.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2
Reviewer Name: Amir Emamifar
Institution and Country: 1. OUH, Svendborg Hospital 2. University of Southern Denmark, Faculty of Health Sciences
Please state any competing interests or state 'None declared': none declared

1. in the abstract please revise the following sentence: " adequate medications .....with RA diagnosed" or remove it.
Reply: We have removed the sentence : " adequate medications .....with RA diagnosed" and re-written the Conclusion as: "This study demonstrates that patients with RA are at an increased risk of developing HL. Findings highlight the need of disease-modifying treatment and scheduled auditory examinations for HL prevention and early detection for RA patients." (Please see page 3.)

2. Please add statistical significance level to table 2,3,4 for all variables.
Reply: Thanks for the suggestion. Yes, we have added statistical significance level to Tables 2, 3, and 4.

3. in Table 4, do consider to perform analysis for each drug separately specially for DMARDs and TNF groups.
Reply: Thanks for the suggestion. We have further performed analysis to include each drug separately specially for DMARDs and TNF groups and to revise the manuscript using the new data: "Table 4 shows that medications were associated with reduced incident HL for RA patients. Near 99% of RA patients used NSAIDs and users had a HL incidence of 2.98 per 1000 person-years, with an aHR of 0.12 (95% CI = 0.07-0.20) compared with non-users who had an incidence of 30.1 per 1000 person-years for HL. RA patients on medications of adalimumab (n = 950) had the lowest HL incidence of 0.64 per 1000 person-years with an aHR of 0.23 (95% CI = 0.10-0.55), compared with non-users who had an incidence of 3.23 per 1000 person-years." (Please see page 12 paragraph 1.)

4. please discuss why autoimmune comorbid diseases are associated with lower incidence of Hearing loss. autoimmunity is a possible pathology due to destruction of the cochlear hair cells by deposition of immune complex.
Reply: Thanks for raising the inspirational suggestion. Yes, autoimmune diseases were more prevalent in patients with RA than in controls at the baseline. However, RA patients with autoimmune comorbidity were not at a further increased risk of hearing loss. We are unable to explain. In the Discussion section in the Revision, We adopted your comment and stated:
"However, it is interest to note that most of the comorbidities are associated with further increased incidence of HL, greater for the RA cohort than for the non-RA cohort, except hypothyroidism, and autoimmune diseases (Table 3). Autoimmune disease is a possible pathology associated with sensorineural hearing loss because of destruction of the cochlear hair cells.39 Our study failed to prove this relationship." (Please see page 14 lines 5-7.)

Reviewer: 1
Reviewer Name: Marcia Midori Shinzato
Institution and Country: Universidade Federal da Grande Dourados, Brazil
Please state any competing interests or state ‘None declared’: None declared

Comment: Thanks to the authors for this interesting population-based study that helped clarify the relationship between hearing loss and rheumatoid arthritis. However, I think that a better definition of HL and the types of HL (sensorineural, conductive or mixed; high, mid or low frequency) have to be described or if these data are not available they have to be discussed as another limitation of the study.

Reply: 1. Thanks for your specific comment. We have followed the suggestion to perform further data analysis to evaluate the relationship between the types of HL (sensorineural, conductive or mixed) and rheumatoid arthritis. Results are presented in Table 5. In the revision, we stated: “Further evaluation on the subtype HL showed that RA patients had only few cases of conductive HL, but were at increased risk of sensorineural HL and mixed HL with adjusted HRs of 2.35 (95% CI = 1.91–2.89) and 1.77 (95% CI = 1.54–2.03), respectively (Table 5). (Please see page 12 paragraph 2.)

2. However, information on “high, mid or low frequency of HL” was unavailable from the Taiwan National Health Insurance Research Database. And we have considered it as another limitation of this study : “Hearing impairments by specific sound frequency were not measured to differentiate high, mid or low frequency HL.” (Please see page 16 paragraph 2 last 2 lines.)