PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Primary Sjogren's Syndrome and the Risk of Acute Pancreatitis : A Nationwide Cohort Study
AUTHORS	Chang, Chi Ching; Chang, Yu-Sheng; Wang, Shu-Hung; Lin, Shyr-Yi; Chen, Yi-Hsuan; Chen, Jin Hua

VERSION 1 - REVIEW

REVIEWER	R Hal Scofield University of Oklahoma Health Sciences Center Oklahoma Medical Research Foundation USA
REVIEW RETURNED	02-Nov-2016

GENERAL COMMENTS	Chang and colleagues studied acute pancreatitis among patients with Sjogren's. This is a nation-wide cohort study of hospitalization claims, which makes it powerful but also brings some limitations. I have the following comments - 1. The patients are taken from a catastrophic disease status that must be applied for by the patient's physician. Is there any way to know what percentages of pSS patients have this status? Of course, there must be benefits that encourage application. 2. I think in formal writing the authors should not use steroids to mean glucocorticoid or corticosteroids, since in fact there are many kinds of steroids. 3. Does use of hydroxychloroquine interact with gallstones? That is, are gallstones less common among those taking HCQ; therefore, account for the effect of HCQ in this way. 4. I do not understand the statement in the Discussion that 'judicious hydroxychloroquine might be considered as a risk factor', on page 15, line 33. I thought HCQ use was associated with less pancreatitis. I am not sure what I am missing. 5. The authors discussed Ig4-related illness, at least a little. This does seem like a potential confounder, as there are only a few cases of pancreatitis and small contamination of IgG4-related disease with pancreatitis might make a large difference in the outcome. But, certainly anti-Ro/La is not found in patients with IgG4-related disease. Because of this as well as the association of anti-Ro with extra-glandular disease, can the authors determine whether anti-Ro is associated with pancreatitis. Anti-Ro is not shown in Table 3.

REVIEWER	Benjamin Fisher Rheumatology Research Group, Institute of Inflammation and Ageing University of Birmingham UK
REVIEW RETURNED	30-Jan-2017

GENERAL COMMENTS	The authors have conducted a nested case-control study within a population based nationwide National Insurance claims database. They identified that there was an increased risk of acute pancreatitis in the group with Sjögren's syndrome, although the overall incidence remains low. I have a few points: 1. Verification of the diagnosis of PSS for a catastrophic illness card requires fulfilment of the 2002 AECG criteria. These in turn require exclusion of patients with Hep C, but interestingly almost 4% of the PSS cohort is Hep C positive. This should be discussed. 2. A number of co-morbidities associated with acute pancreatitis are higher in the PSS cohort. Although the association between acute pancreatitis and PSS remains statistically significant in the multivariate analysis (Table 2), statistical significance is borderline and the multivariate analysis does not include other factors such as steroids which the authors found to be associated with acute analysis in the PSS only population (Table 3). Therefore it is quite possible that other confounders may explain the association, including unmeasured confounding connected with metabolic syndrome, and I think this should be mentioned. In line with this, the conclusions should be more cautious e.g. strength and limitation point number 1 should read that there is 'an association', and not that PSS 'increases the risk' of acute pancreatitis, and the second paragraph of the discussion should not state that this study 'proves' that PSS patients have a higher risk. I would also remove the last sentence of the discussion – I am not convinced on the basis of the data presented that PSS patients should be 'carefully monitored' for acute pancreatitis. 3. On page 15 the discussion states that 'judicious hydroxychloroquine might be considered a risk factor'. However the data presented suggest that hydroxychloroquine is associated with a lower HR so it might be protective (or else is not being used in patients with more severe systemic manifestations). 4. It is possible that results may be confounded by the presence of IgG4 disease as the authors themselves state. It remains possible that patients may have been misclassified depending on how the biopsy is reported and especially if IgG4 staining was not performed. This should be acknowledged in the discussion. 5. The authors' present alcoholism as a co-morbidity in Table 1 where it is associated with PSS, but state in the discussion on page 15 and in the strength and limitations bullet points, that data on alcoholism was not available. Do they mean alcohol intake was not available, rather than alcoholism as a co-morbidity? 6. There is a statement on page 15 that is unclear: 'The defected oral mucosa of PSS patients might be susceptible to stimulation by alcohol.' I am uncertain of what the authors are saying. If it is that alcohol can cause unpleasant sensations in some patients with dry mouth (which is correct), then their observed association between alcoholism and PSS might well indicate some misclassification, and of course alcoholism can cause parotidomegaly. This issue should be discussed further. 7. Furthermore, given that alcoholism is associated with PSS in this cohort, it is unclear why this has not been included in the univariate

	and multivariate models in Table 2. It would be good to see this data.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: R Hal Scofield
Institution and Country: University of Oklahoma Health Sciences Center, Oklahoma Medical Research Foundation, USA Please state any competing interests or state 'None declared': None

Please leave your comments for the authors below Chang and colleagues studied acute pancreatitis among patients with Sjogren's. This is a nation-wide cohort study of hospitalization claims, which makes it powerful but also brings some limitations. I have the following comments -

1. The patients are taken from a catastrophic disease status that must be applied for by the patient's physician. Is there any way to know what percentages of pSS patients have this status? Of course, there must be benefits that encourage application.

Ans: Thanks for your comment. Although we don't have the certification rate of pSS patients, the following reasons make us believe the rate is high. First, the certification of pSS is open information for patients and a convention for rheumatologist in daily practice. Second, as mentioned in (Discussion, paragraph 2) certification may exempt patients from related medicalexpense during the long-term follow-up period. Finally, the application process is simple for the physician while the complex peer review was performed by the Health Insurance Bureau. These reasons encourage physicians to apply certificate for their patients once the criteria fulfilled.

2. I think in formal writing the authors should not use steroids to mean glucocorticoid or corticosteroids, since in fact there are many kinds of steroids.
Ans: Indeed, there are many kinds of steroid in Taiwan. In the study, we have converted different kinds of steroids to the dose equivalent to prednisolone according to the glucocorticosteroid efficacy.And the converted dose was applied in the whole work.

3. Does use of hydroxychloroquine interact with gallstones? That is, are gallstones less common among those taking HCQ; therefore, account for the effect of HCQ in this way.
Ans: Thanks for your interesting point. However, in our data, we could only found the association. Further study is needed to understand the underlying mechanism.

4. I do not understand the statement in the Discussion that 'judicious hydroxychloroquine might be considered as a risk factor', on page 15, line 33. I thought HCQ use was associated with less pancreatitis. I am not sure what I am missing.
Ans: Thanks for your suggestion. We have changed this sentence to "without usinghydroxychloroquine might be considered as a risk factor" (Discussion, paragraph 6, line 3)

5. The authors discussed Ig4-related illness, at least a little. This does seem like a potential confounder, as there are only a few cases of pancreatitis and small contamination of IgG4-related disease with pancreatitis might make a large difference in the outcome. But, certainly anti-Ro/La is not found in patients with IgG4-related disease. Because of this as well as the association of anti-Ro with extra-glandular disease, can the authors determine whether anti-Ro is associated with

pancreatitis. Anti-Ro is not shown in Table 3.
Ans: Thanks for your recommendation.

(1) IgG4-RD is indeed an important concern in our study. However, for the certification of Sjogren's syndrome catastrophic illness, either positive anti-Ro and/or anti-La antibody or more than one focus revealed by lip biopsy is required. In IgG4-RD, anti-Ro/La antibodies are rarely present and the typical pathology features are (1)infiltrates of IgG4+ plasmacytes, (2)intense fibrosis and (3)obliterative phlebitis rather than lymphocyte infiltration. Thus, we believe the contamination of IgG4-RD was minimal. (Discussion, paragraph 6, line 19-23)
(2) can the authors determine whether anti-Ro is associated with pancreatitis. Anti-Ro is not shown in Table 3.
Ans: This is an important suggestion. However, we do not have the result of the examination in the claim-based data. Thus, whether anti-Roantibody is associated with the risk of acute pancreatitis needs further study to confirm.

Reviewer: 2
Reviewer Name: Benjamin Fisher
Institution and Country: Rheumatology Research Group, Institute of Inflammation and Ageing, University of Birmingham, UK Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below The authors have conducted a nested case-control study within a population based nationwide National Insurance claims database. They identified that there was an increased risk of acute pancreatitis in the group with Sjögren's syndrome, although the overall incidence remains low. I have a few points:
1. Verification of the diagnosis of PSS for a catastrophic illness card requires fulfilment of the 2002 AECG criteria. These in turn require exclusion of patients with Hep C, but interestingly almost 4% of the PSS cohort is Hep C positive. This should be discussed.

Ans: Thanks for your important point.

We added a paragraph aboutthis issue in discussion (Discussion, paragraph 5). "HCV is associated with both Sjogren's syndrome and acute pancreatitis andmight be an important confounder in our study. Furthermore, patients with HCV should be excludedaccording to the 2002 AECG criteria. However, the pathogenesis of the association between Sjogren's syndrome and HCV were not fully known and the sicca syndrome in HCV patients ispSS, secondary Sjogren's syndrome or only SS-like symptomsremains controversial. Moreover, neither correcting HCV in the multivariate Cox model northe analysis after excluding pSS patients with prior HCV and their matched controlsresulted in differentoutcome.Thus, the initial study design was not altered and HCV was not excluded."

2. A number of co-morbidities associated with acute pancreatitis are higher in the PSS cohort. Although the association between acute pancreatitis and PSS remains statistically significant in the multivariate analysis (Table 2), statistical significance is borderline and the multivariate analysis does not include other factors such as steroids which the authors found to be associated with acute analysis in the PSS only population (Table 3). Therefore it is quite possible that other confounders may explain the association, including unmeasured confounding connected with metabolic syndrome, and I think this should be mentioned. In line with this, the conclusions should be more cautious e.g. strength and limitation point number 1 should read that there is 'an association', and not that PSS 'increases the risk' of acute pancreatitis, and the second paragraph of the discussion should not state that this study 'proves' that PSS patients have a higher risk. I would also remove the last sentence of the discussion – I am not convinced on the basis of the data presented that PSS patients should be 'carefully monitored' for acute pancreatitis.

Ans: Thanks for your suggestion. In this work, pSS cohort had significantly higher incidence of acute pancreatitis compared to randomly selected age- and sex-matched non-pSS controls. In fact, this was sufficient to assume the significant association between acute pancreatitis and pSS. However, comorbidities were found significantly higher in the pSS cohort. Although we thought that came from the far lower medical utility in the control cohort and these factors other than HCV were not likely to bias the selection of the pSS and control cohorts, we still chose a conservative way, which may lead to over-correction, to correct all these factors. Thus, factors possibly associated with acute pancreatitis but external to pSSwere treated aspotential"confounders" in the analysis (table 2).After these factors corrected, pSS was still significantly associated with acute pancreatitis. On the contrary, pSS related factors, such as medications including immunosupressants and steroid were added in the analyzed in Table 3 to identify which features in the pSS cohort were "mediators", that influence the risk of acute pancreatitis.

The additional factors in table 3 were not included in the analysis in table 2, because we thought these factors were related to pSS. Thus, as your suggestion, we could not tell the higher risk of acute pancreatitis in pSS patients came from the pathogenesis of pSS per se, medications applied to treat pSS or other comorbidities found associated with pSS. In particular, we could not tell the increased risk was resulted from the side effect of steroid and cyclophosphamide or the clinical condition leaded to the use of these medications.

Thus, we made the following changes:

(1) We changed 'prove' to "demonstrate". (Discussion, paragraph 2, line 1)
(2) We changed the last sentence of discussion "pSS patients should be 'carefully monitored' for acute pancreatitis." to "acute pancratitis should be considered one of the differential diagnoses when related symtptoms present" (Discussion, paragraph 7, line 4-5)

3. On page 15 the discussion states that 'judicious hydroxychloroquine might be considered a risk factor'. However the data presented suggest that hydroxychloroquine is associated with a lower HR so it might be protective (or else is not being used in patients with more severe systemic manifestations).

Ans: Thanks for your suggestion. We have changed this sentence to "without using hydroxychloroquine might be considered as a risk factor"(Discussion, paragraph 6, line 3)

4. It is possible that results may be confounded by the presence of IgG4 disease as the authors themselves state. It remains possible that patients may have been misclassified depending on how the biopsy is reported and especially if IgG4 staining was not performed. This should be acknowledged in the discussion.

Ans: Thanks for your recommendation. IgG4-RD is indeed an important concern in our study. However, for the certification of Sjogren's syndrome catastrophic illness, either positive anti-Ro and/or anti-La antibody or more than one focus revealed by lip biopsy is required. In IgG4-RD, anti-Ro/La antibodies are rarely present and the typical pathology features are (1)infiltrates of IgG4+ plasmacytes, (2)intense fibrosis and (3)obliterative phlebitis rather than lymphocyte infiltration. Thus, we believe the contamination of IgG4-RD was minimal. (Discussion, paragraph 6, line 19-23)

5. The authors' present alcoholism as a co-morbidity in Table 1 where it is associated with PSS, but state in the discussion on page 15 and in the strength and limitations bullet points, that data on alcoholism was not available. Do they mean alcohol intake was not available, rather than alcoholism as a co-morbidity?

Ans:
Thanks for your suggestion to clarify our discussion. We have changed "Data on alcoholism and smoking" (Discussion, paragraph 6, line 7) to "Data on alcohol consumption and smoking" in our discussion.

6. There is a statement on page 15 that is unclear: 'The defected oral mucosa of PSS patients might be susceptible to stimulation by alcohol.' I am uncertain of what the authors are saying. If it is that alcohol can cause unpleasant sensations in some patients with dry mouth (which is correct), then their observed association between alcoholism and PSS might well indicate some misclassification, and of course alcoholism can cause parotidomegaly. This issue should be discussed further.
Ans: Thanks for your important suggestion. "Alcoholism"in our study was defined as the presence of related ICD-9CM codes (listed in the method) prior to the diagnosis of pSS. Unlike other comorbidities, alcoholism was easily underestimated because that we could only identify those went to a doctor. Those who were relatively healthy, in a low socioeconomic status or unwilling to quit alcohol would not be identified. Even more, once they visited doctors for other medical problems, theinformation might be concealedoralcoholismmight not be particularly coded or be coded in a low priority when relatively irrelevant to their major medical problems. Thus, we believed the coding of alcoholism was related to the medical utilization, which resulted in a significant lower rate of alcoholism in the control cohort. Otherwise, we could not know whether the alcohol consumptiondecreased after dry mouth aggravated as our inference. We have added related statement in the discussion(Discussion, paragraph 6, line 7-17).

7. Furthermore, given that alcoholism is associated with PSS in this cohort, it is unclear why this has not been included in the univariate and multivariate models in Table 2. It would be good to see this data.

Ans: Thanks for your important comment. In fact, alcoholism wasincluded in our initial analysis and resulted in a very wide 95%CI due to the relatively few cases. Thus, we omitted the data finally for the possible misclassification resulted from the reasons mentioned above and the lack of statistic power on this issue. We have added the statement in our discussion(Discussion, paragraph 6 ,line7-17) to make this issue clearer.

VERSION 2 – REVIEW

REVIEWER	Benjamin Fisher Rheumatology Research Group, Institute of Inflammation and Ageing, University of Birmingham, UK
REVIEW RETURNED	17-Mar-2017

GENERAL COMMENTS	Thank you for your comments. Can I suggest the following minor changes to help clarity:

	1. In the discussion the new following sentence: 'However, the pathogenesis of the association between Sjogren's syndrome and HCV were not fully known and the sicca syndrome in HCV patients is pSS, secondary Sjogren's syndrome or only SS-like symptoms remains controversial' could be changed to something along the lines of: 'However, the pathogenesis of the association between Sjögren's syndrome and HCV is not fully known and whether the sicca syndrome in HCV patients is due to pSS, secondary Sjögren's syndrome or only SS-like symptoms remains controversial.' 2. In the discussion the following sentences: 'The defected oral mucosa of pSS patients might be susceptible to stimulation by alcohol. However, we could not know whether the alcohol consumption decreased after dry mouth aggravated as our inference' could be changed to something along the lines of :'Dryness of the oral mucosa in pSS can result in alcohol intolerance. However, we do not know whether average alcohol consumption decreased after the onset of dry mouth' 3. In the strengths and limitations: 'This is the first nationwide population-based cohort study that demonstrated the patients with Sjogren's syndrome increase the risk of acute pancreatitis' could be changed to 'This is the first nationwide population-based cohort study that has demonstrated that patients with Sjögren's syndrome have an increased risk of acute pancreatitis.' The next phrase 'Data on alcoholism and smoking' should be changed to 'Data on alcohol intake and smoking'.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

1. However, the pathogenesis of the association between Sjogren's syndrome and HCV were not fully known and the sicca syndrome in HCV patients is pSS, secondary Sjogren's syndrome or only SS-like symptoms remains controversial---change to---- However, the pathogenesis of the association between Sjögren's syndrome and HCV is not fully known and whether the sicca syndrome in HCV patients is due to pSS, secondary Sjögren's syndrome or only SS-like symptoms remains controversial.
2. The defected oral mucosa of pSS patients might be susceptible to stimulation by alcohol. However, we could not know whether the alcohol consumption decreased after dry mouth aggravated as our inference'----change to -----Dryness of the oral mucosa in pSS can result in alcohol intolerance. However, we do not know whether average alcohol consumption decreased after the onset of dry mouth'
3. This is the first nationwide population-based cohort study that demonstrated the patients with Sjogren's syndrome increase the risk of acute pancreatitis---- changed to ---This is the first nationwide population-based cohort study that has demonstrated that patients with Sjögren's syndrome have an increased risk of acute pancreatitis.
4. Data on alcoholism and smoking--- changed to---Data on alcohol intake and smoking.