

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Prevalence and characteristics of thoracic ossification of the posterior longitudinal ligament in 3,299 Black patients: a cross-sectional study of a prospectively registered database
<b>AUTHORS</b>	Yoshihara, Hiroyuki; Horowitz, Evan; Nadarajah, Vidushan

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Nouri, Aria Yale University School of Medicine, Department of Neurosurgery
<b>REVIEW RETURNED</b>	10-Dec-2021

<b>GENERAL COMMENTS</b>	<p>This is an interesting paper, and I think prevalence studies of various types of degenerative pathologies of the spine is important to determine what is indeed pathologic, what could be the etiology and to determine their clinical impact. The association with DM is an important finding, as this has been proposed as a risk factor but not clearly validated.</p> <p>I have a couple of comments. It is important to take into consideration that the term "black" may not be appropriate. While I understand that this derived from the response of the survey, black represents a large ethnic group. It would be similar with the term "white", what would white mean? does that include all of europe, and large portions of asia, and latin american and australia? I am not quite sure how to address this but it may be more appropriate to say african-american ancestry. You may also want to keep "black" but clearly describe such a unclarity in the limitations.</p> <p>I also understand the limitation of literature on the subject and the discussion therefore of cervical OPLL in the discussion section. It is relevant to note the prevalence of cervical OPLL in patients with DCM was previously published in different geographical regions (PMID: 27861250). While published for the cervical OPLL, recent studies have also have mentioned potential factors of OPLL progression and it may be worthy to mention this.</p>
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<b>REVIEWER</b>	Cheung, Jason The University of Hong Kong
<b>REVIEW RETURNED</b>	25-Dec-2021

<b>GENERAL COMMENTS</b>	<p>It is not ethnically sensitive or appropriate to use "black" throughout the paper. This is only subjugating based on skin color. You should either use African or African-American instead.</p> <p>It is important to note clearly this isn't a prevalence study since these are selected trauma patients and not a general population study hence the findings are not representative of the population.</p>
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	<p>Also this is cross-sectional. How many would actually develop symptoms are therefore clinically relevant is important vs those who have some ossification that won't be managed at all in their lifetime.</p> <p>What was the study population? How many of these patients had clinical symptoms? What "trauma" was involved. Did patients suffer trauma due to myelopathy? It would be more interesting to see cervical OPLL involvement as well which in trauma situation i would expect the cervical spine screening to have been done. How many actually had a chest trauma? Would fractures through the OPLL cause issues with correct identification?</p> <p>I'm surprised the authors didn't take the opportunity to also assess for the presence of OYL in the patient population. This is more clinically relevant since double ossification is higher risk of surgical complications</p> <p>I hope the authors aren't trying to salami slice with multiple studies based on the above.</p> <p>The authors should quote a unique natural history study on these ossifications: Chris Yuk Kwan Tang, Kenneth Man Chee Cheung, Dino Samartzis, Jason Pui Yin Cheung. The Natural History of Ossification of Yellow Ligament of the Thoracic Spine on MRI: A Population-Based Cohort Study Global Spine J. 2021 Apr;11(3):321-330. doi: 10.1177/2192568220903766. Epub 2020 Jan 31.</p> <p>It is more important to understand the canal occupancy ratio based on these ossifications. This should be studied</p> <p>How were calcifications considered? Did all three reviewers look at all 3000 images? Were there reliability issues? What are the bias/errors?</p> <p>Stats are very basic and superficial with only t-test and only a simple univariate comparison. The data is a lot and should be carefully dissected and further deep analysis needed.</p> <p>You had cases of 5 years old. Would the patients not have these formed yet? Also for the older group, no neurology? No prev surgery? The population needs to be clarified</p> <p>The number of patients in this study with ossification is very low. This may lead to statistical insignificance. What was the sample size calculation for the analyses? Lack of BMI and DM relationship is surprising and should be adequately studied and explained. Would obesity grading be more useful vs absolute BMI measurement? Bear in mind the difference in definition to Asian populations.</p>
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<b>REVIEWER</b>	Fujimori, Takahito Hyogo Coll Med
<b>REVIEW RETURNED</b>	22-Mar-2022

<b>GENERAL COMMENTS</b>	The authors examined the prevalence of T-OPLL in Blacks. Preferably, they should have investigated the prevalence of cervical OPLL, which is relatively frequent, instead of the thoracic
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	spine. Although the novelty is limited, it may be worth publishing because there have been no previous reports on Blacks.
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### VERSION 1 – AUTHOR RESPONSE

**Reviewer: 1**

**Dr. Aria Nouri, Yale University School of Medicine**

Comments to the Author:

This is an interesting paper, and I think prevalence studies of various types of degenerative pathologies of the spine is important to determine what is indeed pathologic, what could be the etiology and to determine their clinical impact. The association with DM is an important finding, as this has been proposed as a risk factor but not clearly validated.

**I have a couple of comments. It is important to take into consideration that the term "black" may not be appropriate. While I understand that this derived from the response of the survey, black represents a large ethnic group. It would be similar with the term "white", what would white mean? does that include all of europe, and large portions of asia, and latin american and australia? I am not quite sure how to address this but it may be more appropriate to say african-american ancestry. You may also want to keep "black" but clearly describe such a unclarity in the limitations.**

Answer: In the study populations section, it's written "We used "Black" because this was the term used on the questionnaire and "Black" can include "African-American" and "Caribbean-American." There are many "Caribbean-American" in the New York City area and they may feel insulted if we use "African-American". In addition, hospitals should not use "Black" if it's not ethically sensitive.

**I also understand the limitation of literature on the subject and the discussion therefore of cervical OPLL in the discussion section. It is relevant to note the prevalence of cervical OPLL in patients with DCM was previously published in different geographical regions (PMID: 27861250). While published for the cervical OPLL, recent studies have also have mentioned potential factors of OPLL progression and it may be worthy to mention this.**

Answer: The purpose of this study was to examine the prevalence and characteristics of T-OPLL in the Black patients, not cervical OPLL. So, we cannot discuss cervical OPLL much based on our results. Regarding different geographical regions, in the discussion section, it's written "OPLL has been assumed to occur predominantly in the Asian population. Our study showed the prevalence of T-OPLL in the Black population seems to be equivalent to that in the Asian population based on the CT analysis." We would like people to know that epidemiology studies in the Black population are extremely limited.

Our study was to examine the prevalence and characteristics of T-OPLL, not OPLL progression. We found an article by Yoshimura et al. stating that "OPLL showed a significant association with the femoral neck BMD, presence of DISH and plasma pentosidine levels." However, our study content does not include these factors which makes it difficult to lead a discussion.

Yoshimura N, Nagata K, Muraki S, et al. Prevalence and progression of radiographic ossification of the posterior longitudinal ligament and associated factors in the Japanese population: a 3-year follow-up of the ROAD study. *Osteoporos Int.* 2014 Mar;25(3):1089-98.

**Reviewer: 2**

**Dr. Jason Cheung, The University of Hong Kong**

Comments to the Author:

**It is not ethnically sensitive or appropriate to use "black" throughout the paper. This is only subjugging based on skin color. You should either use African or African-American instead.**

Answer: In the study populations section, it's written "We used "Black" because this was the term used on the questionnaire and "Black" can include "African-American" and "Caribbean-American." There are many "Caribbean-American" in the New York City area and they may feel insulted if we use "African-American". In addition, hospitals should not use "Black" if it's not ethically sensitive.

**It is important to note clearly this isn't a prevalence study since these are selected trauma patients and not a general population study hence the findings are not representative of the population. Also this is cross-sectional. How many would actually develop symptoms are therefore clinically relevant is important vs those who have some ossification that won't be managed at all in their lifetime.**

Answer: In the discussion section, it's written "First, the participants in this study may not represent the general population and may have a selection bias due to the limited area (New York City). However, because it is unethical to obtain CT scans of normal volunteers, we think that our study participants may represent the best possible sampling for the general population. Second, there was no information regarding the clinical presentation caused by T-OPLL. Thus, the association between T-OPLL and clinical presentation could not be assessed." To the best of our knowledge, there is no previous article which reported the prevalence of ossification disease using CT and large number of "real general population."

To the best of our knowledge, there is one previous article (Fujimori et al.) which reported the prevalence and clinical presentation of ossification disease using large number of subjects, but it was the neurological symptom related to the trauma. As a real problem, it's almost impossible to get CT scan of 3,000 general population and investigate the clinical presentation. The reviewer needs to understand the reality of this kind of prevalence study.

Furthermore, the purpose of this study is "to examine the prevalence and characteristics of T-OPLL in the Black patients."

Mori K, Imai S, Kasahara T, et al. Prevalence, distribution, and morphology of thoracic ossification of the posterior longitudinal ligament in Japanese: results of CT-based cross-sectional study. *Spine.* 2014;39:394-9.

Kim TJ, Bae KW, Uhm WS, et al. Prevalence of ossification of the posterior longitudinal ligament of the cervical spine. *Joint Bone Spine*. 2008;75:471-4.

Fujimori T, Le H, Hu SS, et al. Ossification of the posterior longitudinal ligament of the cervical spine in 3161 patients: a CT-based study. *Spine*. 2015;40:E394-403.

Fujimori T, Watabe T, Iwamoto Y, et al. Prevalence, concomitance, and distribution of ossification of the spinal ligaments: results of whole spine CT scans in 1500 Japanese patients. *Spine*. 2016;41:1668-76.

Liang H, Liu G, Lu S, et al. Epidemiology of ossification of the spinal ligaments and associated factors in the Chinese population: a cross-sectional study of 2000 consecutive individuals. *BMC Musculoskelet Disord*. 2019;20(1):253.

Bakhsh W, Saleh A, Yokogawa N, et al. Cervical Ossification of the Posterior Longitudinal Ligament: A Computed Tomography-Based Epidemiological Study of 2917 Patients. *Global Spine J*. 2019;9(8):820-825.

### **What was the study population?**

Answer: In the study populations section, it's written "All patients who underwent chest CT for the trauma screening and whose race was classified as "Black" on the questionnaire were recruited in the study from Mar 2019 to Mar 2020."

### **How many of these patients had clinical symptoms?**

Answer: Please see the above.

### **What "trauma" was involved. Did patients suffer trauma due to myelopathy?**

Answer: "Trauma screening" includes all types of trauma at the Emergency Department.

### **It would be more interesting to see cervical OPLL involvement as well which in trauma situation i would expect the cervical spine screening to have been done.**

Answer: First, the purpose of this study is "to examine the prevalence and characteristics of T-OPLL in the Black patients." We feel the reviewer is asking for the outcomes of cervical spine surgery when the authors are reporting the outcomes of thoracic spine surgery. Second, previous studies (as below) reported the prevalence of cervical OPLL in Black population as a part of the study.

Fujimori T, Le H, Hu SS, et al. Ossification of the posterior longitudinal ligament of the cervical spine in 3161 patients: a CT-based study. *Spine*. 2015;40:E394-403.

Bakhsh W, Saleh A, Yokogawa N, et al. Cervical Ossification of the Posterior Longitudinal Ligament: A Computed Tomography-Based Epidemiological Study of 2917 Patients. *Global Spine J*. 2019;9(8):820-825.

**How many actually had a chest trauma?**

Answer: This question is nothing to do with the purpose of our study.

**Would fractures through the OPLL cause issues with correct identification?**

Answer: We did not find such cases.

**I'm surprised the authors didn't take the opportunity to also assess for the presence of OYL in the patient population. This is more clinically relevant since double ossification is higher risk of surgical complications**

Answer: First, the purpose of this study is "to examine the prevalence and characteristics of T-OPLL in the Black patients." We feel the reviewer is asking for the outcomes of posterior thoracic spine surgery when the authors are reporting the outcomes of anterior thoracic spine surgery.

**I hope the authors aren't trying to salami slice with multiple studies based on the above.**

Answer: We consider each ossification disease of spine needs enough separate discussion, particularly when the prevalence in Black population was not reported before and there are plenty of results to report.

**The authors should quote a unique natural history study on these ossifications:**

**Chris Yuk Kwan Tang, Kenneth Man Chee Cheung, Dino Samartzis, Jason Pui Yin Cheung. The Natural History of Ossification of Yellow Ligament of the Thoracic Spine on MRI: A Population-Based Cohort Study**

**Global Spine J. 2021 Apr;11(3):321-330. doi: 10.1177/2192568220903766. Epub 2020 Jan 31.**

Answer: Our study is nothing to do with the natural history. And we did not make any discussion about the natural history.

**It is more important to understand the canal occupancy ratio based on these ossifications. This should be studied**

Answer: In the discussion section, it's written "In our study, none of T-OPLL occupied more than 40% of the spina canal and most of T-OPLL occupied less than 25%."

**How were calcifications considered?**

Answer: In the study populations section, it's written "Osteophytes located near the uncovertebral joint or at the corners of the vertebrae were assumed to be degenerative in nature and were considered calcified disc (not considered OPLL)."

**Did all three reviewers look at all 3000 images? Were there reliability issues? What are the bias/errors?**

Answer: In the radiographic assessment section, it's written "Images were reviewed by two orthopaedic surgery residents (V.N. and E.H.), who were trained by an experienced orthopaedic spine surgeon (H.Y.) to identify and classify OPLL via CT scan. After screening all images, T-OPLL cases were reviewed again and confirmed by H.Y.. Differences were settled by consensus to minimize intra- and inter-observer bias and errors." In the discussion section, it's written "Kappa analysis to determine inter-observer and intra-observer reliabilities was not performed because the expected prevalence was quite low; however, controversial cases were discussed and determined by all authors."

**Stats are very basic and superficial with only t-test and only a simple univariate comparison. The data is a lot and should be carefully dissected and further deep analysis needed.**

Answer: Reported risk factors of OPLL are not as many. We only have the data of BMI and DM at this point. We cannot perform multivariate analysis only with 2 variables. Actually, previous articles performed only univariate analysis.

**You had cases of 5 years old. Would the patients not have these formed yet? Also for the older group, no neurology? No prev surgery? The population needs to be clarified**

Answer: We did not report any cases of 5 years old.

**The number of patients in this study with ossification is very low. This may lead to statistical insignificance. What was the sample size calculation for the analyses?**

Answer: In Fujimori's paper, they wrote the calculation process and found "A sample size of at least 1521 participants was estimated to be necessary to examine the prevalence of OPLL." So, 3,299 patients should be more than enough.

Fujimori T, Le H, Hu SS, et al. Ossification of the posterior longitudinal ligament of the cervical spine in 3161 patients: a CT-based study. *Spine*. 2015;40:E394-403.

**Lack of BMI and DM relationship is surprising and should be adequately studied and explained. Would obesity grading be more useful vs absolute BMI measurement? Bear in mind the difference in definition to Asian populations.**

Answer: Our study revealed no difference in the mean BMI between patients with and without T-OPLL (P = 0.44). This is a surprising result for us too. But this is the fact of Black population. Regarding obesity grading, we feel the reviewer is making an unreasonable demand. In fact, previous articles never performed obesity grading. But our study demonstrated that the presence of DM was significantly higher in patients with T-OPLL than those without T-OPLL (P < 0.0001).

Reviewer: 3

**Dr. Takahito Fujimori, Hyogo Coll Med**

Comments to the Author:

**The authors examined the prevalence of T-OPLL in Black patients. Preferably, they should have investigated the prevalence of cervical OPLL, which is relatively frequent, instead of the thoracic spine. Although the novelty is limited, it may be worth publishing because there have been no previous reports on Black patients.**

Answer: Thank you for the supporting comments. Previous studies (as below) reported the prevalence of cervical OPLL in Black population as a part of the study.

Fujimori T, Le H, Hu SS, et al. Ossification of the posterior longitudinal ligament of the cervical spine in 3161 patients: a CT-based study. *Spine*. 2015;40:E394-403.

Bakhsh W, Saleh A, Yokogawa N, et al. Cervical Ossification of the Posterior Longitudinal Ligament: A Computed Tomography-Based Epidemiological Study of 2917 Patients. *Global Spine J*. 2019;9(8):820-825.