PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Prognostic value of Modified Early Warning Score generated in a Chinese emergency department: A prospective cohort study
AUTHORS	Xie, Xiaohua; Huang, Wenlong; Liu, Qiongling; Tan, Wei; Pan, Lu; Wang, Lei; Zhang, Jian; Wang, Yunyun; Zeng, Y

VERSION 1 – REVIEW

REVIEWER	Tom Abbott University College London Hospital, UK
REVIEW RETURNED	21-May-2018

GENERAL COMMENTS	Thanks for the opportunity to review this paper, which is clearly written. This is a relatively small, single-centre study with ~300 participants, compared to many in this field, which are often multi-centre. In the UK, MEWS has largely been replaced with the better validated National Early Warning Score (NEWS) and the editors may wish to consider whether this study is appropriately sized, novel or cutting-edge for this prestigious journal. Specific comments: 1. The authors may wish to consider whether they have appropriately addressed all the items on the STROBE checklist clearly enough. Eg. clearly defined the main exposure and outcome in the methods section. 2. Ethics approval is mentioned. However, there is no committee reference number, which would usually be supplied. In addition, the consent process is not described. 3. Was this study registered prospectively with a registry (e.g. Research Registry). While this is not mandatory for observational studies, it is good practice. Was the statistical analysis planned before starting the analysis. 4. The statistical analysis does not contain sufficient detail in order to replicate the analysis. In addition, the primary hypothesis was about predictive ability, yet the methods to assess this are only described in three lines on page 8. Whereas, more simple statistics that do address the main hypothesis are described in much more detail. 5. How was confounding addressed in the statistical analysis? This is not clear.

	6. Sample size. I could not see a sample size estimate. Was a power calculation/sample size calculation conducted before starting? 7. Limitations. The authors do not fully address external validity/generalisability in detail in the discussion. Patients were excluded if they did not have complete data. A total of 133 patients were excluded. However, the implication of this is not discussed i.e. potential selection bias.

REVIEWER	Dr Jeff Keep King's College Hospital, London, UK
REVIEW RETURNED	29-May-2018

GENERAL COMMENTS	A review by a fluent English speaker is essential. There is no mention of ethics approval or waiver. An important topic to add to the growing evidence base of the use of early warning scores in emergency departments. Unfortunately, only one outcome has been looked at, mortality, rather than admission to hospital and admission to critical care which is a shame. Patients admitted for end of life care have not been analysed separately. The hospital appears to be using its own triage system which would make reproducing this study almost impossible. I would like to see this paper again but with a clearer understanding that early warning scores need to be studied to see how they can work alongside current systems to aid with triage and escalation from the emergency department.

REVIEWER	Dr. Nanayakkara, Drs. van den Ende VU medical center, The Netherlands
REVIEW RETURNED	02-Jun-2018

GENERAL COMMENTS	Summary of the research: This study validated the Modified Early Warning Score as a predictor for in-hospital mortality in Chinese patients triaged in a specific way in the ED. Furthermore it defined a new cut-off point for the MEWS to increase the sensitivity for predicting in-hospital mortality. Strong points: - The background literature and study rationale are clearly articulated. - Appropriate methodology to answer questions - Results are presented clearly and seem to be interpreted in a comprehensible way. Limitations: - This is a single-centred study - The study is conducted using a score-system which is only used in Chinese hospitals. This limits the generalizability of the findings. Minor issues: - P6 L47: Were all patients evaluated by the same triage nurse? - P7 L3: Was the MEWS measured before any intervention? For instance fluid challenges might change the score. - P7 L43: In the Netherlands, some patients are send home to die. Is this something that is happening in China as well? This might influence the results.

	- P9 L6 “… majority of patients was Han” It might be good to add a percentage here? - Did patient have to sign informed consent? I can not find this in the paper.

VERSION 1 – AUTHOR RESPONSE

Response to Tom Abbott
Comment 1: "This is a relatively small, single-centre study with ~300 participants, compared to many in this field, which are often multi-centre. In the UK, MEWS has largely been replaced with the better validated National Early Warning Score (NEWS) and the editors may wish to consider whether this study is appropriately sized, novel or cutting-edge for this prestigious journal."
Response: while MEWS or the NEWS widely applied into Western setting hospitals, limited studies conducted in Chinese hospital settings. The strength of this study was providing a new cut-off point of increasing the sensitivity for predicting in-hospital mortality and admission to intensive care unit at China. The sample size calculation of this study was also added in this revised manuscript.
Comment 2: "The authors may wish to consider whether they have appropriately addressed all the items on the STROBE checklist clearly enough. Eg. clearly defined the main exposure and outcome in the methods section."
Response: thanks for your advice! This revised manuscript clearly defined the main outcomes in the method section and revised the STROBE checklist accordingly. "Outcomes: The primary outcome was a composite of in-hospital mortality and admission to intensive care unit. The secondary outcome was using MEWS to predict hospitalised and discharged patients".

Comment 3: "Ethics approval is mentioned. However, there is no committee reference number, which would usually be supplied. In addition, the consent process is not described."
Response: this revised manuscript has added one section to state "Ethics statement: This study was approved by the medical ethical committee of the Second People’s Hospital of Shenzhen (No. 20141201005). Written informed consent was obtained from research participants or patients' legal agents.".

Comment 4: "Was this study registered prospectively with a registry (e.g. Research Registry). While this is not mandatory for observational studies, it is good practice. Was the statistical analysis planned before starting the analysis?"
Response: we will consider our future observational studies registered prospectively with a research registry. But this study planed data analysis before implementing this study.

Comment 5: "The statistical analysis does not contain sufficient detail in order to replicate the analysis. In addition, the primary hypothesis was about predictive ability, yet the methods to assess this are only described in three lines on page 8. Whereas, more simple statistics that do address the main hypothesis are described in much more detail."
Response: this revised manuscript rewrote this section of statistical analysis.

Comment 6: "How was confounding addressed in the statistical analysis? This is not clear."
Response: this revised manuscript added regression analysis results, and addressed confounding variables of age and gender (new Table 4).

Comment 7: "Sample size. I could not see a sample size estimate. Was a power calculation/sample size calculation conducted before starting?"
Response: This revised manuscript in the method section "Sample size calculation: This study calculated sample size using G*Power 3.1.9.2 (http://www.softpedia.com/get/Science-CAD/G-

Power.shtml). The estimated sample size was 319 with an accuracy index of 0.95, a marginal error of 0.05 with 95% confidence level and 80% power". The actually enrolled subjects were 383 in this study.

Comment 8: "Limitations. The authors do not fully address external validity/generalisability in detail in the discussion. Patients were excluded if they did not have complete data. A total of 133 patients were excluded. However, the implication of this is not discussed i.e. potential selection bias."
Response: this revised manuscript added this study limitation of "potential selection bias" in Discussion section. "While the actual number of enrolled subjects was 383 (higher than the required sample size of 319), there were 133 patients excluded in the analysis due to missing data resulting in potential selection bias. Thus, future research should implement strategies to minimise missing data in patient report forms."

Response to Dr Jeff Keep
Comment 1: "A review by a fluent English speaker is essential."
Response: this revised manuscript has been edited by a professional English language editor before resubmission.

Comment 2: "There is no mention of ethics approval or waiver."
Response: this revised manuscript added "Ethics statement: written informed consent was obtained from research participants or patients' legal agents."

Comment 3: "An important topic to add to the growing evidence base of the use of early warning scores in emergency departments. Unfortunately, only one outcome has been looked at, mortality, rather than admission to hospital and admission to critical care which is a shame. Patients admitted for end of life care have not been analyzed separately. The hospital appears to be using its own triage system which would make reproducing this study almost impossible."
Response: this revised manuscript added one primary outcome admission to Intensive Care Unit (new Figure 3), and the secondary outcome of using MEWS to predict hospitalised and discharged patients (new Figure 4).

Comment 4: "I would like to see this paper again but with a clearer understanding that early warning scores need to be studied to see how they can work alongside current systems to aid with triage and escalation from the emergency department."
Response: this study provided a new cut-off point for the MEWS by ROC curve analysis to increase the sensitivity for predicting in-hospital mortality. This new cut-off point for the MEWS will help nurses to make better care monitoring, if the patient's MEWS score is higher than 6, the monitoring frequency will change into 15 minutes per time and it's a warning signal of reporting physicians and preparing for rescuing.

Responses to Dr. Nanayakkara, Drs. van den Ende
Comment 1: "This study validated the Modified Early Warning Score as a predictor for in-hospital mortality in Chinese patients triaged in a specific way in the ED. Furthermore it defined a new cut-off point for the MEWS to increase the sensitivity for predicting in-hospital mortality.
Strong points:
- The background literature and study rationale are clearly articulated.
- Appropriate methodology to answer questions
- Results are presented clearly and seem to be interpreted in a comprehensible way.
Limitations:
- This is a single-centered study

- The study is conducted using a score-system which is only used in Chinese hospitals. This limits the generalizability of the findings."
Response: thanks for your pertinent comments.

Comment 2: "Minor issues:
- P6 L47: Were all patients evaluated by the same triage nurse?
Response: yes, the same triage nurse.

- P7 L3: Was the MEWS measured before any intervention? For instance fluid challenges might change the score.
Response: yes, the MEWS measured before any intervention.

- P7 L43: In the Netherlands, some patients are sent home to die. Is this something that is happening in China as well? This might influence the results.
Response: in China we have similar situation that "patients are sent home to die", but this situation was one of study exclusion criteria.

- P9 L6 "… majority of patients was Han" It might be good to add a percentage here?
Response: we added 98.2% accordingly in this revised manuscript.

- Did patient have to sign informed consent? I cannot find this in the paper."
Response: this revised manuscript added "Ethics statement: written informed consent was obtained from research participants or patients' legal agents."

Comment 3: "We have implemented an additional requirement to all articles to include 'Patient and Public Involvement' statement within the main text of your main document. Please refer below for more information regarding this new instruction."
Response: this revised manuscript added a section of "Participant involvement and data collection" in the 4th paragraph of Method section.
Comment 4: "Authors must include a statement in the methods section of the manuscript under the sub-heading 'Patient and Public Involvement'."
Response: this revised manuscript added it accordingly.

Comment 5: "How was the development of the research question and outcome measures informed by patients' priorities, experience, and preferences?"
Response: the development of the research question and outcome measures informed by patients' priorities such as in-hospital mortality, critical care unit admission etc.

Comment 6: "How did you involve patients in the design of this study?"
Response: no patients were involved in the design of this study.

Comment 7: "Were patients involved in the recruitment to and conduct of the study?"
Response: this revised manuscript added a section of "Participant involvement and data collection" in the 4th paragraph of Method section.
Comment 8: "How will the results be disseminated to study participants?"
Response: it will be disseminated in a format of publication posted in the hospital's billboards.

Comment 9: "Patient advisers should also be thanked in the contributorship statement/acknowledgements. If patients and or public were not involved please state this."
Response: no patient advisers were involved in this study. But we do "thank all patients for participating in this study. " in this revised manuscript.

VERSION 2 – REVIEW

REVIEWER	Tom Abbott Queen Mary University of London, Barts and the London School of Medicine & Dentistry
REVIEW RETURNED	06-Jul-2018

GENERAL COMMENTS	This manuscript is greatly improved compared to the previous version of the paper. It is more clearly organised and easier to read. The outcomes are more clearly stated. However, the secondary outcome as listed "was using MEWS to predict hospitalised and discharged patients". This is NOT an outcome and I am not clear what the secondary outcome is. Is it length of stay? Is it days hospitalised within a certain period? I would encourage the authors to make this much more clear.

REVIEWER	Dr J W Keep King's College Hospital, London UK
REVIEW RETURNED	25-Jul-2018

GENERAL COMMENTS	The utility of Early Warning Scores in emergency department patients is an interesting subject and a strong body of evidence is emerging to which this paper will add. It is unfortunate that the authors have used MEWS and not NEWS and/or NEWS2 that was published in December 2017. Personally, I don't like to see a score of '3.5' or '4.5' which doesn't exist and only causes confusion. The authors could discuss how the calculation of an EWS in the ED will alter management.

REVIEWER	Eva van den Ende VUmc, the Netherlands
REVIEW RETURNED	31-Jul-2018

GENERAL COMMENTS	In my opinion, Xiaohua Xie at al. has added and corrected all necessary things. Minor issue: ‘Figure 1 The flow chart of study procedure’ “n=21andn=65” needs interspace.

VERSION 2 – AUTHOR RESPONSE

Response to Tom Abbott

Comment 1: "This manuscript is greatly improved compared to the previous version of the paper. It is more clearly organised and easier to read. The outcomes are more clearly stated. However, the secondary outcome as listed "was using MEWS to predict hospitalised and discharged patients". This is NOT an outcome and I am not clear what the secondary outcome is. Is it length of stay? Is it days hospitalised within a certain period? I would encourage the authors to make this much more clear."

Response: sorry for the confusion. Previous prospective cohort studies (e.g. Abbott et al. 2015, 2016) reported that “hospital length of stay” was not associated with NEWS scores, so this study didn’t take

“hospital length of stay” as one of study outcomes. The secondary outcome of this study was using MEWS for prediction whether admitted to general ward unit or discharged from hospital. We have clarified it accordingly in this revised manuscript.

[Abbott TEF et al. (2015). A single-centre observational cohort study of admission National Early Warning Score (NEWS). Resuscitation, 92: 89-93; Abbott TEF et al. (2016) A single-centre cohort study of National Early Warning Score (NEWS) and near patient testing in acute medical admissions. European Journal of Internal Medicine, in press]

Response to Dr Jeff Keep

Comment 1: "The utility of Early Warning Scores in emergency department patients is an interesting subject and a strong body of evidence is emerging to which this paper will add. It is unfortunate that the authors have used MEWS and not NEWS and/or NEWS2 that was published in December 2017."

Response: thanks for your advice, we will follow your advice on using NEWS and/or NEWS2 in our multicenter cohort study. The current single center study was undertaking from May to September 2017, so the current manuscript reported study findings using MEWS.

Comment 2: " Personally, I don't like to see a score of '3.5' or '4.5' which doesn't exist and only causes confusion."

Response: sorry for the confusion, this revised manuscript deleted scores of 3.5 or 4.5 accordingly, only kept the comparison results of the scores of <4 and ≥4.

Comment 3: " The authors could discuss how the calculation of an EWS in the ED will alter management."

Response: this revised manuscript added content of how calculating MEWS in the ED will alter management in clinical settings at the end of this manuscript: “As patients with MEWS equal or higher than 4 had higher rates of in-hospital mortality and admission to ICU, calculating MEWS may be an important indicator for closely monitoring patients, requesting immediately contacting doctor-in-charge, and establishing a rapid response intervention team. In this studied hospital, the triage system in the ED has already added MEWS as one of vital parameter monitors, and designed an algorithm in the triage system which can calculate MEWS automatically.”.

Response to Dr. Eva van den Ende

Comment 1: "Minor issues: Figure 1 The flow chart of study procedure’ “n=21andn=65” needs interspace.”

Response: new Figure 1 in this revised manuscript has addressed the interspace issues, thanks.