Author’s response to reviews

Title: Establishment and utility assessment of the Posterior Reversible Encephalopathy Syndrome early warning score (PEWS) scale

Authors:

Li-Ping Zou (zouliping21@sina.com)
Hui Li (lihuheihei@163.com)
Li-Ying Liu (liuliying0812@hotmail.com)
Yang-Yang Wang (schopenhauersays@gmail.com)
Ying Liu (liuyingdr@163.com)
Jing Chen (chenjing@scmc.com.cn)
Lin-Yan Hu (huli3188@aliyun.com)
Meng-Jia Liu (liumengjiawang@126.com)
Meng-Na Zhang (zhangmengna2014@sina.com)
Qian Lu (drluqian@163.com)
Shu-Fang Ma (mashufang1990@sina.com)

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Author’s response to reviews:

Dear Editor DR. Naoum P Issa:

We are grateful for your letter and for the reviewers’ comments concerning our manuscript entitled “Establishment and utility assessment of Posterior Reversible Encephalopathy Syndrome early warning scoring (PEWS) scale” (manuscript number: NURL-D-18-00117). Your comments and feedback greatly helped us revise and improve our paper, as well as refine the significance of our research. Below are the main revisions that we have implemented and our responses to the reviewers’ comments.
Editor Comments:

Having received a review of your manuscript the major critique is that additional editing of the manuscript for grammar and word usage is needed. Additional statistical comparisons are also needed.

Editorial comments here are provided in addition to the comments from a reviewer.

Introduction

This is a clear introduction to PRES, but some specific edits include:

1. Keep the tense the same in a given sentence (and preferably in the same paragraph). For example, keep the sentence in the present tense in the sentence that starts “These studies suggest two possible kinds of pathophysiological mechanisms...”

Response: Thank you for your suggestion. We have modified the tense of some sentences. Now, they are consistent with the tense of the example sentence. The modified sentences are shown in page 6.

2. Rephrase the sentence starting “We hypothesize that the distribution of lesions resulting from blood vessel endothelial injury and other reasons can be atypical,...” for clarity. Do you mean something like: “We hypothesize that while lesions associated with self-regulation of the cerebrovascular system are usually restricted to the posterior brain, the distribution of lesions resulting from chemical endothelial injury often includes anterior brain regions.”

Response: We are really sorry for our ambiguous English expression. Thank you for your help. We have changed the expression. The modified sentences are shown in page 7.

3. Use the term “gold standard” rather than “golden standard”.

Response: Thank you for your suggestion. We have corrected the term in page 7.

4. The last paragraph should be removed, saving only a rewritten version of the sentence “Under these circumstances, we do need a practical and operable early warning scale for the early diagnosis and treatment of PRES.” which can be the last sentence of the prior paragraph.
Response: Thank you for your suggestion. Cohort studies have shown that PRES in hematological malignancies patients is associated with poorer prognosis. Thus, we corrected the last paragraph as follows: “Cohort studies showed that the presence of PRES in patients with hematological malignancies indicates poorer prognosis and higher mortality, especially after hematopoietic stem cell transplantation (HSCT)[3,9]. We do need a practical and operable early warning scale for the early diagnosis and treatment of PRES.”

Methods

1. For part one. To what does the “current database” refer? Are “professional imaging physicians” the same as radiologists? How was the PEWS scale established?

Response: We are sorry for our ambiguous English expression. We have corrected the term to “radiologists.” The “current database” refers to the medical records from 5 medical centers. For the process of the establishment of the PEWS scale, we first entered the keyword “posterior reversible encephalopathy syndrome” or “PRES” into the medical record systems of the 5 centers and then collected the clinical information of the patients whose diagnoses were in accordance with PRES. Subsequently, we listed all the symptoms they presented by frequency and only those that have been reported as relevant factors and could be observed in our patients were included as variables of symptoms. We also included 3 other categories of variables into our scale, namely, brain imaging result, EEG feature, and prognosis.

2. For part two. It is not clear what the interventions listed are. Does the phrase “...stopped once” mean “...stopped at once” (as in immediately)? Does the phrase “...in advance” mean “...earlier than scheduled?”

Response: We are sorry for our ambiguous English expression. We have corrected the sentence as “Early preventive chemotherapy adjustment program included the following: 1) suspension of Methotrexate intrathecal injection and vincristine administration for one time; and 2) dexamethasone decrement earlier than scheduled.” The modified sentences are shown in page 9.

3. EEG is described as including “complete sleep periods,” but it is not clear what constitutes a complete sleep period (e.g., REM sleep is unlikely in a 4 hour hospital recording).

Response: We apologize for our unclear English expression. Our patients are all children under 12 years old, and the REM sleep period for this age group is relatively longer. To ensure that we record the REM period, all the patients routinely underwent sleep deprivation the night before the EEG examination. We added this to the manuscript in page 9. Thank you again.
Results

Part 1

1. Change the sentence “Up to 19 patients experienced headaches, which were intense and mostly located in the forehead and posterior occipital lobes.” to “Nineteen patients experienced headaches, which were intense and mostly located in the forehead and occiput.”

Response: Thank you for your suggestion. We have deleted this sentence in the revised manuscript and modified “Patients’ characteristics” section in page 10.

2. The statement “By comparing the clinical characteristics and prognosis of children with PRES in terms of hematologic malignancies and other diseases, we concluded that children with hematological malignancies presented poor prognosis.” is presented without a statistical test. Please include this statement only if upheld by a statistical test and provide p value.

Response: Thank you for your suggestion. We have deleted this Section in the revised manuscript.

3. The data in “Patients’ characteristics” section is better summarized in the tables; this section can be reduced to a description of the implications and statistical comparisons of the tabulated data.

Response: Thank you for your suggestion. The “Patients’ characteristics” section has been corrected as follows: “We recruited 31 patients diagnosed with PRES, 16 males and 15 females. The median age of the patients was 7 years old (range 3–12 years), and 74.2% of the patients were younger than 10 years old. Only 4 of 29 patients experienced seizure once. The other patients experienced multiple episodes, and the maximum number of seizure attacks can be more than 10 times. After the onset of PRES, 9 patients presented notable confusion, and 4 patients were in a coma. The initial symptom for 23 patients (74.2%) was seizure. For 6 patients (19.4%), the first symptom was confusion. For 2 patients (6.5%), the initial symptom was visual impairment. The clinical symptoms and prognosis of patients with and without hematological malignancies are listed in Table 1.

By comparing the clinical characteristics and prognosis of children with PRES in terms of hematologic malignancies and other diseases, we found no statistical difference in the results of the abovementioned two groups of patients. However, partial remission and death in patients in hematological malignancies group were higher than in the non-hematological malignancies group. The small sample size led to the lack of statistical difference. We concluded that children with hematological malignancies might present poor prognosis.”
The modified “Patients’ characteristics” section was in page 10.

4. Kappa score is not appropriate for comparing PEWS to MRI diagnosis; a receiver-operating characteristic would be a more appropriate test. P-values should be presented when comparing the distributions of PEWS scores between PRES and other encephalopathy cases.

5. When reporting sensitivity, specificity, and NPP/PPP confidence intervals should not be reported (especially since the CI exceeds 1.0).

Response: Thank you for your suggestion. We have changed our statistical analysis method to receiver-operating characteristic test, and the curve is as follows (Figure 2). The Youden Index is 12. Since PRES is a serious disease, we set the cutoff value at 10 for higher sensitivity. The sensitivity and specificity were 0.941 and 0.867, respectively. The positive predictive value and negative predictive value were 0.998 and 0.195, respectively.

We added this to the manuscript in page 12.

Figure 2: Receiver operating characteristic (ROC) curve of PEWS scale for PRES patients. PEWS scale was able to detect PRES with a sensitivity of 94.1% and a specificity of 86.7%. Area under the curve (AUC)= 0.982, P=0.000, 95%CI: 0.949-1.000.

Part 2

1. It is not clear the meaning of the sentence “No neurologic symptoms were observed by altering the chemotherapy regimen.”

Response: Thank you for your suggestion. We have changed the sentence to “After adjusting chemotherapy regimens, the patient did not experience headache, hypertension, seizure or disturbance of consciousness.” in page 13.

2. Summary statistics for this group should be presented.

Response: Thank you for your suggestion. We have added table 5 to describe this group of patients.
Table 5 Prospective intervention phase PEWS scale scores of 16 patients

3. The sentence “We also designed the flowchart of PRES early warning scoring scale to help clarify its use. (Figure 3)” should be moved to the Discussion section.

Response: Thank you for your suggestion. We have moved the sentence to the Discussion section in page 15.

Figures

1. Figure legends are needed.

Response:

Fig.1 Figure legend:

PRES: Posterior reversible encephalopathy syndrome

No-PRES : Encephalitis

Two groups were compared. The median score for the PRES group was 15.5 (range 10–19), and the median score for the No-PRES (Encephalitis) group was 8 (range 6–12).

Fig.2 Figure legend:

Receiver operating characteristic (ROC) curve of PEWS scale for patients. PEWS scale was able to detect PRES with a sensitivity of 94.1% and a specificity of 86.7%. Area under the curve (AUC)= 0.982, P=0.000, 95%CI: 0.949-1.000.

Fig.3 Figure legend:

A: female, five years old, EEG showed focal low amplitude slow wave, MRI was normal, PEWS 7.
B: female, five years old, EEG showed focal (right parietal and temporal lobe) epileptic discharge, MRI was normal, PEWS 10.

C: male, five years old, EEG showed slow wave background and epileptic discharge, MRI showed bilateral parieto-occipital subcortical white matter long T1 signal, long T2 signal, and equal DWI signal, PEWS 13.

Abbreviations: EEG: electroencephalogram; MRI: magnetic resonance imaging; PEWS: posterior reversible encephalopathy syndrome early warning score

Fig.4 Figure legend:

The flowchart of PRES early warning score scale.

2. In Figure 3, change “Perfor” to “Perform” and “Regiments” to “Regimens”

Response: Thank you for your suggestion. We have corrected the terms in Figure 4.