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RESEARCH

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Validation of PREdiction of DELIRium in ICu patients (PRE-DELIRIC) among patients in intensive care units: A retrospective cohort study

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Abstract

Background: An intensive care unit (ICU) delirium prediction tool, PREdiction of DELIRium in ICu patients (PRE-DELIRIC), has been developed and calibrated in a multinational project. However, there is a lack of evidence regarding the predictive ability of the PRE-DELIRIC among Chinese ICU patients.

Aims and objectives: To evaluate the predictive validity (discrimination and calibration) of PRE-DELIRIC.

Methods: A retrospective cohort study was conducted. Consecutive participants (a) admitted to the ICU for ≥24 hours, (b) aged ≥18 years, and (c) admitted to the ICU for the first time were included. Ten predictors (age, APACHE-II, urgent and admission category, urea level, metabolic acidosis, infection, coma, sedation, and morphine use) assessed within 24 hours upon ICU admission were assessed. Delirium was assessed using the Confusion Assessment Method for ICU. Outcomes included ICU length of stay and mortality. Discrimination and calibration were determined by the areas under the receiver operating characteristic curve (AUROC), box plot, and calibration plot.

Results: A total of 375 ICU patients were included, with 44.0% of patients being delirious. Delirium was significantly associated with age, PRE-DELIRIC score, ICU length of stay, and mortality. The AUROC was 0.81 (95% confidence interval, 0.77-0.86). The optimal cut-off point identified by max Youden index was 49%. The calibration plot of pooled data demonstrated a calibration slope of 0.894 and an intercept of −0.178.

Design: This is a retrospective cohort study.

Conclusions: The PRE-DELIRIC has high predictive value and is suggested to be adopted in ICUs for early initiation of preventive interventions against delirium among high-risk patients.

Relevance to clinical practice: Clinicians can adopt the PRE-DELIRIC among ICU patients to screen patients at high risk of developing delirium. Early initiative interventions could be implemented to reduce the negative impacts of ICU delirium.

KEYWORDS

delirium, ICU, PREDELIRIC, prevention, risk factor

1 | BACKGROUND

As a common acute mental disorder in the intensive care unit (ICU), delirium is reported to affect up to 87% of patients.[1] Patients with delirium suffer more hazards, such as increased duration of intubation, longer hospital stay, long-term cognitive impairment (loss of memory), and higher mortality.[2-6] Delirium also puts a huge burden on families, nurses, and the whole society. Family members of people with delirium have reported experiencing more depressive episodes and greater care burdens.[7] Caring for delirious patients increased the workload and psychological burden of nurses.[8] It was found that delirium raised ICU costs by 39%.[9]

There are many risk factors of delirium, such as patient factors (age, comorbidity), acute illness factors (hypoxia, infection), and environmental factors (immobilization, social isolation, sensory deprivation, sleep deprivation).[10,11] Among these, environmental factors are believed to be modifiable.[12] Some preventive and early non-pharmacological management interventions targeting environmental factors have been recommended as effective, including family participation, early mobilization, and sleep promotion.[13-15] A stratified prediction model may therefore be used to identify patients at high risk of developing delirium, allowing targeted prophylactic interventions to then be taken to prevent delirium, thus making the best use of available medical resources.[16]

An ICU delirium prediction model, named the PREdiction of DELIRium in ICu patients (PRE-DELIRIC), has been previously developed[17] and calibrated in a multinational project.[18] PRE-DELIRIC involves 10 variables assessed at 24 hours upon admission to the ICU, including age, Acute Physiology and Chronic Health Evaluation (APACHE-II) score, coma, admission category (surgical, medical, trauma, neurosurgical), infection, metabolic acidosis, morphine use, sedative use, urgent admission, and urea. A previous study showed that PRE-DELIRIC had a satisfactory area under receiver operating characteristic curve (AUROC) of 0.75.[18] Researchers have validated PRE-DELIRIC in a general ICU of a university hospital in Sweden, and the results showed an AUROC of 0.77.[19] Wassenaar et al recruited 2178 patients from 11 ICUs in seven countries and showed that PRE-DELIRIC had an AUROC of 0.74.[20] Although the PRE-DELIRIC has been validated in several countries, there is a lack of evidence about its predictive ability among Chinese ICU patients. This study aims to evaluate the predictive ability of a Chinese version of PRE-DELIRIC, which may be useful for early detection and initiation of preventive interventions against delirium among high-risk patients.

What is known about this topic

- Delirium is a severe problem among ICU patients worldwide.
- A stratified prediction model can be used to identify patients at high risk of developing delirium and allow early preventive interventions.
- The PRE-DELIRIC has been developed and validated in several countries; however, there is a lack of evidence about its predictive ability among Chinese ICU patients.

What this paper adds

- The PRE-DELIRIC has a good discrimination ability, with an AUROC of 0.81 (95% CI, 0.77-0.86).
- The calibration plot of pooled data demonstrated good calibration ability of PRE-DELIRIC, with a calibration slope of 0.894 and an intercept of −0.178.
- The PRE-DELIRIC is suggested to be adopted in ICUs for early initiation of preventive interventions against delirium among high-risk patients.

2 | METHODS

This study was conducted in accordance with the Transparent Reporting of a multivariate prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement.[21]

2.1 | Study design and setting

We conducted a retrospective cohort study of patients admitted to an 18-bed surgical ICU in a comprehensive tertiary A teaching hospital in Guangzhou, China, and an 18-bed general ICU in a comprehensive tertiary A teaching hospital in Lanzhou, China, from April 2019 to October 2019.

2.2 | Study population

All patients who were admitted to the two hospitals during the study period from 1 April 2019 to 31 October 2019 were included if they (a) had stayed in the ICU for ≥24 hours, (b) were aged ≥18 years old, and (c) were in the ICU for the first time. Patients were excluded if they (a) had a history of severe mental illness (diagnosed with dementia, confusion, or delirium upon admission), (b) were admitted with alcohol-related delirium, or (c) were at the end stage of cancer.

2.3 | Delirium assessment

All ICU patients were assessed via the simplified Chinese version of the Confusion Assessment Method for ICU (CAM-ICU) three times daily by well-trained nurses who had no involvement in the study. The simplified Chinese version of CAM-ICU was part of the clinical practice in the two participating ICUs and was reported to have good validity and reliability among ICU patients in Mainland China, with a sensitivity of 93% and specificity of 91%.[22] The CAM-ICU is comprised of four features, namely, (a) fluctuation of mental status, (b) inattention, (c) altered level of consciousness, and (d) disorganized thinking.[23] Delirium is defined as at least one positive CAM-ICU screening during the patients' complete intensive care stay.

2.4 | Clinical outcomes

We collected patients' clinical outcomes, including ICU length of stay and mortality, from the electronic medical case system. ICU length of stay is determined by the total number of days a patient has stayed in the ICU. Mortality refers to the total number of deaths among all eligible patients.

2.5 | Predictor definition

Identical to Boogaard's study, the PRE-DELIRIC model includes 10 objectively and clearly defined variables assessed within 24 hours of admission to the ICU, namely, age, APACHE-II score, coma, admission category (surgical, medical, trauma, neurosurgical), infection, metabolic acidosis, morphine use, sedative use, urgent admission, and urea (Data S1).[17] All data were recorded in the electronic medical case system by physicians and nurses in the participating ICUs and were extracted by two individual investigators who did not participate in any assessment of the mentioned predictors.

2.6 | Sample size

The sample size was calculated by the Sample Size Calculator for one proportional cross-sectional study.[24] With precision = 0.05, confidence level = 0.95, proportion = 0.5, and population = 10 000, we estimated a sample size of 370. Based on the requirement of a minimum of 10 delirious patients per predictor (n = 10), a minimum threshold of 100 patients with delirious symptoms was set.[25,26] Our study included a total of 375 eligible patients, meeting the sample size requirements.

2.7 | Absence of data

We identified a very small proportion of absent data. Two values of APACHE-II (2/375, 0.5%) were found to be missing because of a lack of record by physicians. Data for all the other nine variables were complete. We imputed the mean values of APACHE-II for the two missing values.

2.8 | Statistical analysis

We used IBM SPSS 23.0 and R statistics version 3.6.3, utilizing the ROCR package for all analyses.[27] For the clinical characteristics of ICU patients, normally distributed variables are presented as mean ± SD and non-normally variables and distributed continuous variables as median and interquartile range and categorical frequency and percentage, respectively.

Clinical outcomes between patients with and without delirium were compared using two independent sample *t*, Mann-Whitney *U*, χ^2, or Fisher's exact tests, as appropriate. All statistical tests were two-sided, and $P < .05$ was considered statistically significant.

The predictive ability of the model was assessed in two aspects: discrimination ability and calibration ability. First, the predictive ability of the model to discriminate between delirious and non-delirious patients was evaluated using the AUROC curve[28] and box plot with a discrimination slope.[29] The optimal cut-off was selected on the basis

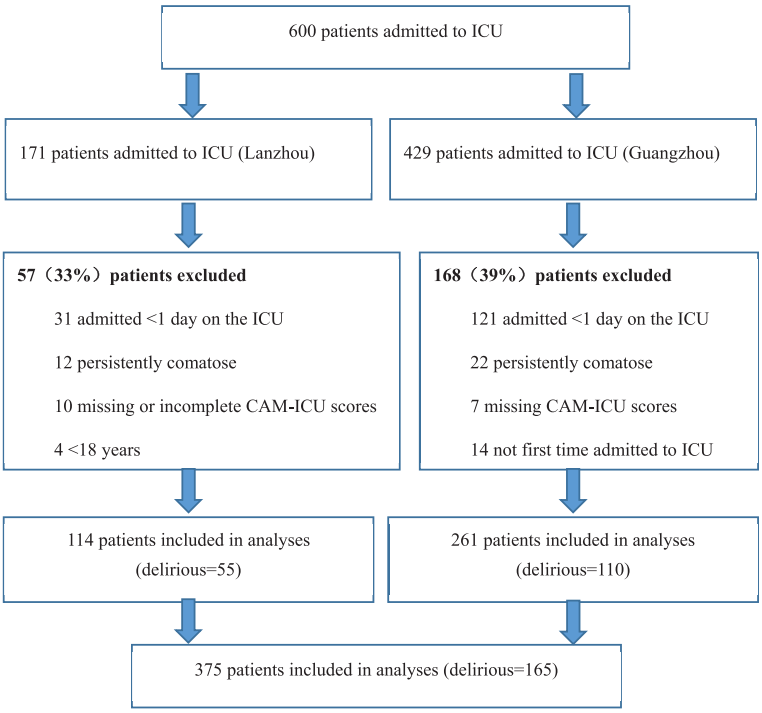

FIGURE 1 Flowchart of inclusion. CAM-ICU, confusion assessment method for intensive care unit

of max Youden index, and the sensitivity, specificity, and positive and negative likelihood ratios for five other conventionally chosen cut-off points (40%, 45%, 50%, 55%, and 60%) were shown to illustrate the discriminative ability of the model.[28] Second, we used a calibration plot with calibration slope and intercept to show agreement between observed outcomes and predictions.[30]

2.9 | Ethical considerations

Ethical approval was obtained from the University Survey and Behavioural Research Ethics committee (SBRE-18-685). Waiver of consent for clinical data collection was approved by the hospital ethics committee because of the non-interventional and retrospective nature of this study. All data were encrypted, kept strictly confidential, and were only accessible by the investigators.

3 | RESULTS

3.1 | General characteristics

A total of 600 consecutive patients from the two study ICUs were screened, and 225 patients were excluded according to the inclusion and exclusion criteria. Specific reasons for exclusion are shown in Figure 1. Of the remaining 375 study participants, screening with CAM-ICU indicated that 165 (44.0%) patients developed delirium. Table 1 shows the patients' characteristics. The mean age of patients was 58.7 ± 16.5 years; 217 (57.9%) of participants were male. The mean APACHE-II score was 16.5 ± 6.5 points. The majority of the patients were surgical (54.1%), followed by medical (25.9%), neurological (10.7%), and trauma (3.7%). Overall sedative and morphine use was 61.9% and 71.5%, respectively.

TABLE 1 Clinical characteristics of studied ICU patients (n = 375)

Characteristics	
Age (y), mean ± SD	58.7 ± 16.5
Male gender, n (%)	217 (57.9%)
APACHE II score, mean ± SD	16.5 ± 6.5
Reasons for ICU admission: n (%)	
Surgical	203 (54.1%)
Medical	97 (25.9%)
Trauma	14 (3.7%)
Neurological	40 (10.7%)
Others	21 (5.6%)
Sedative use, n (%)	232 (61.9)
Morphine use, n (%)	268 (71.5)
Metabolic acidosis, n (%)	80 (21.3)
Infection, n (%)	225 (60.0)
Mechanical ventilation, n (%)	216 (57.6)
ICU length of stay (d), median (IQR)	3 (2-6)
Mortality, n (%)	17 (4.5)
Delirious, n (%)	165 (44.0)

Abbreviations: APACHE II Acute Physiology and Chronic Health Evaluation II; ICU, intensive care units; IQR, interquartile range.

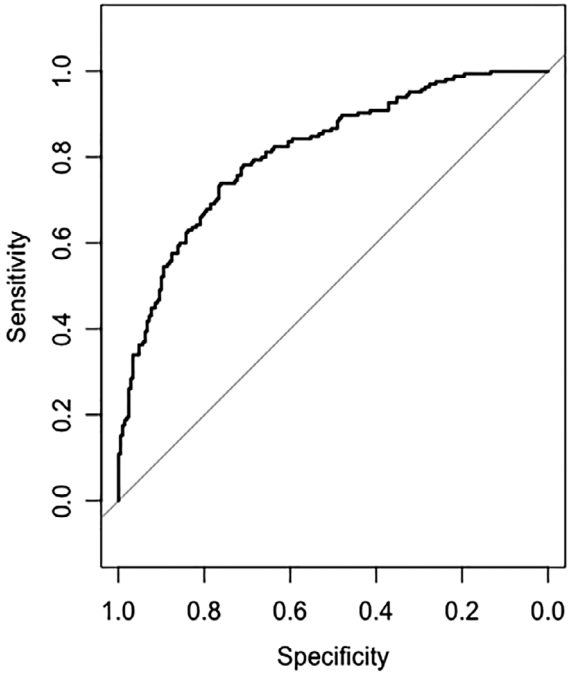

FIGURE 2 Receiver operating characteristics of PRE-DELIRIC model (areas under the ROC: 0.812, 95% confidence interval: 0.769-0.855)

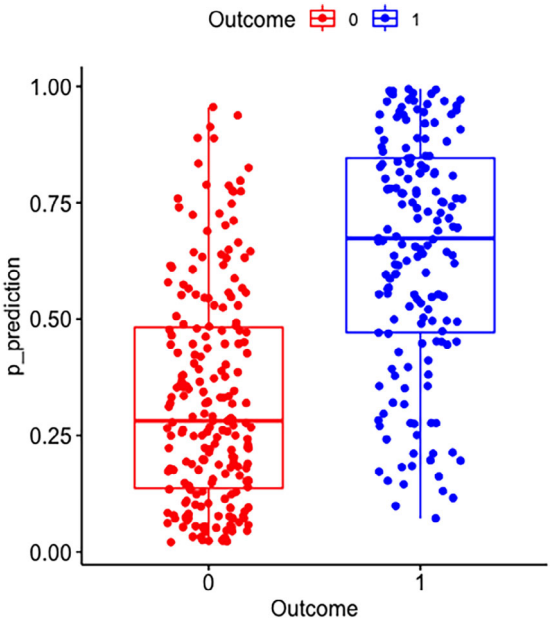

FIGURE 3 Calibration plot of pooled data, with calibration slope of 0.894 and intercept of −0.178

3.2 | Model performance

The receiver operating characteristic (ROC) curve for the PRE-DELIRIC model equation was applied to our data (Figure 2). The overall AUROC was 0.81 (95% confidence interval [CI], 0.77-0.86). According to the max Youden index, the optimal cut-off point was 49%, with a sensitivity of 73.9% and specificity of 76.2%. The sensitivity, specificity, and positive and negative likelihood ratios for the other five conventionally chosen cut-off points are shown in Table S1, which demonstrate the good discriminative ability of the PRE-DELIRIC model.

Our data were also evaluated using a box plot of pooled data (Figure S1). A discrimination slope of 0.311 was found, indicating that higher predicted risk corresponded to a higher likelihood of delirium event.

The actual outcome vs predicted outcome was plotted (Figure 3). The calibration plot of pooled data demonstrated a calibration slope of 0.894 and an intercept of −0.178. Together with the AUROC of 0.81, the calibration slope showed a direct mathematical relation with discrimination, allowing confirmation of the well-fitted PRE-DELIRIC model.

3.3 | Comparison of delirious and non-delirious groups

Clinical characteristics of the delirious and non-delirious groups were collected (Table S2). Results showed that delirium was associated with significantly higher age, longer duration of ICU stay, higher mortality, and higher PRE-DELIRIC score (all $P < .001$). Gender and use of mechanical ventilation were not significantly different between the two groups.

4 | DISCUSSION

4.1 | Model performance

The PRE-DELIRIC model is of important value for the prediction of delirium. Although the model was developed and validated in other countries, the predictive value of the model in China has remained unknown. In this study, we observed that the discrimination ability of the PRE-DELIRIC model for Chinese ICU patients was similar to that reported in previous validation studies. The calibration ability of the model also exhibited good performance, indicating the usefulness of the PRE-DELIRIC model in identifying ICU patients at high risk (predicted probability >49%) of developing delirium.

The model resulted in an AUROC of 0.81. An AUROC of 1 shows a perfect diagnostic value, while 0.8 signifies moderate to good performance. The value obtained in this study was similar to that in the external validation of the original model development study (AUROC = 0.84)[17] and slightly better than a previous multinational recalibration study (AUROC = 0.75).[18] The higher AUROC in our study may be explained by the slightly higher variability with regard to delirium incidence and patient demographics. Our delirium incidence (44%) was found to be greater compared with the previous study by Boogaard et al (39%).[18] Meanwhile, our patient demographics demonstrated higher proportions for sedation (62%), morphine use (71%), and infection (60%) compared with the previous study, which gave values of 16% to 56%, 9% to 58%, and 15% to 55% for sedation, morphine use, and infection, respectively.[18] The Pain, Agitation and Delirium guideline has highlighted the strong association of the use of sedatives and morphine with increased delirium incidence, which supports our findings.[31] In addition, the slightly better discrimination ability obtained in our study is evident from the box plot result. Consequently, the higher event cases construe a better model performance and indicate that the model can be utilized in the study settings.

Moreover, the calibration was optimized in this study. A calibration slope of 1 and an intercept of 0 show a perfect calibration. The study results produced a calibration slope of 0.894 and an intercept of −0.178, which were comparable with the perfect values. In the Boogaard et al recalibration study, a stepwise approach was followed to achieve a calibration slope of 1 and an intercept of 0.[18] However, this study utilized the original intercept and coefficient, resulting in a similar calibration with the developmental model in Boogaard et al (slope = 0.93, intercept = −0.29).[17] The discriminative slope result also demonstrated higher discriminative power between delirious and non-delirium patients. Therefore, the 10 predictors in the PRE-DELIRIC model were found to be appropriate, and the use of the PRE-DELIRIC model in clinical practice was supported.

4.2 | Clinical outcomes and delirium prevention

The clinical outcomes of ICU length of stay and mortality between delirious and non-delirious patients were compared. Mortality was identified in 7% of patients, and it occurred more commonly in delirious patients. This was similar to the general trend reported in scientific literature that delirium is a strong independent predictor of mortality, with every day with delirium independently associated with a 10% increase in the hazard of death.[32] A systematic review of 42 studies also found that, compared with non-delirious patients, delirious patients had significantly higher mortality (risk ratio, 2.19) and longer ICU length of stay (risk ratio, 1.38).[33]

The increased ICU length of stay and mortality associated with delirium in ICU patients warrant its prevention. Previous reviews have reported the effectiveness of non-pharmacological delirium prevention practices, such as early mobilization, family participation, and the use of multicomponent interventions.[34-36] However, the application of such practices for all ICU patients requires excessive medical resources, including ICU nurses, physicians, and mobilization equipment.[37] According to the Neuman Systems Model, delirium prevention targeted to high-risk patients may better enhance the beneficial effects of preventive practices.[38] Delirium is highly preventable and

reversible through adequate interventions based on risk factors and risk levels.[12] Recent guidelines have thus recommended delirium prevention activities in vulnerable persons.[39] Consequently, in light of the discriminative power and optimized calibration of PRE-DELIRIC, the routine use of delirium preventive measures in the ICU should be widely endorsed to reduce the high incidence of delirium, decrease its deleterious effects on patient outcomes, and cut high costs related to these effects.

4.3 | Implementation for clinical practice

The prediction model in our study can offer an effective tool for ICU physicians and nurses to detect high-risk patients and implement preventive interventions at an early stage. Critical care nurses who provide care for 24 hours a day play a vital role in early delirium assessment, detection, and prevention. In the presence of limited resources (ICU nurses, physicians, and mobilisation equipment), targeting high-risk patients via delirium risk stratification could improve the feasibility of the wider implementation of effective interventions. Furthermore, early identification of delirium could prevent its development and subsequent adverse outcomes, such as increased mechanical ventilation, length of ICU stay, and mortality. The prediction model could be used to change the behaviour of the ICU team[40] and thus impact the severity of delirium development, ultimately improving clinical outcomes, including length of ICU stay and mortality.

4.4 | Limitations

There were several limitations in this study. First, the participating patients were from two large tertiary A-level hospitals and therefore were more likely to have more severe diseases or undergo more complicated surgeries than patients from general hospitals. Second, the PRE-DELIRIC model evaluated in our study would require updating in the future as new risk factors emerge.[28] The new risk factors would need to be made available on ICU admission or 24 hours after ICU admission, which may help contribute to the earlier delirium screening of high-risk patients in the ICU. Third, although we used a series of cut-off values (40%, 45%, 50%, 55%, and 60%) to discriminate patients' risk, the risk of developing delirium is actually not dichotomous but is continuous.

5 | CONCLUSION

The PRE-DELIRIC demonstrated a good discriminative and calibration power and may thus be useful in identifying ICU patients at high risk of developing delirium. Nurses/Medical workers are recommended to adopt this prediction model in ICUs for early detection and initiation of preventive interventions against delirium among high-risk patients.

AUTHOR CONTRIBUTIONS

Surui Liang: Conceptualization; methodology; data curation; writing-original draft preparation. **Janita Pak Chun Chau:** Conceptualization; methodology; writing-reviewing; editing. **Suzanne Hoi Shan Lo:** Conceptualization; methodology; writing-reviewing; editing. **Liping Bai:** Data curation; writing-reviewing; editing. **Li Yao:** Data curation; writing-reviewing; editing. **Kai Chow Choi:** Methodology; data curation; writing-reviewing; Editing.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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