Author’s response to reviews

Title: Epidemiology of Ossification of the Spinal Ligaments and Associated Factors in the Chinese population: a cross-sectional study of 2,000 consecutive individuals

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Author’s response to reviews:

Dear editor,

Thank you very much for giving us an opportunity to revise our manuscript. We have studied reviewer’s comments carefully and appreciate the positive comments of reviewers. We have been best efforts to revise the manuscript and incorporate the comments and suggestion of reviewers. The point-by-point responses to the comments are described in detail below. We hope that you and reviewers will find the revised manuscript is satisfactory and acceptable.

With best wishes,

Yours sincerely,

Qin-Ming Fei
Dr. Fujimori (Reviewer 1)

Comment 1. The author should mention more information about the area of the study performed.

Response: We thank Dr. Fujimori for this important suggestion. We have added corresponding contents as suggested in the Methods section.

“From October 2010 to September 2013, a total of consecutive 2059 Chinese individuals from East China who underwent fluorin-18 fluorodeoxyglucose positron emission tomography and CT (PET/CT) for the purpose of cancer screening in our hospital were selected.” (Methods section, line 35, page 3)

Comment 2. As the author mentioned, there is no clear consensus about the diagnosis criteria of ossification of the spinal ligament. However, there have been several similar previous studies. As for cervical OPLL, many studies defined OPLL as 2mm thickness. However, as for OALL, 3mm thickness may be too small for satisfying the criteria of DISH. Originally, DISH mean large ossifications locating anterolateral vertebra in thoracolumbar spine. Why did the author choose 3mm thickness for criteria? Please explain it.

The author should also clarify the criteria of OLF.

The authors need to show the examples of diagnosis of ossification of the spinal ligament.

Response: We greatly admire Dr. Fujimori’s work in this field and thank you for this insightful comment. Our study is also inspired by your research in this field.

Regarding the diagnostic criteria for DISH, we have reviewed articles about this disease. Various authors use different definitions for the diagnosis of DISH. These range from hyperostosis linking two vertebral bodies, without intervening disc disease and extend to different numbers of vertebrae connected by confluent anterior longitudinal ligament related new bone. Our diagnostic criteria is based on the commonest criteria in this field. In our study, diagnostic criteria of DISH is that the presence of contiguous ligamentous ossification involving three or more intervertebral disk levels with anterior or lateral bridging, suggested by Resnick’s criteria [1,2]. So, the prerequisite for meeting this diagnostic criterion must first be that the presence of 4 or more...
consecutive fused vertebral bodies with contiguous ligamentous ossification. After checking our research data again, among all the DISH that meet the requirement in our research, the thinnest DISH have a thickness of 4.5 mm and the thickest reaches 30.8mm. About 85% of DISH are more than 6 mm thickness in our study. Therefore we think this is in line with the criteria. As you said, originally, DISH mean large ossifications locating anterolateral vertebra in thoracolumbar spine. The thickness criteria of 3mm is for OALL, not for DISH. For DISH, it has to be the presence of contiguous ligamentous ossification involving three or more intervertebral disk levels with anterior or lateral bridging. In order to more clearly explain the diagnostic criteria of DISH, we have modified the corresponding description in the article. (Methods section, line 5-9, page 4)

“DISH was diagnosed according to the commonly used diagnostic criteria, defined by Resnick and Niwayama [19]. The criteria are as follows: (1) the presence of contiguous ligamentous ossification involving three or more intervertebral disk levels(4 or more consecutive fused vertebral bodies) with anterior or lateral bridging; (2) preserved intervertebral disc space; and (3) absence of apophyseal joint ankylosis and sacroiliac joint fusion.” (Methods section, line 5-9, page 4)

Regarding the diagnostic criteria for OLF, we reviewed all the articles about this disease in this field. In the study of Fujimori et al[3], OLF ossification in Japanese was defined as ossification of the ligamentum flavum with more than 4 mm thickness in the axial plane images. In the study of Kim et al[4], OLF in Korean indicates an ossified mass that is presented in the ligamentum flavum between two adjacent laminae. On axial CT scan, OLF developed from the capsular insertion at the facet joint along the yellow ligament. In the study of Moon et al[5], they defined OLF as a compressed spinal cord with a midline hypointense signal mass at the posterior margin of the spinal canal on MRI. In the study of Mori et al[6], a positive case of OLF in Japanese was defined as a distinctive ossified plaque within the yellow ligament. They classified OLF into the following 5 subtypes: small, medium, large, extralarge, and central type. An ossification that is distinctly identified on CT scan despite being smaller than 3 mm in its thickness was designated as “small”. In the study of Lang et al[7], the radiographic characteristics of OLF in Chinese were high-density spots, strips, and irregularly shaped areas on the level of facet joints, inside the vertebral plate and outside the dural sac on CT scan. It is worth noting that in his research related to the Chinese population he measured and showed the thickness of the OLF. “A total of 3,898 ligamentum flava were ossified, with the average thickness of 3.03 ± 0.76 mm (range 1.4 – 7.1 mm)”[7]. In addition, when we evaluated the images, we found a certain amount of relatively small OLF. These should be the early stage of ossification of the ligamentum flavum.( Fig. 1, Fig. 2, Fig. 3) (In the response letter in the Supplementary Material). Therefore, on the basis of studies mentioned above, we think it is reasonable to define the thickness of OLF as greater than 2 mm on axial CT scan in our study.
Fig. 1 OLF is located at T12. Axial CT image shows the thickness of OLF is 2.5mm. (Measurement of the vertical distance between the thickest point of ossified ligament and the lamina was defined as the thickness of OLF)

Fig. 2 OLF is located at T5. Axial CT image shows the thickness of OLF is 3mm.

Fig. 3 OLF is located at T11. Axial CT image shows the thickness of OLF is 3.1mm.

These three pictures are in the response letter in the Supplementary Material


Comment 3.

Cervical OPLL
Most of the study reported that cervical OPLL was more common in men than in women. However, this study showed the opposite result. In this study, OPLL and OLF was more common in women, although OALL and ONL was common in men. Did the author think that women had more ossification of the spinal ligament? Please explain the result in discussion.

Response:

We are very grateful to Dr. Fujimori for your comments. Your comments are very important and helpful for our article. In the original version of this article, the prevalence of C-OPLL was 4.1 % (men, 4.1 %; women, 4.1 %). The prevalence is accurate to one digit after the decimal point. We think that this will lead to confusion for reviewers and lead to inaccurate expression of the results. So we correct the prevalence and the prevalence is accurate to two decimal places in our study. The real prevalence of C-OPLL was 4.10 % (men, 4.12 %; women, 4.06 %).

We don’t think that women had more ossification of the spinal ligament. We think this question needs to be answered according to the type and location of ossification. In order to answer this question better, we added Tables 5 and 6 to our article. Table 5 and 6 give a summary of studies performed by various authors on the prevalence of OSL. It can be seen from the Table 5 and 6 that, the overwhelming majority of previous studies are consistent in the results regarding the gender difference in C-OPLL, T-OPLL, and DISH prevalence. C-OPLL and DISH are more common in men, while T-OPLL is more common in women. Our results are also consistent with previous findings. But for T-OLF, the results of previous studies are inconsistent. Four studies[4,10,16,29] showed that T-OLF occurs predominantly in men, while two others[9,31] showed the opposite result. In our study, T-OLF was more common in women. Another problem is that our current study showed that the prevalence of C-OPLL in men is almost equal to that in women. (men 4.12 %, women 4.06 %). In Japan and Korea, the prevalence of C-OPLL has been considered to have a male predominance of roughly 2:1 to 3:1.

In view of the above phenomena and problems, we have revised and added discussions to explain these results (Discussion section, line 17-37, page 11 and Table 5, Table 6).

“Table 5 and 6 give a summary of studies performed by various authors on the prevalence of OSL by sex. Our data showed that T-OPLL is significantly more common in women, while DISH is significantly more common in men. The results of the multiple regression analysis revealed that males are three times more likely to suffer from DISH. Consistent with previous evidence[6,16,32,39-47], female preponderance of T-OPLL and male preponderance of DISH were confirmed. With regard to the gender difference in the prevalence of C-OPLL, our current study showed that the prevalence of C-OPLL in men is almost equal to that in women. (men 4.12 %, women 4.06 %). The C-OPLL prevalence rate of men in our study is far lower than that of previous studies using CT scan [16,26]. In Japan and Korea, the prevalence has been considered to have a male predominance of roughly 2:1 to 3:1[48]. Although eastern Asians are thought to be genetically similar, the discrepancy could be attributed to different reasons, such as age...
distribution, sex ratio, sample size, target population, or selection bias. In addition, lifestyle factors and dietary habits, including bad sleeping habits[49], high-salt and low-protein diet[50], were associated with an increased risk of OPLL. Some studies have shown that the coexistence of other disorders such as obesity[51], diabetes mellitus[52], hypoparathyroidism[5], and hormonal imbalance[53], are contributory factors in OPLL. Therefore, these multiple factors may lead to different results. For T-OLF, through a review of literature, we encountered 6 epidemiological studies reporting the prevalence of T-OLF. But the results regarding the gender difference in T-OLF prevalence are inconsistent. Four studies[4,10,16,29] showed that T-OLF occurs predominantly in men, while two others[9,31] showed the opposite result. In this study, T-OLF was significantly more common in women (men 36.10 %, women 40.75 %). Additional large-scale, multi-center studies is therefore necessary to confirm the cause for these differences.” (Discussion section, line 17-37, page 11)

Comment 4.
Thoracic OPLL

Thoracic OPLL is much more rare disease than cervical OPLL. It is incomprehensible that prevalence of thoracic OPLL and cervical OPLL was both 4.1% in women.

The authors may need to check more women objects.

Response:

We are very grateful to Dr. Fujimori for pointing out this problem in our article. We checked the data of OPLL carefully and once again evaluated the images of these people.

Two women who we thought had T-OLF are actually degenerative osteophytes. They located at the corner of the vertebral body and they are different in morphology from ossification of the spinal ligament. Another woman's ossification was actually only located in the cervical spine (C7 vertebral body level and C7/T1 intervertebral disc level), but when collating data, we mistakenly counted it in the cervical spine (C7, C7/T1) and thoracic spine (T1 vertebral body level) (in the original version, this person was counted in both the C-OPLL and T-OPLL). We are very sorry for our negligence and thank Dr. Fujimori for pointing out this problem. We have removed the above three women in the T-OPLL group and revised all relevant data, tables and figures in this article.(Abstract section: line 15, line 18-19, page 2;Result section: line 8-12, line 16, line 19-22 page 6; line 8 page 7; Discussion section: line 17, 28 page 10; line 6-8 page 11;Table 2; Table 3; Figure 2; Figure 3; Figure 4).The truth is that a total of 45 subjects had thoracic OPLL (T-OPLL), including 21 men and 24 women. The prevalence of T-OPLL was 2.25 % (men, 1.57 %; women, 3.61%).
Comment 5. Multivariate logistic analysis. Only odds ratio of "gender" in DISH was 3.1. However, most of odds ratios of parameters were nearly 1. This means the effect of these parameters were weak.

Response:

We thank Dr. Fujimori for this suggestion. We think interpretation of logistic analysis results need to be based on the type and unit of variables. Gender is categorical variable. In our study, Males showed a strong association with DISH (odds ratio, 3.15; 95% confidence interval, 1.27-7.78; P = 0.013). So it means males are three times more likely to suffer from DISH. But for age, BMI, and spinal sagittal parameters, they are continuous variable. In our study, for example, BMI was found to be significantly associated with the presence of C-OPLL (odds ratio, 1.27; 95% confidence interval, 1.12-1.45; P < 0.001). Although OR is nearly 1, it means for every one unit increment of BMI, the risk of developing C-OPLL increases by 27%. Another example in our study, increased age is found to be a significant associated factor for the presence of DISH (odds ratio, 1.08; 95% confidence interval, 1.05-1.11; P < 0.001). It means for every one year increase, the risk of developing DISH increases by 8%.

Considering that there have been limited data on the association between these parameters and OSL, we think that these data and results are useful for comparison and validation of future research and will contribute to a better understanding of the disease. In order to express these results more better in our article, we have modified the corresponding contents in the abstract (Abstract section, line 20-22, page 2) and result sections (Result section, line 10-13, page 10).

Dr. Wada (Reviewer 2)

Comment 1. Please cite some representative literatures about clinical problems of OSL. (pg. 3, lines from 9 to 11)

Response: We thank Dr. Wada for this suggestion. Your suggestion is important, and we have modified and added corresponding contents as suggested. (Background section, line 9-16, page 3)

“OPLL and OLF are common causes of spinal stenosis and spinal cord compression, which can cause various degrees of neurological symptoms[3,4]. But many affected individuals are usually asymptomatic when the lesions are small[5]. DISH is a skeletal disease characterized by progressive ossification of the anterolateral side of the spine[6]. Although DISH is thought to be an asymptomatic condition in most affected individuals not aware of its presence, several clinical symptoms have been reported including pain, restriction of spinal movements, dysphagia at
Comment 2. Please describe to which level C7 / T1 and T12 / L1 were included. (pg. 3, in paragraph of radio graphic assessment)

Response:

We thank Dr. Wada for this important suggestion and appreciate your attention to detail. We have added some corresponding contents as suggested in the Methods section. (Methods section, line 10-13, page 4)

“For statistics on the prevalence and distribution of OSL, if OPLL was located at C7/T1 or T12/L1 intervertebral level, they were included in the cervical and thoracic segments, respectively. Similarly, OALL, bridging the adjacent vertebrae at C7/T1 or T12/L1 intervertebral level, were included in the cervical and thoracic segments, respectively.” (Methods section, line 10-13, page 4)

Comment 3. It is necessary to differentiate DISH from ankylosing spine. So, I think it should be stated that there were no fusion of sacroiliac joints in DISH. Please describe this point in the paragraph of radiographic assessment. (pg. 5-6)

Response:

We are very grateful for Dr. Wada’s comments. Your suggestion makes our article more rigorous. We have modified and added corresponding contents. (Methods section, line 5-9, page 4)

“DISH was diagnosed according to the commonly used diagnostic criteria, defined by Resnick and Niwayama [19]. The criteria are as follows: (1) the presence of contiguous ligamentous ossification involving three or more intervertebral disk levels (4 or more consecutive fused vertebral bodies) with anterior or lateral bridging; (2) preserved intervertebral disc space; and (3) absence of apophyseal joint ankylosis and sacroiliac joint fusion.” (Methods section, line 5-9, page 4)

Comment 4. Typing mistakes (unit of cervical lordosis). (pg. 5 and 8)

Response: Thank you very much for discovering our mistakes. We are very sorry for this error and we have corrected this mistake. (pg. 5 and 8)
Comment 5. Did you mean "when patients with clinical symptoms induced by OPLL" equal as "when there is no OPLL of the lumbar levels"? The frequency of L-OPLL was 0.8% in this study. So, you may not be emphasize like the sentence; "when clinical symptoms induced by OPLL are present, we recommend thorough evaluation of whole spine using CT". Please reconsider this point in discussion. (pg. 11, lines from 14 to 15)

Response:

We are very grateful for Dr. Wada’s comments. In this paragraph of discussion (Discussion section, line 2-16, page 11), we mainly want to express the following meaning.

In our study, based on the results “21% of subjects with C-OPLL had T-OPLL, 44% of C-OPLL had T-OLF, 38% of T-OPLL had C-OPLL, 53% of T-OPLL had T-OLF, 19% of L-OPLL had C-OPLL, 44% of L-OPLL had T-OPLL, and 56% of L-OPLL had T-OLF among general Chinese population”, we found that subjects with OPLL generally have a predisposition to coexist with multiple-regional lesions and approximately half of the subjects with OPLL coexist with T-OLF.

This means, for example, if a person has L-OPLL, then he has a 44 percent chance of having T-OPLL, and a 56 percent chance of having T-OLF. If a person has T-OPLL, then he has a 38 percent chance of having C-OPLL, and a 53 percent chance of having T-OLF. And if another person has C-OPLL, then he has a 21 percent chance of having T-OPLL and a 44 percent chance of having T-OLF. These show that there is a high possibility of coexistence between them. In addition our research is based on the general population and many affected individuals are usually asymptomatic when the lesions are small. But for patients with neurological symptoms induced by one kind of OPLL (located in the cervical, thoracic, or lumbar spine), they are certainly more likely than the general population to have co-existing ossification in other areas (C-OPLL, T-OPLL, L-OPLL, or T-OLF). Therefore, we said “for patients with clinical symptoms induced by OPLL, we recommend thorough evaluation of whole spine using CT”. Because we think it will be helpful for the diagnosis and treatment of patients' disease and prevent misdiagnosis.

The above is what we want to express. If you find this point is not appropriate, we will continue to modify this content. Thanks again for your advice.

Comment 6. Presence or absence of OSL, especially OPLL may affect the flexibility of the thoracic spine in sagittal plane. I think that this point will be a limitation for measuring the thoracic kyphosis on CT in the supine position. Please consider adding this point as a limitation.

Response:
We are very grateful to Dr. Wada for your comment. Your comment is very helpful for our article.

We agree with your opinion and make corresponding modifications in the article. (Discussion section, line 26-28, page 13)

“OSL can have an influence on the flexibility of the spinal column, so there may be a limitation for measuring spinal sagittal parameters in the supine position.” (Discussion section, line 26-28, page 13)