Intensive Care Med (2014) 40:361–369
DOI 10.1007/s00134-013-3202-7

ORIGINAL

# Recalibration of the delirium prediction model for ICU patients (PRE-DELIRIC): a multinational observational study

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Received: 5 July 2013
Accepted: 18 December 2013
Published online: 18 January 2014


**Take-home message** The delirium prediction model for ICU patients (PRE-DELIRIC) is relevant for recognizing patients' delirium risk in order to take preventive measures. In this multinational study, we recalibrated the PRE-DELIRIC model. Despite differences in the incidence of predictors between the centers in the different countries the performance of the PRE-DELIRIC-model remained good. Following validation of the PRE-DELIRIC model it may facilitate implementation of strategies to prevent delirium and aid improvements in delirium management of ICU patients.

**Electronic supplementary material** The online version of this article (doi:10.1007/s00134-013-3202-7) contains supplementary material, which is available to authorized users.

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**Abstract** *Purpose:* Recalibration and determining discriminative power, internationally, of the existing delirium prediction model (PRE-DELIRIC) for intensive care patients. *Methods:* A prospective multicenter cohort study was performed in eight intensive care units (ICUs) in six countries. The ten predictors (age, APACHE-II, urgent and admission category, infection, coma, sedation, morphine use, urea level, metabolic acidosis) were collected within 24 h

after ICU admission. The confusion assessment method for the intensive care unit (CAM-ICU) was used to identify ICU delirium. CAM-ICU screening compliance and inter-rater reliability measurements were used to secure the quality of the data. *Results:* A total of 2,852 adult ICU patients were screened of which 1,824 (64 %) were eligible for the study. Main reasons for exclusion were length of stay <1 day (19.1 %) and sustained coma (4.1 %). CAM-ICU compliance was mean (SD) 82 ± 16 % and inter-rater reliability 0.87 ± 0.17. The median delirium incidence was 22.5 % (IQR 12.8–36.6 %). Although the incidence of all ten predictors differed significantly between centers, the area under the receiver operating characteristic (AUROC) curve of the eight participating centers remained good: 0.77 (95 % CI 0.74–0.79). The linear predictor and intercept of the prediction rule were adjusted and resulted in improved re-calibration of the PRE-DELIRIC model. *Conclusions:* In this multinational study, we recalibrated the PRE-DELIRIC model. Despite differences in the incidence of predictors between the centers in the different countries, the performance of the PRE-DELIRIC-model remained good. Following validation of the PRE-DELIRIC model, it may facilitate implementation of strategies to prevent delirium and aid improvements in delirium management of ICU patients.

**Keywords** Delirium · Prediction model · Recalibration · Critical care

## Introduction

Delirium, the acute onset of confusion and consciousness disturbances with a fluctuating course [1], occurs frequently in critically ill patients [2–4]. Delirium is associated with a prolonged stay in the intensive care unit (ICU) and hospital, increased morbidity and mortality rate, higher costs [2, 3, 5] and adverse long-term outcome [6, 7]. There are several delirium assessment tools for ICU patients such as the confusion assessment method for the intensive care unit (CAM-ICU). Although recent studies [8, 9] showed a lower accuracy of the CAM-ICU than in the original studies [10, 11], this screening tool has the highest sensitivity and specificity [12, 13]. Structured delirium screenings results in better recognition of delirious patients [14] that may facilitate early treatment [15, 16]. Besides adequate delirium treatment, prevention of delirium is crucial. While some preliminary studies have reported effective preventive interventions in both non-critically ill [17, 18] and ICU patients [19], applying these interventions in all ICU patients is time consuming, inefficient, and exposes a substantial number of patients to unnecessary risks to possible side effects of drugs used for delirium prevention. A readily available prediction model to identify high-risk patients would facilitate the use of preventive interventions. Recently, the PRE-DELIRIC prediction model was developed and validated for ICU patients [20], based on identified risk factors for delirium in ICU patients [21]. The development of the prediction model including the relevance of different delirium-associated risk factors in daily ICU practice, such as use of sedatives, morphine, and presence of an infection, are discussed more extensively in the original article [21]. The discriminative power of the PRE-DELIRIC model was high in predicting delirium with an onset at median day 2 after ICU admission [20]. Using the PRE-DELIRIC model is effective in predicting delirium and can be used to guide preventive therapy in critically ill patients [22], to stratify patients in testing the effectiveness of any considered intervention and to better inform caregivers and families.

The PRE-DELIRIC model consists of ten predictors that are readily available within 24 h following ICU admission and, with an area under the receiver operating characteristic curve (AUROC) of 0.85 [20] has a good performance. Since the PRE-DELIRIC model was developed and validated in the Netherlands, the multinational performance of this model has not been known. In view of relevant differences in case mix and ICU treatment between countries, a good multinational performance of the PRE-DELIRIC model is warranted prior to worldwide implementation.

In the present multinational study, we recalibrated the model and determined the discriminative power of the PRE-DELIRIC model.

## Methods

### Study design

Prospective observational multicenter study carried out in eight general intensive care units for adult patients in six countries (Australia, Belgium, Germany, Spain, Sweden, United Kingdom). The regional Medical Ethical Committee of Arnhem–Nijmegen, The Netherlands (study number 2010/365) approved the study and waived the need for informed consent, and since CAM-ICU determinations were part of clinical practice in all centers, no additional interventions were carried out, so data collection was not burdensome to patients, and data were captured and analyzed anonymously. All participating centers obtained ethics approval for data collection from the Ethical Committee of their own institution.

## Study population

Each participating center included all eligible ICU patients during a period of 3 months. The first center started with inclusion in October 2011 and the last center started in June 2012. Patients were excluded if they were: delirious within 24 h after ICU admission; sustained comatose during complete ICU stay; admitted to the ICU for less than 1 day; suffering from serious auditory or visual disorders; unable to understand the language of the included center; severely mentally disabled; suffering from a serious receptive aphasia; or if the compliance rate of the delirium screening was <80 % during a patient's stay in the ICU. To exclude a potential source of bias, the assessors of the CAM-ICU were not aware of collecting the data of the predictors nor of the PRE-DELIRIC score, and did not receive the calculated risk for developing delirium for their patient.

## Delirium screening

In order to detect delirium, all ICU patients were assessed by well-trained ICU nurses with the validated delirium assessment tool, the CAM-ICU [10, 11], at least twice daily. Identical to the original study [20], delirium was defined as at least one positive CAM-ICU screening during a patient's complete intensive care stay. CAM-ICU was part of clinical practice in all participating hospitals.

## Data collection

Data relating to delirium screening were collected during patients' complete ICU stay. The ten predictors of the PRE-DELIRIC model as originally defined [20] were collected within the first 24 h after ICU admission: age, APACHE-II score, coma, urgent admission (unplanned ICU admission), admission category (surgical, medical, trauma, neurology/neurosurgical), infection, coma, use of sedatives, morphine use (three dosages groups), urea level, and metabolic acidosis [20]. All predictors can be objectively measured and are well defined (Supplementary Appendix A).

A secured web based electronic clinical report form (E-CRF) was filled out for each screened patient using a unique login and password for each participating center. Consecutive patients received a unique anonymous number. For privacy reasons, only the participating centers were able to identify their patients, based on the E-CRF-numbers.

## Data management and quality checks

To ensure the quality of the data, the compliance with the CAM-ICU was calculated monthly. Compliance was calculated as the percentage of assessments performed per day in relation to the total number of assessments that should have been performed. To determine the quality of the performed delirium screenings during the study period, monthly inter-rater reliability measurements were performed for all patients admitted to the ICU on a given day each month. For this, the CAM-ICU screenings assessed by the intensive care nurse were compared with the scores assessed by a dedicated delirium expert nurse or investigator in each center.

We determined a priori that a CAM-ICU screening compliance >80 % and an inter-rater reliability of >0.80 Cohen's kappa indicated reliable data. The performance of the PRE-DELIRIC model was calculated after excluding data of the center(s) who did not achieve this compliance or kappa from the analysis. Exclusion and re-analysis was performed per center. If exclusion of this center did not affect the performance of the PRE-DELIRIC model significantly, its results were included in the final analyses.

## Statistical analysis

Missing predictor data were imputed in a similar way as in the original study [20]. We assumed that, if a blood value was not determined, most likely the missing variable had a normal value, so the mean normal value of the study population was imputed. For other missing variables, we assumed that they had a normal or negative value (i.e. no infection, no metabolic acidosis) or a mean value (e.g., APACHE-II score) of the study population and imputed the mean value of the variable derived from the delirium or non-delirium group, depending on the results of the delirium assessment. The percentage of missing data ranged between <1.0 and 9.8 %. We recorded incomplete data for the presence of infection (9.8 %), highest urea level (1.8 %), APACHE-II score (1.5 %), and metabolic acidosis (<1.0 %). Data for all other variables were complete.

To determine the performance of the PRE-DELIRIC model for each participating center, the original linear predictors were used to calculate the probability of developing delirium for each patient. The estimated prognostic ability of the model was determined using the AUROC of the calculated total predicted probability per patient and his/her delirium outcome.

In order to optimize the calibration of the model, the linear predictors and the intercept in a logistic regression model. For this, a generally accepted [23, 24] standard statistical stepwise approach was followed in order to achieve a calibration slope of 1 and an intercept of 0, as a measure of perfect calibration. To test this, we used the weights of the linear predictors in a logistic regression analysis resulting in an intercept and a calibration slope. The first approach was to estimate a new intercept and use a fixed calibration slope of 1. Next, we estimated the intercept as well as the calibration slope. Then, we

estimated the intercept for each center separately, again with a fixed calibration slope, followed by estimation of the intercept as well as calibration slope per center. With the last approach to optimize the calibration, we then applied a general linear mixed model fit by Laplace approximation, using the mean estimated intercept and mean estimated calibration slope. In order to determine if recalibration could be biased by data of the largest group of patients from one center, we also calculated an intercept and linear predictor using weighted data. In order to test the calibration, we used the Hosmer–Lemeshow goodness-of-fit statistics before and after recalibration [25], and to judge the calibration and recalibration visually, we used calibration belts as described by Finazzi et al. [26].

Statistical analyses were performed using statistical package for social sciences (SPSS®) 20.01, and R statistics v.2.10.1 [27] using the rms package [28].

### Sample size

The PRE-DELIRIC model consists of ten predictors. We would needed at least 10–15 patients with delirium and 10–15 patients without delirium per predictor for the validation and re-calibration, so in total at least 300 patients. This formula was based on the recommendation for the development of a new prediction model [23]. With an anticipated delirium incidence of 15–30 %, and an attrition of 25 %, we aimed to enroll at least 1,350 patients.

## Results

A total of 2,852 ICU patients were screened, with 1,824 (64 %) patients included in the analysis. The most frequent reason for exclusion was a length of stay on the ICU <1 day (19.1 %), followed by sustained coma (4.1 %), and development of delirium within 24 h (3.5 %) (Fig. 1). The mean ± SD age of patients was 60 ± 17 years, the mean APACHE-II score was 19 ± 9, and 57 % of the included patients were male. Most patients, over 50 %, had a predicted delirium chance between 10 and 20 % (Supplementary Appendix B).

The median delirium incidence was 22.5 % (IQR 12.8–36.6 %). The median time until first positive CAM-ICU occurred was 3 days [1–6]. Of note, apart from the considerable variation in delirium incidence, there were important differences between countries concerning the incidence of delirium predictors (Table 1).

### CAM-ICU compliance and inter rater reliability

The overall CAM-ICU compliance was 82 ± 16 % (minimum 52 %, maximum 100 %) and the mean inter-rater reliability measurements were 0.87 ± 0.17 Cohen's kappa (minimum 0.57, maximum 1.00) (Supplementary Appendix C). In total, 461 inter-rater measurements were performed. There were 10 false negative scores and 11 false positive scores resulting in a sensitivity of 0.93 (95 % CI 0.86–0.95) and a specificity of 0.97 (95 % CI 0.95–0.98).

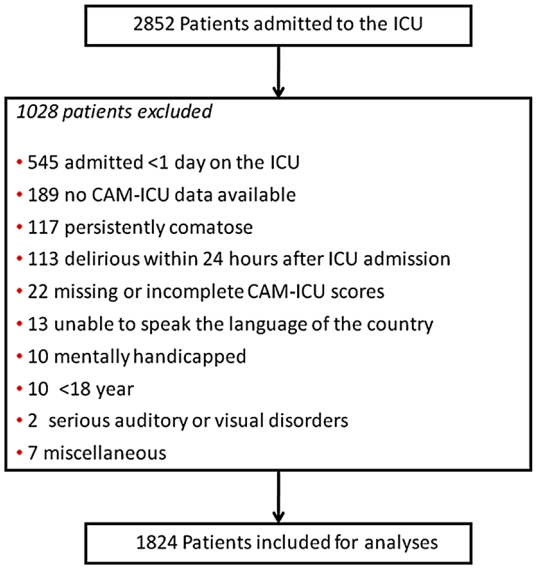


**Fig. 1** Flowchart of inclusion

### Discrimination and recalibration of the PRE-DELIRIC

To determine the discriminative power of the PRE-DELIRIC model, the AUROC was calculated per center and overall. The mean AUROC of the eight participating centers was 0.77 (95 % CI 0.74–0.79) (Supplementary Appendix D). The AUROC of the model in the early onset delirium group was 0.82 (95 % CI 0.79–0.84) and for the late onset delirium group 0.68 (95 % CI 0.66–0.71). The sensitivity of the PRE-DELIRIC model in this study was 0.70 and the specificity was 0.73, with positive and negative likelihood ratios of 2.43 and 0.39, respectively. After discarding all data of the centers with an overall CAM-ICU compliance below 80 % (Supplementary Appendix B), the AUROC remained similar at 0.79 (95 % 0.76–0.82). The mean inter-rater reliability of all centers was >0.80.

To recalibrate the prediction model, four different approaches were used and calculated, as described in "Statistical analysis". None of the first three approaches resulted in a good calibration, defined as a calibration slope of nearly 1 and an intercept of nearly 0 (data not shown). Using the general linear mixed model method resulted in an adjustment of the original intercept (−6.31 × 0.4724 − 1.0545). To optimize the calibration slope, each linear predictor was then multiplied by 0.4724

**Table 1** Patient characteristics and predictors of included patients of the participating hospitals

| | Antwerp, Belgium ($n = 566$) | Berlin, Germany ($n = 223$) | Madrid, Spain ($n = 128$) | Stockholm, Sweden ($n = 77$) | Brisbane, Australia ($n = 329$) | Canberra, Australia ($n = 195$) | Prescot, UK ($n = 235$) | Kent, UK ($n = 71$) |
|---|---|---|---|---|---|---|---|---|
| Age, years (mean ± SD) | 61 ± 15 | 62 ± 16 | 60 ± 17 | 61 ± 17 | 55 ± 18 | 63 ± 16 | 62 ± 17 | 62 ± 17 |
| APACHE-II points (mean, SD) | 26 ± 8 | 17 ± 8 | 8 ± 5 | 14 ± 7 | 16 ± 6 | 18 ± 6 | 17 ± 7 | 15 ± 7 |
| No coma | 499 (88 %) | 184 (83 %) | 114 (89 %) | 47 (61 %) | 239 (73 %) | 146 (75 %) | 138 (59 %) | 38 (54 %) |
| Coma due to | | | | | | | | |
| Medication induced | 58 (10 %) | 37 (17 %) | 14 (11 %) | 23 (30 %) | 31 (9 %) | 34 (17 %) | 70 (30 %) | 28 (39 %) |
| Miscellaneous | 0 | 2 (1 %) | 0 | 1 (1 %) | 5 (2 %) | 4 (2 %) | 4 (2 %) | 5 (7 %) |
| Combination | 9 (2 %) | 0 | 0 | 6 (8 %) | 54 (16 %) | 11 (6 %) | 23 (10 %) | 0 |
| No morphine use | 347 (79 %) | 203 (91 %) | 77 (61 %) | 25 (42 %) | 258 (82 %) | 182 (94 %) | 175 (75 %) | 66 (93 %) |
| Morphine 0.01–7.1 mg/day | 30 (7 %) | 10 (5 %) | 13 (10 %) | 11 (18 %) | 7 (2 %) | 2 (1 %) | 4 (2 %) | 0 |
| Morphine 7.2–18.6 mg/day | 41 (9 %) | 8 (4 %) | 23 (18 %) | 15 (25 %) | 19 (6 %) | 3 (2 %) | 6 (3 %) | 0 |
| Morphine >18.6 mg/day | 20 (5 %) | 2 (1 %) | 13 (10 %) | 9 (15 %) | 31 (10 %) | 7 (4 %) | 48 (21 %) | 5 (7 %) |
| Sedated | 194 (34 %) | 35 (16 %) | 21 (16 %) | 43 (56 %) | 271 (82 %) | 83 (43 %) | 94 (40 %) | 33 (47 %) |
| Urgent admission | 330 (58 %) | 114 (51 %) | 45 (35 %) | 61 (79 %) | 159 (48 %) | 149 (76 %) | 228 (97 %) | 61 (86 %) |
| Diagnose group | | | | | | | | |
| Surgical | 286 (51 %) | 110 (49 %) | 92 (72 %) | 26 (34 %) | 196 (60 %) | 63 (32 %) | 65 (28 %) | 31 (44 %) |
| Medical | 164 (29 %) | 55 (25 %) | 8 (6 %) | 39 (51 %) | 77 (23 %) | 112 (57 %) | 161 (69 %) | 38 (54 %) |
| Trauma | 1 (0 %) | 24 (11 %) | 2 (2 %) | 12 (16 %) | 42 (13 %) | 12 (6 %) | 4 (2 %) | 2 (3 %) |
| Neurology/neurosurgical | 115 (20 %) | 34 (15 %) | 26 (20 %) | 0 | 14 (4 %) | 8 (4 %) | 5 (2 %) | 0 |
| Infection or strong suspicion | 92 (16 %) | 39 (18 %) | 19 (15 %) | 51 (66 %) | 99 (30 %) | 80 (41 %) | 97 (41 %) | 39 (55 %) |
| Metabolic acidosis | 205 (36 %) | 18 (8 %) | 26 (20 %) | 29 (38 %) | 57 (17 %) | 91 (47 %) | 90 (38 %) | 9 (13 %) |
| Highest urea level in mmol/L | 4.9 ± 3.7 | 16.0 ± 11.3 | 15.5 ± 7.6 | 11.1 ± 8.7 | 7.9 ± 6.4 | 9.3 ± 5.9 | 11.5 ± 9.6 | 13.5 ± 12.7 |
| Delirious, *n* (%) | 86 (15 %) | 60 (27 %) | 23 (18 %) | 30 (39 %) | 42 (13 %) | 23 (12 %) | 73 (31 %) | 26 (37 %) |

Data are expressed as mean ± standard deviation, unless reported otherwise

**Table 2** PRE-DELIRIC formula, old and new intercept and linear predictors

| | Original values of linear predictors | New values of linear predictors |
|---|---|---|
| Intercept | −6.3131 | −4.0369 |
| Age (per year) | 0.0387 | 0.0183 |
| APACHE-II score per point | 0.0575 | 0.0272 |
| Coma | | |
| No | 0 | 0 |
| Drug-induced | 0.5458 | 0.2578 |
| Miscellaneous | 2.2695 | 1.0721 |
| Combination | 2.8283 | 1.3361 |
| Admission category | | |
| Surgery | 0 | 0 |
| Medical | 0.3061 | 0.1446 |
| Trauma | 1.1253 | 0.5316 |
| Neurology–surgery | 1.3793 | 0.6516 |
| Presence of infection | 1.0509 | 0.4965 |
| Presence of metabolic acidosis | 0.2918 | 0.1378 |
| Use of morphine | | |
| None | 0 | 0 |
| 0.01–7.1 mg | 0.4078 | 0.1926 |
| 7.2–18.6 mg | 0.1323 | 0.0625 |
| >18.6 mg | 0.5110 | 0.2414 |
| Use of sedatives | 1.3932 | 0.6581 |
| Urea concentration (per mmol/L) | 0.0298 | 0.0141 |
| Urgent admission | 0.4004 | 0.1891 |

resulting in new predicted probabilities (Supplementary Appendix D) per center. Table 2 reflects the old and new linear predictors and the intercept. This recalibration resulted in improvement of the calibration curve (Fig. 2a, b), with a calibration slope of 1.09 and an intercept of 0.08. Following adjustment of the calibration slope, the AUROC remained similar: 0.76 (95 % CI 0.74–0.79). The Hosmer–Lemeshow test improved, Chi-square 797.95 ($p < 0.0001$) before recalibration to Chi-square 15.85 ($p = 0.045$) after recalibration, indicating a better overall calibration.

Sequentially, we calculated a new intercept and linear predictor using weighted data to determine if the center with the largest sample size biased our results. This resulted in a poorer calibration (data not shown). Importantly, in this center, no inter-rater reliability was measured and it had the highest APACHE-II score with a relatively low delirium incidence.

## Discussion

We have previously shown that the prediction of delirium by caregivers is inaccurate and that the PRE-DELIRIC model is of additional value [20]. However, as the model was developed and validated in the Netherlands, the predictive value of the model in other countries was unknown. In this multinational study, we determined that the discriminative power of the PRE-DELIRIC model for ICU patients was similar to the previous study and the calibration of the model was optimized.

In our study, we found important differences between countries regarding the incidence of the ten predictors as

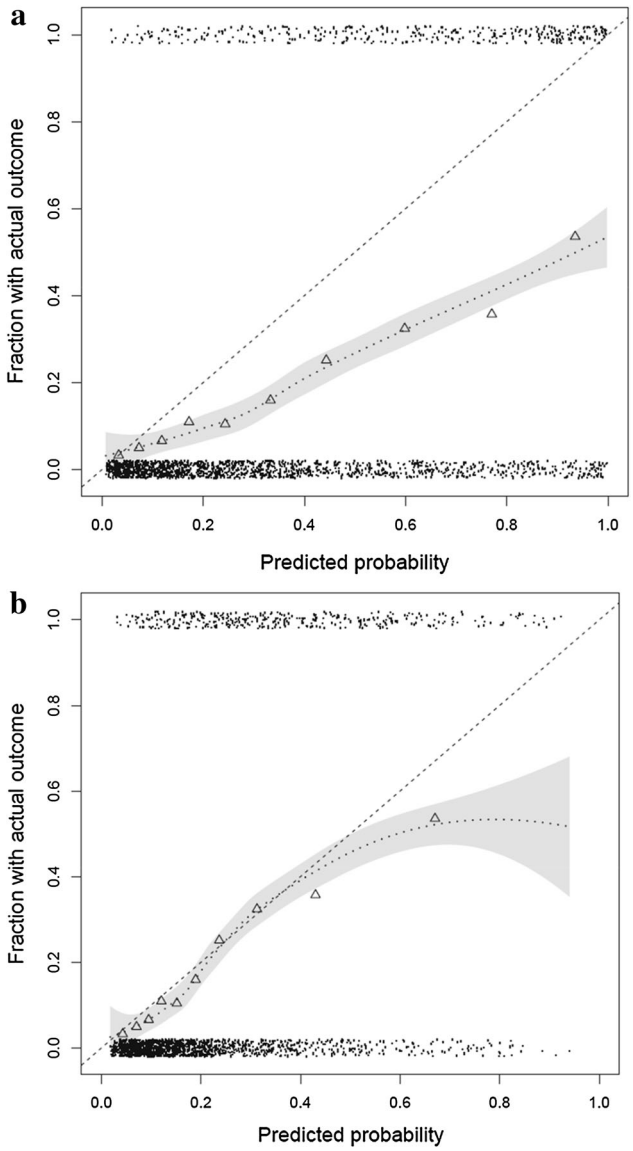


**Fig. 2** **a** Calibration belt before recalibration. **b** Calibration belt after recalibration

well as the delirium incidence, which could potentially be explained by differences in case mix, severity of illness, and differences in ICU admission policies, such as sedation protocols, and other ICU treatments. Although, remarkably, and in line with other studies [29, 30], in our study the most sedated patients, and patients in coma within the first 24 h after ICU admission, have the highest rate of delirium (Table 1). Nevertheless, since no information was collected that may explain the reason of the observed differences in data entered into the model, we cannot further speculate about this and other differences. The differences in incidence of the predictors, and the already existing slightly overestimation of the model in the Dutch population [20], necessitated halving the coefficient values of the predictors in order to optimize the calibration of the model in the multinational population. Despite these differences between the countries, the discriminative power of the PRE-DELIRIC model was not affected, indicating that the most important predictors for the development of delirium on the ICU are included in the model.

Furthermore, in this multinational study, we only collected data of predictors which are in the PRE-DELIRIC model. Although we feel that other risk factors such as excessive alcohol consumption is clearly a very important risk factor for developing delirium, this risk factor was not in the original PRE-DELIRIC model [20]. Regarding the purpose of this study, it is not appropriate to include other/additional risk factors. This would result in the development of a completely new delirium prediction model. Without the risk factor alcohol withdrawal, the predictive value of the original model was high, and, despite us not measuring the prevalence of alcohol withdrawal in this multinational study, the performance of the model remained high. Alcohol withdrawal (acute withdrawal, delirium tremens, and its clinical manifestation) should be clearly distinguished from delirium itself. However, it is important to recognize that alcohol consumption itself is a risk factor for "plain" delirium [31, 32]. We feel that we do not need a prediction model for patients with a high alcohol consumption or withdrawal, these patients have a high risk and delirium preventive measures are anyway indicated for this group.

The increased morbidity and mortality associated with delirium in ICU patients warrant its prevention. There is some evidence that delirium prevention, i.e. by haloperidol, is effective in non-cardiac surgery ICU patients [19]. Importantly, the estimate of the efficacy of haloperidol in this study [19] is likely diluted since the preventive intervention was used in all patients, irrespective of their delirium risk. Theoretically, exclusion of ICU patients with a low risk of developing delirium may better reveal the beneficial effects of preventive measures. Indeed, with use of the PRE-DELIRIC model, we previously showed that a low dose of haloperidol was associated with a reduced rate of delirium and mortality among ICU patients with a predicted risk of developing delirium >50 %, and seems even more effective in the highest risk (predicted risk >90 %) group [22]. However, this study was a pre-post design study that needs to be confirmed in a RCT, but it illustrates the need for a delirium prediction model to facilitate the conduct of future prevention studies.

Importantly, the PRE-DELIRIC model is a static prediction model producing a single risk prediction value 24 h after ICU admission. However, delirium in ICU patients is a complex, dynamic, and multi-factorial syndrome. The current PRE-DELIRIC model may require on-going validation as new therapies and interventions emerge. For example, the use of new sedatives or

analgesics may affect the development of delirium [33–35], and consequently could affect the performance of the model. Different risk factors may emerge in the future that may need to be investigated and included in the current PRE-DELIRIC model. In addition, since some patients develop delirium within 24 h after ICU admission, an early delirium prediction model appears necessary in order to facilitate preventive measures in high-risk patients immediately after ICU admission.

Furthermore, the discriminative power of the model remained similar and the calibration was optimized. Regarding the calibration plot, there is still some overestimation of the PRE-DELRIC model for patients with a calculated risk of 50 % and higher. It appears plausible that, for the high-risk group, the study was underpowered, resulting in the observed overestimation. However, in these patients with a high risk of developing delirium, it is recommendable anyway to take preventive interventions, so the small overestimation of the model would not affect clinical decision making.

Our study has several limitations we wish to address. In our multinational study, the discriminative power remained good. During the recalibration process, it appeared that the most optimal way to recalibrate the model was to estimate new intercept and linear predictors for each center separately. The best performance can be achieved when a prediction model is tailored to suit each individual ICU. This would result in the best discriminative power and calibration of such a model, but would impair comparisons between centers. Therefore, we feel it is desirable to have a prediction model that can be used in all hospitals, and we chose to use the mean estimated new linear predictors and intercept of all hospitals. In this way, the discriminative power remained high. Nevertheless, centers need to take into account that there can be some over- or underestimation in the prediction of delirium when using the PRE-DELIRIC model in their ICU, especially in the highest risk group. Therefore, caution is needed with the use of the model in patient populations with a high probability of delirium. In addition, since the PRE-DELIRIC model is now recalibrated using multinational data, a prospective multinational validation of the recalibration is warranted.

Second, coma represented by RASS level −3 or less is an important predictor in the PRE-DELIRIC model, but coma can be biased by the effect of sedation which is suggested to be a confounder for delirium [36]. In our study, we did not collect data on the duration of coma or on the relationship with sedation and with the onset of delirium. However, when excluding the predictor 'sedation or coma' from the model, this did not influence the discriminative power (data not shown), indicating that this did not affect our results to an important extent. Third, for missing data, we did not use a specific imputation technique [37]; in our view, a clinically relevant method to handle missing values. We assumed, similar to the original PRE-DELIRIC study [20], that a missing variable had a normal value, as there were apparently no indications to measure this variable, and consequently imputed the normal value. Since the incidence of missing values was low, our results were not importantly affected using this imputation technique. Fourth, we assessed the presence of delirium using the CAM-ICU. The performance of this assessment tool in daily practice has recently been re-evaluated [8, 9], and has also been discussed in sedated patients [38, 39] and may not be as accurate as in the original validation studies [10, 11]; however, ongoing bedside education results in a better performance [40]. On the other hand, in the re-evaluation studies, the CAM-ICU was measured only once and compared with an expert screening, while, in our multinational study, the delirium diagnosis was based on all consecutive CAM-ICU screenings during a patient's complete ICU stay, increasing its sensitivity. Finally, we set threshold values for good data quality concerning CAM-ICU compliance and even inter-rater reliability measurements. Although not all centers achieved these thresholds, we demonstrated that this did not significantly affect our results. These issues increase the generalizability of our results, because the lower compliance with CAM-ICU screening may simply reflect real-life clinical practice.

## Conclusion

The discriminative value of the PRE-DELIRIC model to predict delirium in ICU patients was confirmed and the predictive value of the model improved after recalibration in this multinational study. However, following recalibration, the model needs to be prospectively validated in order to support its use in clinical practice. Furthermore, caution is needed in the use of the model in patient populations with a high probability of delirium.

**Acknowledgments** The authors would like to thank Amanda McCairn and Sue Dowling (research nurses, Whiston Hospital), Anna Schandl (PhD student, Karolinska University Hospital, Stockholm) Lena James and Rod Hurford (Princess Alexandra Hospital, Brisbane, Australia) Walter Verbrugghe, Petra Vertongen (MD/staff member and data management, Antwerp University Hospital, Belgium) for their help in collecting the patient data.

**Conflicts of interest** The authors declare that they have no competing interests.

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