PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The relationship between right-to-left shunt and migraine in patients with epilepsy: a single-centre, cross-sectional study in China
AUTHORS	Zhang, Lin; Zhu, Xi; Qiu, XIangmiao; Li, Yajiao; Chen, Yucheng; Wang, Hui; He, Shixu; Lai, Wanlin; Peng, Anjiao; Ning, Mingming; Chen, Lei

VERSION 1 – REVIEW

REVIEWER	JJ Coughlan University Hospital Limerick, Ireland
REVIEW RETURNED	03-Jun-2018

GENERAL COMMENTS	This is an interesting paper. Given the recent positive trials for PFO closure for cryptogenic stroke, it is inevitable that there will be a resurgence of interest in the relationship between PFOs and other conditions that have been linked. However, I would have several reservations with the paper in its current format. I will detail these here: 1. Firstly, there are issues with English grammar, particularly the incorrect use of verb tenses throughout. 2. The tables (Especially Table 2) would be easier to interpret if they were also expressed with percentages. 3. While the study details exclusion criteria explicitly, it does not detail the inclusion criteria. 4. The authors mention R-L shunt and grade it as 0-3. Am I to take it that Grade 0 indicates no PFO? Or do all patients in this study have a RLS of some description? This is unclear. I am assuming it indicates no PFO with RLS? Also the terminology is confusing-why not use PFO throughout rather than switching between PFO and RLS 5. The conclusion states that moderate to large RLS was associated with migraine and states that it should be screened for. Should it be screened for? There is no defined treatment for management of RLS in Migraine and therefore screening may be of no benefit. 6. PRIMA and MIST are two RCT studies of PFO closure for migraine. PRIMA: https://www.ncbi.nlm.nih.gov/pubmed/26908949 MIST: https://www.ncbi.nlm.nih.gov/m/pubmed/18316488/?i=5&from=Migra

	ine%20Intervention%20With%20STARFlex%20Technology%20(MIST)%20Trial Neither of these trials seem to be referenced in this paper. 7. Similarly the recent PFO closure studies for cryptogenic stroke could be alluded to. Similarly to the migraine trials, they had initial negative RCTs. With better patient selection and longer follow up, subsequent trials showed a reduction in their primary endpoint. 8. There has been a resurgence of interest in sham control trials in interventional cardiology also in recent months. Perhaps a large, well designed sham controlled trial with modern PFO closure devices for patients with large PFOs is what is required? Particularly given the subjective nature of migraines and their vulnerability to bias and placebo effect. 9. Overall the prevalence of PFO (R-L Shunt Grade 1-3) in the cohort appears to be high at 41%. This is not mentioned?

REVIEWER	Masahiro Nakamori Department Neurology, Suiseikai Kajikawa Hospital, 1-1-23 Higashisenda Machi, Naka-ku, Hiroshima 730-0053, JAPAN
REVIEW RETURNED	07-Jun-2018

GENERAL COMMENTS	Comments for the Authors The authors analyzed the relationship between right-to-left shunt and migraine in patients with epilepsy, and revealed that moderate to large shunt was associated with migraine. I think it is practical and very interesting issue. This article was written well, but I concern several critical points of this study. Major; 1. I concern the method of logistic regression analysis. Why did you choose these factors? Especially, 8 of 14 factors were AEDs (Table 3)! Generally, factors were selected according to p-value (eg. $p<0.10$ or 0.20) of univariate analysis among backgrounds in Table 1. It is critical. 2. In Table 2 you listed 4 AEDs, although in Table 3 you listed 8 AEDs. I suspect you deliberately listed the factors in order to show the significant differences. 3. I agree the discussion of your article, but I cannot understand the difference between migraine with epilepsy and migraine without epilepsy in the point of pathophysiology. Please discuss in detail. Minor; 1. Abbreviations (PWM, RLS, FBTCS) are not common. I think these abbreviations are not widely accepted. I recommend to use full terms. 2. Table 1 In the first line, please insert the term ‘sex’ or ‘gender’. In the16th line, Please insert the term AEDs. The position of the number of p value is shifted. Please correct. I cannot understand the number of ‘Seizures onset with visual

	symptoms' and 'History of febrile seizures'. Please correct sure overall. 3. Table 2 It is kind to add the percentage of the patients. The position of the number of p value is shifted. Please correct sure overall.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:
Reviewer: 1
Reviewer Name: JJ Coughlan
Institution and Country: University Hospital Limerick, Ireland
This is an interesting paper. Given the recent positive trials for PFO closure for cryptogenic stroke, it is inevitable that there will be a resurgence of interest in the relationship between PFOs and other conditions that have been linked.
However, I would have several reservations with the paper in its current format. I will detail these here:

1. Firstly, there are issues with English grammar, particularly the incorrect use of verb tenses throughout.

Response: Thanks for your advice. Our native language is not English. We improved the quality of language with the help of Elsevier Language Editing Services.

2. The tables (Especially Table 2) would be easier to interpret if they were also expressed with percentages.

Response: Yes, we added the percentage of the patients in Table 2.

3. While the study details exclusion criteria explicitly, it does not detail the inclusion criteria.

Response: We added the statements of "inclusion criteria" as follow: (1) patients with epilepsy or possible epilepsy (patients with possible epilepsy will be followed to establish the diagnosis of epilepsy); (2) the clinical history and medical records of epilepsy can be obtained. Please see 'METHODS' section.

4. The authors mention R-L shunt and grade it as 0-3. Am I to take it that Grade 0 indicates no PFO? Or do all patients in this study have a RLS of some description? This is unclear. I am assuming it indicates no PFO with RLS? Also the terminology is confusing-why not use PFO throughout rather than switching between PFO and RLS

Response: Thank you. Our statement is not clear enough. Grade 0 does not necessarily indicate no PFO because both transthoracic echocardiography and transesophageal echocardiography do not have 100% sensitivity and specificity. In addition, not all PFO can show RLS. And not all RLS come from PFO. As to the problems of terminology, PFO is not a direct cause of cryptogenic stroke and migraine. RLS via the PFO is a fundamental cause of cryptogenic stroke and migraine.1 Therefore, we thought it is not appropriate to use 'PFO' instead of 'RLS'. As studies in migraine without epilepsy, we are also focusing on RLS rather than PFO. So, it is more appropriate to use RLS, and we also changed related statements in the article, especially in the INTRODUCTION and DISCUSSION, to improve confusing terminology.

5. The conclusion states that moderate to large RLS was associated with migraine and states that it should be screened for. Should it be screened for? There is no defined treatment for management of RLS in Migraine and therefore screening may be of no benefit.

Response: Thank you. Our original statement is inappropriate. For this proposal, we added a prerequisite that treatment for RLS has definitely been shown to be effective in migraine. We also added related statements in the DISCUSSION (paragraph 5).

6. PRIMA and MIST are two RCT studies of PFO closure for migraine.
PRIMA: https://www.ncbi.nlm.nih.gov/pubmed/26908949
MIST: https://www.ncbi.nlm.nih.gov/m/pubmed/18316488
Neither of these trials seem to be referenced in this paper.

Response: Thank you. We added them into this paper.

7. Similarly the recent PFO closure studies for cryptogenic stroke could be alluded to. Similarly to the migraine trials, they had initial negative RCTs. With better patient selection and longer follow up, subsequent trials showed a reduction in their primary endpoint.

Response: This is a very good suggestion. We added related statements in the DISCUSSION (paragraph 5) as follow: There are clinical trials showing that the occlusion of RLS did not increase responder rate defined as 50% reduction in migraine attacks; however, it significantly reduced headache days. Randomized controlled trials (RCTs) looking at the effect of PFO closure on migraine were initially conducted. Similarly to the stroke trials, they had initial negative RCTs. With better patient selection and longer follow-up, subsequent trials may show more cessation of migraine headache.

8. There has been a resurgence of interest in sham control trials in interventional cardiology also in recent months. Perhaps a large, well-designed sham controlled trial with modern PFO closure devices for patients with large PFOs is what is required? Particularly given the subjective nature of migraines and their vulnerability to bias and placebo effect.

Response: Thank you. We added statements about the study design in the DISCUSSION (paragraph 5) according to your advice.

9. Overall the prevalence of PFO (R-L Shunt Grade 1-3) in the cohort appears to be high at 41%. This is not mentioned?

Response: We think it is not appropriate to discuss this phenomenon in this paper for two reasons, as follows: 1) the prevalence of RLS is 27.8% in 126 controls (we still recruited controls). Therefore, we think a high prevalence of RLS in patients with epilepsy may occur. However, we need more healthy controls to prove it. This may be an exciting finding and we hope to support this idea in the future; 2) the prevalence of RLS in healthy Chinese people was reported to be up to 52%. Therefore, we think race may affect the prevalence of RLS in this study. We need further investigation to confirm the prevalence of RLS in patients with epilepsy and volunteers. Therefore, we want to mention it in the future.

Reviewer: 2
Reviewer Name: Masahiro Nakamori
Institution and Country: Department Neurology, Suiseikai Kajikawa Hospital, 1-1-23 Higashisenda Machi, Naka-ku, Hiroshima 730-0053, JAPAN

Please state any competing interests or state ‘None declared’: None
Please leave your comments for the authors below
Comments for the Authors
The authors analyzed the relationship between right-to-left shunt and migraine in patients with epilepsy, and revealed that moderate to large shunt was associated with migraine. I think it is practical and very interesting issue. This article was written well, but I concern several critical points of this study.

Major;
1. I concern the method of logistic regression analysis. Why did you choose these factors? Especially, 8 of 14 factors were AEDs (Table 3)! Generally, factors were selected according to p-value (eg. p<0.10 or 0.20) of univariate analysis among backgrounds in Table 1. It is critical.

Response: Thanks for your advice. We re-ran the logistic regression analysis according to your advice. We first added AEDs and seizure frequency. Then we selected factors according to p-value < 0.20 from Table 1. The new Table 3 includes 6 factors as follows: gender, age, right-to-left shunts, duration of epilepsy, familial epilepsy, and number of antiepileptic drugs > 1.

2. In Table 2 you listed 4 AEDs, although in Table 3 you listed 8 AEDs. I suspect you deliberately listed the factors in order to show the significant differences.

Response: We listed all AEDs in Table 1 and 2 to improve reading.

3. I agree the discussion of your article, but I cannot understand the difference between migraine with epilepsy and migraine without epilepsy in the point of pathophysiology. Please discuss in detail.

Response: We added statements to the DISCUSSION according to your advice. Some of the contents are as follows: Migraine in patients without epilepsy has been proved to be associated with CSD and activation of the trigeminovascular system and its constituent neuropeptides.2 In addition, recent studies also suggested the cortical excitatory/inhibitory imbalance due to neuronal and glial ion channels renders patients more vulnerable to an headache attack.2 Migraine in patients with epilepsy is not only associated with the aforementioned mechanisms, but also is usually considered to be associated with abnormal neuronal excitability induced by genetic variants.3-7 However, the high prevalence of migraine in patients with epilepsy cannot be fully explained by genetic variants.

Minor;
1. Abbreviations (PWM, RLS, FBTCS) are not common. I think these abbreviations are not widely accepted. I recommend to use full terms.

Response: Yes, we have used the full terms instead of ‘FBTCS’, ‘RLS’ and ‘PWE’.

2. Table 1
In the first line, please insert the term ‘sex’ or ‘gender’.
In the16th line, Please insert the term AEDs.
The position of the number of p value is shifted. Please correct.
I cannot understand the number of ‘Seizures onset with visual symptoms’ and ’History of febrile seizures’. Please correct sure overall.

Response: Thanks your kindly reminder. We have corrected the first three problems. For the fourth question, we think you mean that the sum of patients is not 339. The reason is mentioned in the footnote. Cases with uncertain history were excluded. In new table 1, we deleted the ‘Seizures onset

with visual symptoms' and 'History of febrile seizures', because new Table 1 is too long. And we describe them in the RESULTS.

3. Table 2
It is kind to add the percentage of the patients. The position of the number of p value is shifted. Please correct sure overall.

Response: Yes, we added the percentage of the patients and corrected the position of the number of p value.

References
1 Kim BJ, Kim NY, Kang DW, et al. Provoked right-to-left shunt in patent foramen ovale associates with ischemic stroke in posterior circulation. Stroke 2014;45;12:3707-10.
2 Pietrobon D, Moskowitz MA. Pathophysiology of migraine. Annu Rev Physiol 2013;75;365-91.
3 Finocchi C, Del Sette M. Migraine with aura and patent foramen ovale: myth or reality? Neurol Sci 2015;36 Suppl 1;61-6.
4 Ludvigsson P, Hesdorffer D, Olafsson E, et al. Migraine with aura is a risk factor for unprovoked seizures in children. Ann Neurol 2006;59;1:210-3.
5 Nozari A, Dilekoz E, Sukhotinsky I, et al. Microemboli may link spreading depression, migraine aura, and patent foramen ovale. Ann Neurol 2010;67;2:221-9.
6 Winawer MR, Connors R. Evidence for a shared genetic susceptibility to migraine and epilepsy. Epilepsia 2013;54;2:288-95.
7 Eickhoff M, Kovac S, Shahabi P, et al. Spreading depression triggers ictaform activity in partially disinhibited neuronal tissues. Exp Neurol 2014;253;1-15.

VERSION 2 – REVIEW

REVIEWER	JJ Coughlan University Hospital Limerick, Ireland
REVIEW RETURNED	14-Jul-2018

GENERAL COMMENTS	I would like to thank the authors for the changes they made to the manuscript based on my initial review and suggest it should be accepted for publication.

REVIEWER	Masahiro Nakamori Department of Neurology, Suiseikai Kajikawa Hospital, 1-1-23 Higashisenda Machi, Naka-ku, Hiroshima 730-0053, JAPAN
REVIEW RETURNED	13-Jul-2018

GENERAL COMMENTS	The manuscript is now highly improved. I do agree with the authors response.

VERSION 2 – AUTHOR RESPONSE

Response: Yes, we deleted the statement.

Reviewer(s)' Comments to Author:

Reviewer: 2

Reviewer Name: Masahiro Nakamori

Institution and Country: Department of Neurology, Suiseikai Kajikawa Hospital, 1-1-23 Higashisenda Machi, Naka-ku, Hiroshima 730-0053, JAPAN

Please state any competing interests or state ‘None declared’: None

Please leave your comments for the authors below:

The manuscript is now highly improved. I do agree with the authors response.

Response: Thank you.

Reviewer: 1

Reviewer Name: JJ Coughlan

Institution and Country: University Hospital Limerick, Ireland

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below:

I would like to thank the authors for the changes they made to the manuscript based on my initial review and suggest it should be accepted for publication.

Response: Thank you.