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Validation of a delirium predictive model in patients admitted to surgical intensive care units: a multicenter study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-057890
Article Type:	Original research
Date Submitted by the Author:	03-Oct-2021
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Keywords:	Adult intensive & critical care < ANAESTHETICS, INTENSIVE & CRITICAL CARE, Delirium & cognitive disorders < PSYCHIATRY

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Validation of a delirium predictive model in patients admitted to surgical intensive care units: a multicenter study

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Abstract

Objective To internally and externally validate a delirium predictive model for adult patients admitted to intensive care units (ICUs) following surgery.

Design A prospective, observational, multicenter study.

Setting Three university-affiliated teaching hospitals in Thailand.

Participants Adults aged over 18 years were enrolled if they were admitted to a surgical ICU (SICU) within a week of undergoing an operation.

Main outcome measures Validation was performed of the previously developed delirium predictive model: Age + (5 × SOFA) + (15 × benzodiazepine use) + (20 × DM) + (20 × mechanical ventilation) + (20 × modified IQCODE > 3.42).

Results In all, 380 SICU patients were recruited. Internal validation on 150 patients resulted in an area under a receiver operating characteristic curve (AUROC) of 0.76 (0.683 to 0.837). External validation on 230 patients resulted in an AUROC of 0.85 (0.789 to 0.906). The AUROC of all validation cohorts was 0.83 (0.785 to 0.872). The optimum cutoff value to discriminate between a high and low probability of postoperative delirium in SICU patients was 115. This cutoff offered the highest value for Youden's index (0.50), the best AUROC, and the optimum values for sensitivity (78.9%) and specificity (70.9%).

Conclusions The model developed by the previous study was able to predict the occurrence of postoperative delirium in critically ill surgical patients admitted to SICUs. Consequently, high-risk patients are able to be identified, and both nonpharmacological and pharmacological prevention protocols can be subsequently implemented to improve the clinical outcomes.

Keywords: postoperative delirium, predictive model, surgical intensive care units, validation

Strengths and limitations of this study

- The developed delirium predictive model consists of 6 risk factors was able to predict the occurrence of postoperative delirium in critically ill surgical patients
- The internal and external validation demonstrated moderate to good statistical performance, with the AUROC being comparable to that of the development cohort
- The optimum cutoff value to discriminate between a high and low probability of POD in SICU patients was 115

BACKGROUND

Delirium, a disturbance of consciousness, is both acute and fluctuating. It is characterized by the lessened ability of an individual to focus, maintain, or shift attention. It is also associated with cognitive changes and disruptions in perception that are secondary to a general medical condition. Delirium is an extremely common condition among hospitalized patients. Its incidence varies with the study population, but higher rates are observed among geriatric, postsurgical, intensive care unit (ICU), cardiac surgery, and hip-fracture patients¹⁻⁴. Postoperative delirium (POD) among patients who have been treated with surgery and anesthesia is typically found during the first 3 postoperative days⁵. Although the POD can be transient, it is linked to poor outcomes. These include long stays in postanesthesia care units (PACUs), ICUs, and hospitals; high medical-complication rates; and raised mortality levels⁶.

Several tools for assessing delirium have been validated. Among those is the Confusion Assessment Method for the ICU (CAM-ICU), which shows high sensitivity and specificity⁷. The CAM-ICU has been translated into Thai, and it, too, has demonstrated good sensitivity and specificity for critically ill patients⁸. In Thailand, there are limited data relating to POD as well as delirium among critically ill patients. Muangpaisan *et al.*, 2015⁹ reported the incidence of delirium was 22.5% in hip surgery. Their investigation also identified the following risk factors: age, premorbid function, dementia/cognitive impairment, the nonstop administration of nonsteroidal anti-inflammatory drugs, and postoperative sedative use. Another study reported a 44.0% prevalence of delirium among critically ill, old patients at a medical ICU in northeastern Thailand. That work found that the independent factors related to delirium were the use of physical restraints, a history of stroke, and multiple bed changes¹⁰.

Given that delirium can result in poor clinical outcomes, predictions of its occurrence among patients who are at risk of delirium are especially important. During the recent decade, some predictive scoring systems for delirium have been proposed for use with various

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2
3 populations. For instance, the PRE-DELIRC (PREdiction of DELIRium in ICU patients)
4 delirium risk prediction tool was developed for intensive care patients ¹¹. This model utilizes
5 10 parameters. It had an area under a receiver operating characteristic curve (AUROC) of 0.87
6 (95% confidence interval [CI], 0.85 to 0.89). Temporal validation and external validation
7 resulted in an AUROC of 0.89 (0.86–0.92) and 0.84 (0.82–0.87), respectively ¹¹. Another tool,
8 the Risk Model for Delirium, assesses a number of predisposing risk factors for delirium in hip
9 fracture patients. They are delirium during previous hospitalization; the presence of dementia;
10 substandard performance in a clock-drawing test; advanced age; hearing impairment; visual
11 impairment; the need for domestic help, assistance with meal preparation, or help with physical
12 care; the use of heroin, methadone, or morphine; and the consumption of alcoholic beverages.
13 This model showed good intraclass correlation coefficient (0.77), sensitivity (80.4%), and
14 AUROC (0.73) ¹². Furthermore, Kim *et al* developed the DELirium Prediction based on
15 Hospital Information (Delphi) system for general surgery patients. Delphi demonstrated good
16 AUROCs for both the developed (0.91) and validated models (0.98) ¹³. Nevertheless, each of
17 the above models was developed for specific application with medical critically ill, general
18 surgical, or particular orthopedic patients, and the scoring systems tend to be overly
19 complicated.

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The Siriraj Integrated Perioperative Geriatric (SIPG) Excellent Research Center has
studied the incidence, risk factors, and predictive scores of POD in critically ill surgical
patients. The independent risk factors for delirium identified by a multivariate analysis were
age, diabetes mellitus, severity of disease (assessed by the sequential organ failure assessment
[SOFA] score), perioperative use of benzodiazepine, and mechanical ventilation. The
following predictive score was created:

$$\text{Age} + (5 \times \text{SOFA}) + (15 \times \text{benzodiazepine use}) + (20 \times \text{DM}) + \\ (20 \times \text{mechanical ventilation}) + (20 \times \text{modified IQCODE} > 3.42)$$

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3 Its AUROC was 0.84 (95% CI, 0.786–0.897). A cutoff value of 125 demonstrated a sensitivity
4 of 72.1% and a specificity of 80.9¹⁴. Thus, we were interested in validating the model. To this
5
6 end, internal validation was performed at our hospital, while external validation was conducted
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8 at 2 other academic hospitals. There has been no previous investigation of a predictive model
9
10 for POD in patients in surgical ICUs (SICUs). By identifying critically ill patients at high risk
11
12 of developing POD, a model would enable the implementation of non-pharmacological and
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14 pharmacological preventive measures to avoid severe complications. The aim of this study was
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16 to validate the use of the proposed POD predictive scoring tool in SICUs.
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METHODS

Design

A prospective, observational, cohort study was conducted. The study was approved by the Siriraj Institutional Review Board of the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand (Si 623/2017, Chairperson Prof. Chairat Shayakul, M.D.) on 20 October 2017; the Committee on Human Rights Related to Research Involving Human Subjects, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand (MURA 2017/574, Chairperson Asst. Prof. Chusak Okascharoen, M.D.) on 27 November 2017; and Research Ethics Committee 4 at the Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand (SUR-2560-05016, Chairperson Emeritus Prof. Panja Kulapongs, M.D.) on 28 November 2017. Written informed consent was obtained from the participants before their entry into the study. The trial was registered with the Thai Clinical Trials Registry (TCTR20180105001).

Study population

The study was conducted on 380 SICU patients at 3 hospitals: Siriraj, Ramathibodi, and Maharaj Nakorn Chiang Mai.

The study population comprised patients who were at least 18 years of age and were admitted to a SICU within 7 days of surgery at Siriraj, Ramathibodi, or Maharaj Nakorn Chiang Mai Hospital. In addition, patients for the internal validation cohort were 65 years or older and had been admitted to a Siriraj Hospital SICU^{15, 16} for a stay anticipated to exceed 24 hours. At all 3 hospitals, we excluded SICU patients who had (1) not undergone any operations; (2) communication problems (unable to communicate in Thai, or having a severe visual or auditory impairment interfering with communication); or (3) a Richmond Agitation Sedation Scale (RASS) score of -4 or -5 during the whole of their ICU stay. A flowchart illustrating the

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3 patient selection processes for the development and validation cohorts is presented in Figure 1.
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8 **Measurement instruments**

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10 Delirium was assessed using the Thai version of the CAM-ICU. Delirium was identified by
11 the following 4 features: 1) a change or fluctuation in baseline mental status; 2) inattention;
12 and either 3) an altered level of consciousness; or 4) disorganized thinking ¹⁷. The Thai
13 version has demonstrated satisfactory validity and reliability (specificity, 94.7%; sensitivity,
14 92.3%) ⁸. As to the level of consciousness, it was assessed by the RASS. It utilizes a 10-point
15 scale ranging from -5 to +4. The delirium subtypes were recorded as hypoactive (RASS -1
16 to -3), hyperactive (RASS +1 to +4), and mixed type (hypo- and hyperactive) ¹⁸. With regard
17 to dementia, it was evaluated via the Thai version of the Modified Informant Questionnaire
18 on Cognitive Decline in the Elderly (modified IQCODE). The questionnaire consists of 32
19 items, with assessments of patients being made by their caregivers. The optimal cutoff score
20 for the modified IQCODE is 3.42 (sensitivity, 90%; specificity, 95%; and accuracy, 92%) ¹⁹.
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22 Lastly, the severity of illness at SICU admission was evaluated using the Acute Physiology
23 and Chronic Health Evaluation II (APACHE II) scoring system, and SOFA scores.
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42 **Data collection**

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44 The predisposing and precipitating factors potentially linked to the onset of delirium were
45 grouped as preoperative, intraoperative, and postoperative variables. The preoperative risk
46 factors were demographic variables obtained from a review of an individual patient's medical
47 records and interviews with any proxies. Each patient's cognitive status was measured using
48 the modified IQCODE ¹⁹.
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56 The intraoperative variables were obtained from anesthetic records. They consisted of
57 the surgical type (abdominal, vascular, orthopedic, urological, gynecological, and head and
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3 neck); admission type (emergency or elective); operation time; intraoperative blood loss;
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5 amount of blood transfused; and total fluid intake. Intraoperative hypotension was deemed to
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7 be either a systolic pressure below 90 mmHg or the need to be treated with medications.
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9 Intraoperative hypoxemia was defined as an oxygen saturation (derived from pulse oximetry)
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11 of below 90% for any duration.
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15 The postoperative variables were primarily obtained from the SICU data records. They
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17 were the use of mechanical ventilation, physical restraints, or a Foley's catheter; the presence
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19 of sleep deprivation or shock; exposure to psychoactive drugs (benzodiazepines, opioids, and
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21 sedatives); and the presence of coma (indicated by a RASS score of -4 or -5).
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24 25 26 **Preparation of research team**

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28 The clinical researchers administering the Thai CAM-ICU were physicians and nurses who had
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30 been trained by the principal investigator. To ensure reliability among the assessors, inter-rater
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32 reliability scores were calculated. Once their kappa score reached 0.8, the trained physicians
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34 and nurses were permitted to perform the Thai CAM-ICU assessments.
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37 38 39 **Patient assessments**

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41 Patients provided informed consent in writing. Delirium was evaluated at least twice daily
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43 (once during the 12 hours from 6.00 AM, and once during the 12 hours after 6.00 PM), and
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45 whenever patients developed a mental change. Delirium was screened routinely utilizing a 2-
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47 step process. Initially, the patients' level of consciousness was assessed using the RASS. If the
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49 score was between -3 and +4, the evaluators proceeded to Step 2 (assessment of the patient
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51 with the Thai version of CAM-ICU). However, if Step 1 produced a -4 RASS score (responsive
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53 only to physical stimulus) or a -5 RASS score (unresponsive to physical and verbal stimulus),
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55 Step 2 was not performed. If a patient was found to be sedated in the first step, the dose of the
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3 sedative medication was adjusted. The patient was later assessed with the CAM-ICU once a
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5 RASS score of -3 or higher was achieved.
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8 The second step involved the determination of the patient's delirium level using the Thai
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10 version of CAM-ICU, employing standard methodology. The assessments commenced on the
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12 first day after the patient's operation and continued for 7 days, or until either discharge from
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14 the ICU or the death of the patient. Patients with delirium were further assessed until the CAM-
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16 ICU was negative for 24 hours. Thereafter, the ICU attending physician was notified for further
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18 management.
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23 24 **Internal and external validation**

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26 After development of a predictive model from a prospective cohort study that took place
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28 between February 2016 and February 2017, we did a second prospective cohort study in the
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30 same hospital for internal validation of the model between April 2018 and December 2019. In
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32 the meantime, we externally validated the predictive model with data from intensive care
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34 surgical patients admitted to 2 other university hospitals in Thailand. They were Ramathibodi
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36 Hospital, Mahidol University, and Maharaj Nakorn Chiang Mai Hospital, Chiang Mai
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38 University. Trained intensive care nurses at those hospitals used the CAM-ICU at least twice
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40 daily (Table 1). The validation process was conducted according to the Transparent Reporting
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42 of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD)
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44 Statement²⁰, a guideline specifically designed for the reporting of studies developing or
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46 validating a multivariable prediction model, whether for diagnostic or prognostic purposes.
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54 55 **Statistical analysis**

56 Demographic variables are presented as mean \pm standard deviation and median (interquartile
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58 range [IQR]) for continuous data, and frequency and percentage for categorical data. Group
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3 comparisons were performed using the independent-samples t-test, Mann–Whitney U test, chi-
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5 squared test, or Fisher’s exact test, as appropriate.
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8 In both validation studies, we multiplied regression coefficients for each risk factor in the
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10 predictive model by the observed patients’ values. The outcome was a calculated predicted
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12 probability, on which we built a new AUROC. Finally, an ROC curve was plotted to determine
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14 the best cutoff in terms of Youden’s index, sensitivity, specificity, and 95% CI. The Youden’s
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16 index was the difference between the true and the false positive rates. Maximizing this index
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18 allows an optimal cutoff value to be found from the ROC curve, independently from the
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20 prevalence ^{21, 22}. Finally, to examine how well the model was calibrated, we calculated linear
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22 predictor values for each patient of every cohort by using the coefficients from the model. We
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24 used these linear predictors in a logistic regression model to test whether the prediction rule
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26 was well calibrated, resulting in a calibration slope and an intercept. A calibration slope of 1
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28 and an intercept of 0 show a perfect calibration ^{23, 24}. Statistics were analyzed using PASW
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30 Statistics for Windows (version 18; SPSS Inc., Chicago, IL, USA); and MedCalc statistical
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32 software (version 17.6; MedCalc Software BVBA, Ostend, Belgium).
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RESULTS

Patients

The patients were enrolled between February 2016 and February 2017¹⁴ for the development cohort, and between April 2018 and December 2019 for the internal and external validation studies. In all, 1,437 SICU patients were excluded for the reasons given in Figure. 1, and 380 were recruited. The mean age of the patients in the internal validation cohort was 75.1 ± 7.5 years, while the mean for the patients in the external validation cohort was 56.9 ± 17.3 years. The mean age of all of the patients in the 2 validation cohorts was 64.1 ± 16.8 years. More than half of the patients in the validation cohort were males. Details relating to the demographic and intraoperative data, ICU admission, and the medications used are given in Table 2. There was a higher proportion of patients with hypertension, diabetes mellitus (DM), and cardiac disease in the internal validation cohort than the external validation cohort. The incidence of delirium was 40.0%, 21.3%, and 28.7% in the internal, external, and all validation cohorts, respectively, compared with 24.4% in the development cohort. The majority of patients in all cohorts underwent intra-abdominal surgery. The median SOFA score was 4 (IQR 1–6) for all validation cohorts, which was higher than the median of 3 (IQR 2–6) for the development cohort. The percentage of benzodiazepine use in the development cohort (10% vs. 25.2%; Table 2).

Development study

Of the 412 recruited patients, a total of 162 were excluded for the reasons detailed in Figure. 1. As a result, 250 patients were enrolled, 61 of whom (24.4%) developed delirium (Table 2). The predictive model was derived from a multiple logistic regression that used significant risk factors. The final formula required 6 factors (2 quantitative factors, and 4 binary factors). The formula of the predictive model was:

$$\text{Age} + (5 \times \text{SOFA}) + (15 \times \text{benzodiazepine use}) + (20 \times \text{DM}) +$$

(20 × mechanical ventilation) + (20 × modified IQCODE > 3.42)

The AUROC was 0.84 (95% CI, 0.786–0.897; Figure. 2A). The cutoff value of ≥ 125 demonstrated a sensitivity of 72.1% and a specificity of 80.9%¹⁴.

Validation study

Internal validation of predictive model

For the prospective validation study, we recruited 984 consecutive patients who were aged over 65 years; however, 834 were subsequently excluded (Figure. 1). Of the remaining 150 patients, 60 (40%) developed delirium (Table 2). The internal validation resulted in an AUROC of 0.76 (0.683 to 0.837; Figure. 2B), with a calibration slope of 0.972 and an intercept of 0.009 (Figure. 3A).

External validation of predictive model

We performed the external validation study on critically ill surgical patients admitted to SICUs at Ramathibodi and Maharaj Nakorn Chiang Mai Hospitals. Of the 833 recruited patients, 603 were excluded (Figure. 1). As a result, 230 patients were enrolled: 62 (27%) at Ramathibodi Hospital, and 168 (73%) at Maharaj Nakorn Chiang Mai Hospital. The incidence of delirium in the external validation cohort was 21% (Table 2). The external validation resulted in an AUROC of 0.85 (0.789 to 0.906; Figure. 2C), with a calibration slope of 0.929 and an intercept of 0.006 (Figure. 3B).

Optimal cutoff value of predictive model

The AUROCs of the development, internal, and external validation cohorts were comparable (0.84 for the development cohort, 0.76 for the internal validation cohort, and 0.85 for the external validation cohort; Figure. 2). As no differences in prediction existed between the 3 validation studies, we pooled the data of all validation cohorts (n = 380). That revealed that 109 patients (29%) developed delirium (Table 2). Consequently, the AUROC of all of the

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3 validation cohorts was 0.83 (0.785 to 0.872; Figure. 2D). The recalibration of all validation
4 study showed a calibration slope of 0.945 and an intercept of 0.007. (Fig 3C) The optimum
5 cutoff value to discriminate between a high and low probability of POD in SICU patients was
6 115. This cutoff presented the highest value of Youden's index (0.50), the best AUROC, and
7 the optimum values for sensitivity (78.9%) and specificity (70.9%; Table 3). The last 2 values
8 were similar to the sensitivity (78.8%) and specificity (70.4%) of the development cohort.
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DISCUSSION

Given the high costs of managing delirium and its consequential complications, it is essential to identify individuals at high risk of developing the condition and to deliver evidenced-based preventive measures. This multicenter-study demonstrated the performance of the internal and external validation of a proposed model¹⁴ that had been developed to predict POD in patients admitted postoperatively to an SICU. It is essential to confirm the predictive performance of the model before its use outside the development setting. The external validation showed moderate to good statistical performance, with the AUROC of the external cohort being comparable to that of the development cohort. In addition, the new cutoff value also demonstrated optimum sensitivity and specificity values that were equivalent to those achieved for the development cohort. However, the performance of the internal validation cohort was not as high as the development and external validation cohort (AUROC, 0.76). This was because the internal validation cohort only included patients aged 65 years or older, resulting in a higher incidence of delirium.

Recently, 2 ICU delirium predictive models—the early predictive model for ICU delirium (E-PRE-DELIRIC), and the recalibrated predictive model for ICU delirium (PRE-DELIRIC) have been developed and validated^{11, 25, 26}. These 2 models are currently used in clinical practice and in research to predict the development of delirium in ICUs. The PRE-DELIRIC model consists of 10 predictors that are available during the first 24 hours after admission to an ICU [25]. The E-PRE-DELIRIC is composed of 9 parameters available at time of ICU admission. Wassenaar *et al.*, 2019²⁷ recently conducted an external validation of both assessment tools, using either the CAM-ICU or the Intensive Care Delirium Screening Checklist for delirium assessment. The researchers reported moderate-to-good statistical performances. Nevertheless, the formulas for those 2 models were quite complicated, using several parameters, and they were developed in a mixed-ICU setting (medical and surgical

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3 populations). Given that cognitive impairment (including dementia) and severity of illness have
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5 been recognized as strong predictors for delirium in hospitalized patients,^{28, 29} the E-PRE-
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7 DELIRIC system included only a history of cognitive impairment but no severity scores. In
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9 contrast, the PRE-DELIRIC model included only APACHE II scores, but no information on
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11 cognitive impairment.
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15 The currently proposed predictive model for POD in critically ill surgical patients has
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17 several strengths. Firstly, it was developed specifically for surgical patients, and it
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19 demonstrated high accuracy. In addition, it employs only 5 parameters, which makes it
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21 relatively easy to calculate. Furthermore, dementia is assessed by both the patient's history and
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23 the modified IQCODE assessment tool. A previous study found that the prevalence of dementia
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25 among elderly delirious patients was 5 times higher when evaluated by the modified IQCODE
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27 tool than when using information obtained solely from history taking³⁰. Consequently, the
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29 proposed predictive model was validated in the same hospital and in 2 other academic hospitals.
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31 Although we recruited only elderly patients for the internal validation cohort, the AUROC
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33 showed an acceptable value. For the external validation cohort in the SICUs of the 2 other
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35 hospitals, we performed quality control by determining the inter-rater reliability of CAM-ICU
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37 assessment before commencing the study. There were differences in the patient case-mix of
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39 the external and development validation samples. In particular, relative to the development
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41 group, the external validation cohort had a lower age, a lower percentage of patients with
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43 mechanical ventilation, a higher percentage of dementia, and a lower percentage of
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45 benzodiazepine use. Despite that, the models' discriminative performance showed the same
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47 value (AUROC 0.84 for the development cohort, and 0.85 for the external validation cohort).
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49 In short, for the all-validation cohort, the AUROC was approximately the same as that for the
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51 development and the external validation cohorts. A score of ≥ 115 was the best cutoff value to
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53 predict the occurrence of delirium in SICUs. This cutoff presented the highest value for
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3 Youden's index (0.50), the best AUROC, and the optimum values for sensitivity (78.9%) and
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6 specificity (70.9%). Additionally, the predictive value depends on a disease's prevalence in the
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8 population group that is being diagnosed ³¹. A good model must have sufficient prevalence,
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10 high sensitivity, and high specificity, and it should allow diagnosis before a patient displays
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12 symptoms ^{31, 32}.

17 **Strengths and limitations**

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19 The significant strength of our study is that it was the first multicenter study in Thailand to
20
21 evaluate the performance of a proposed predictive model for delirium in SICUs. The early
22
23 prediction of the development of delirium in ICU patients facilitates the implementation of
24
25 prevention protocols. These interventions can be non-pharmacological (such as cognitive
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27 stimulation, early mobilization, and enhanced sleep ^{33, 34} or pharmacological (like the
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29 prophylactic administration of dexmedetomidine ³⁵ to high-risk patients).

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33 Several limitations need to be addressed. Firstly, only the CAM-ICU was used to assess
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35 delirium. In the current work, the researchers (physicians and nurses) who evaluated delirium
36
37 using this tool were well-trained, and their ratings are therefore regarded as accurate. However,
38
39 other research showed that the accuracies of delirium assessments performed by bedside nurses
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41 in daily practice demonstrated lower sensitivity and specificity than our clinical researchers
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43 achieved ³⁶. The skill level of staff undertaking assessments in a clinical setting may therefore
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45 influence the results of the predictive model. In addition, the internal validation cohort only
46
47 included critically ill elderly patients. The optimum cutoff value that resulted in the best
48
49 sensitivity and specificity might be different from the all-validation and development cohorts.
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51 Moreover, differences in risk factors might affect the predictive model. We did not perform a
52
53 logistic regression for the validation cohort in order to identify independent risk factors for
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55 delirium. This is because the prognostic ability demonstrated by the AUROC of the internal
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3 and external validation groups showed moderate-to-good performance. Lastly, the predictive
4 model only used parameters available at the time of SICU admission. Any changes in patients'
5 conditions during their stay can affect the probability of their developing delirium. Our model
6 did not account for such changes.
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14 **CONCLUSIONS**

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17 The model reported in this study can predict which critically ill surgical patients will develop
18 POD in SICUs. Consequently, high-risk patients can be identified, and both non-
19 pharmacological and pharmacological prevention protocols can be implemented to improve
20 the clinical outcomes. The use of this selective strategy is appropriate in a resource-limited
21 country, in which the administration of a prevention protocol for all critically-ill patients is not
22 viable.
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Contributions

OC and AS contributed to the design of the study. OC, KC and S. Morakul were involved in data management and oversaw the project. KC, S. Mueankwan, S. Morakul, PD, contributed to data collection. CT contributed to data analysis. OC and CT contributed to the interpretation of the results and drafting the manuscript. All authors read and approved the final manuscript.

Funding

This study was supported by the Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand (IO: R016132015). The funders had no role in study design, data collection, and analysis, decision to publish, or preparation of the manuscript.

Competing interests

The authors declare that they have no competing interests.

Data availability statement

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics statements

Patient consent for publication

Not applicable.

Ethics approval

This study was conducted according to the ethical standards established by the 1964 Declaration of Helsinki. The study was approved by the Siriraj Institutional Review Board of the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand (Si 623/2017, Chairperson Prof. Chairat Shayakul, M.D.) on 20 October 2017; the Committee on Human Rights Related to Research Involving Human Subjects, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand (MURA 2017/574, Chairperson Asst. Prof. Chusak Okascharoen, M.D.) on 27 November 2017; and Research Ethics Committee 4 at the Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand (SUR-2560-05016, Chairperson Emeritus Prof. Panja Kulapongs, M.D.) on 28 November 2017. Written informed consent was obtained from the participants before their entry into the study. The trial was registered with the Thai Clinical Trials Registry (TCTR20180105001).

Acknowledgements

The authors gratefully acknowledge the patients who generously agreed to participate in this

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2
3 study, and Assist. Prof. Dr. Chulaluk Komoltri, M.P.H. Biostatistics, for the statistical analyses.
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Table 1. Characteristics of participating hospitals

Participating hospital	Institution	ICU beds for adults	ICU population	CAM-ICU screenings
Siriraj Hospital	Faculty of Medicine Siriraj Hospital, Mahidol University	14 beds	Surgery	2/day; IRR > 0.8
Ramathibodi Hospital	Faculty of Medicine Ramathibodi Hospital, Mahidol University	12 beds	Surgery	2/day; IRR > 0.8
Maharaj Nakorn Chiang Mai Hospital	Faculty of Medicine, Chiang Mai University	7 beds	Surgery	2/day; IRR not measured

Abbreviations: CAM, Confusion Assessment Method; ICU, intensive care unit; IRR, inter-rater reliability expressed as Cohen's κ

Table 2. Characteristics of patients in development and validation groups

Variable	Development (n = 250)	Internal validation (n = 150)	External validation (n = 230)	All validation (n = 380)
Demographic data				
Age (years)	64.2 ± 16.4	75.1 ± 7.5	56.9 ± 17.3	64.1 ± 16.8
Sex; male	121 (48.4%)	84 (56.0%)	128 (55.7%)	212 (55.8%)
Comorbidities				
Hypertension	155 (62.0%)	101 (67.3%)	109 (47.4%)	210 (55.3%)
DM	63 (25.2%)	41 (27.3%)	49 (21.3%)	90 (23.7%)
Cardiac disease	64 (25.6%)	37 (24.7%)	33 (14.3%)	70 (18.4%)
ESRD or CKD stage 4–5	34 (13.6%)	30 (20.0%)	75 (32.6%)	105 (27.6%)
Modified IQCODE score ≥ 3.42	16 (6.4%)	20 (13.3%)	27 (11.7%)	47 (12.4%)
Current alcohol consumption	17 (6.8%)	12 (8.0%)	41 (17.8%)	53 (13.9%)
Incidence of delirium	61 (24.4%)	60 (40.0%)	49 (21.3%)	109 (28.7%)
Type of delirium				
Hypoactive	44 (72%)	16 (26.7%)	26 (11.3%)	42 (11.1%)
Hyperactive	9 (15%)	17 (28.3%)	6 (2.6%)	23 (6.1%)
Mixed	8 (13%)	27 (45%)	17 (7.4%)	44 (11.6%)
Intraoperative data				
Emergency surgery	108 (43.2%)	64 (42.7%)	73 (31.7%)	137 (36.1%)
Type of surgery				
Vascular	52 (20.8%)	43 (28.7%)	26 (11.3%)	69 (18.2%)
Intra-abdominal	88 (35.2%)	79 (52.7%)	81 (35.2%)	160 (42.1%)
Orthopedic	29 (11.6%)	8 (5.3%)	10 (4.3%)	18 (4.7%)
Gynecological	26 (10.4%)	1 (0.7%)	4 (1.7%)	5 (1.3%)
Other	55 (22.0%)	19 (12.7%)	109 (47.4%)	128 (33.7%)
Hypoxia	10 (4.0%)	8 (5.3%)	2 (0.9%)	10 (2.6%)
Intraoperative hypotension	196 (78.4%)	127 (84.7%)	93 (40.4%)	220 (57.9%)
ICU admission				
Sepsis	61 (24.4%)	39 (26.0%)	30 (13.0%)	69 (18.2%)
APACHE II score	9 (6–11)	14 (11–19)	12 (8–17)	12 (9–17)
SOFA score	3 (2–6)	4 (3–6)	4 (1–6)	4 (2–6)
Mechanical ventilation	185 (74.0%)	126 (84.0%)	153 (66.5%)	279 (73.4%)
Medication				
Benzodiazepine	63 (25.2%)	19 (12.7%)	19 (8.3%)	38 (10.0%)
Opioid	244 (97.6%)	140 (93.3%)	203 (88.3%)	343 (90.3%)

Data are presented as mean ± SD, median (IQR), or n (%).

Abbreviations: APACHE II score, Acute Physiology and Chronic Health Evaluation II score; CKD, chronic kidney disease; DM, diabetes mellitus; ESRD, end state renal disease; Modified IQCODE, Modified Informant Questionnaire on Cognitive Decline in the Elderly; SOFA score, Sequential Organ Failure Assessment score

Table 3. Cutoff values of the Delirium Prediction Score

Cutoff value	Development (n = 250)		J	Internal validation (n = 150)		J	External validation (n = 230)		J	All validation (n = 380)		J
	Sensitivity (95% CI)	Specificity (95% CI)		Sensitivity (95% CI)	Specificity (95% CI)		Sensitivity (95% CI)	Specificity (95% CI)		Sensitivity (95% CI)	Specificity (95% CI)	
≥ 100	95.1% (86.3–99.0)	50.3% (42.9–57.6)	0.45	100.0% (94.0–100.0)	21.1% (13.2–31.0)	0.21	87.8% (75.2–95.4)	64.6% (57.2–71.6)	0.5	94.5% (88.4–98.0)	50.2% (44.1–56.3)	0.45
≥ 105	90.2% (79.8–96.3)	56.1% (48.7–63.3)	0.46	96.7% (88.5–99.6)	27.8% (18.9–38.2)	0.25	79.6% (65.7–89.8)	66.7% (59.5–73.7)	0.4	89.0% (81.6–94.2)	53.9% (47.7–59.9)	0.43
≥ 110	83.6% (71.9–91.9)	63.0% (55.7–69.9)	0.47	90.0% (79.5–96.2)	34.4% (24.7–45.2)	0.24	75.5% (61.1–86.7)	75.1% (68.2–81.3)	0.5	83.5% (75.2–89.9)	61.6% (55.6–67.4)	0.45
≥ 115	78.7% (66.3–88.1)	70.4% (63.3–76.8)	0.49	86.7% (75.4–94.1)	50.0% (39.3–60.7)	0.37	69.4% (54.6–81.8)	81.2% (74.8–86.7)	0.5	78.90% (70.0–86.1)	70.9% (65.1–76.2)	0.50
≥ 120	75.4% (62.7–85.5)	74.1% (67.2–80.2)	0.50	83.3% (71.5–91.7)	60.0% (49.1–70.2)	0.47	61.2% (46.2–74.8)	86.2% (80.3–90.9)	0.4	73.3% (64.1–81.4)	77.5% (72.1–82.3)	0.50
≥ 125	72.1% (59.2–82.9)	81.0% (74.6–86.3)	0.53	78.3% (65.8–87.9)	68.9% (58.3 to 78.2)	0.47	55.1% (40.2–69.3)	90.1% (84.7–94.0)	0.4	67.9% (58.3–76.5)	83.0% (78.0–87.3)	0.50
≥ 130	67.2% (54.0–78.7)	87.3% (81.7–91.7)	0.54	61.7% (48.2–73.9)	72.2% (61.8 to 81.2)	0.34	46.9% (32.5–61.7)	93.4% (88.7–96.5)	0.4	55.1% (45.2–64.6)	86.4% (81.7–90.2)	0.42

Abbreviation: J, Youden's index

Figure legends

Figure 1. Flowchart of development and validation studies

Figure 2. Receiver operating characteristic (ROC) curves and calculated areas under the curve (AUC)

(A) Development study of the delirium predictive score

(B) Internal validation study of the delirium predictive score

(C) External validation study of the delirium predictive score

(D) All validation study of the delirium predictive score

Figure 3. Calibration plot of pooled data

(A) Internal validation study of the delirium predictive score (n=150)

(B) External validation study of the delirium predictive score (n=230)

(C) All validation study of the delirium predictive score (n=380)

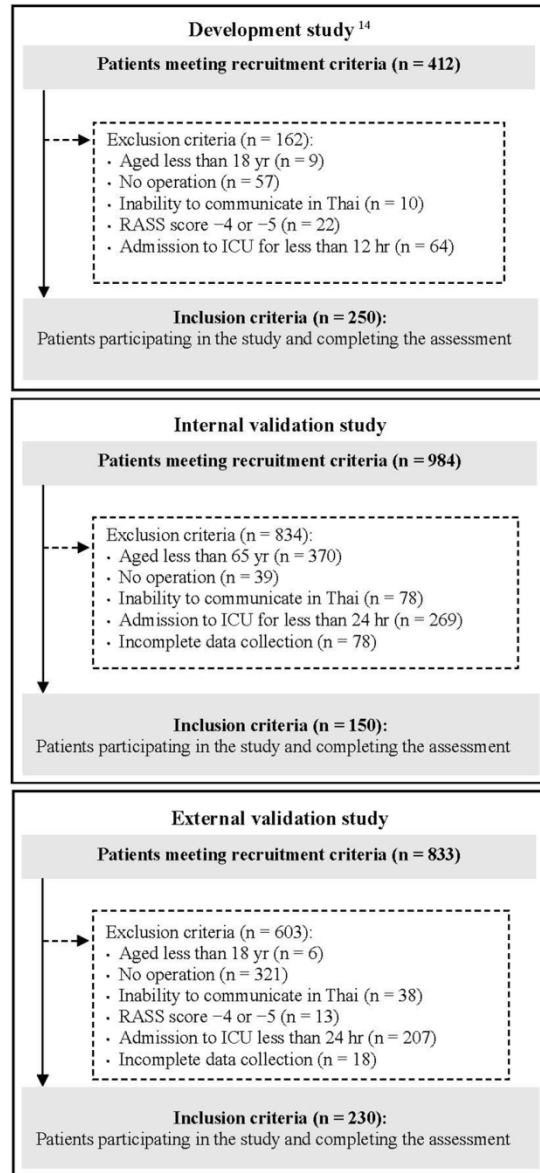


Figure 1

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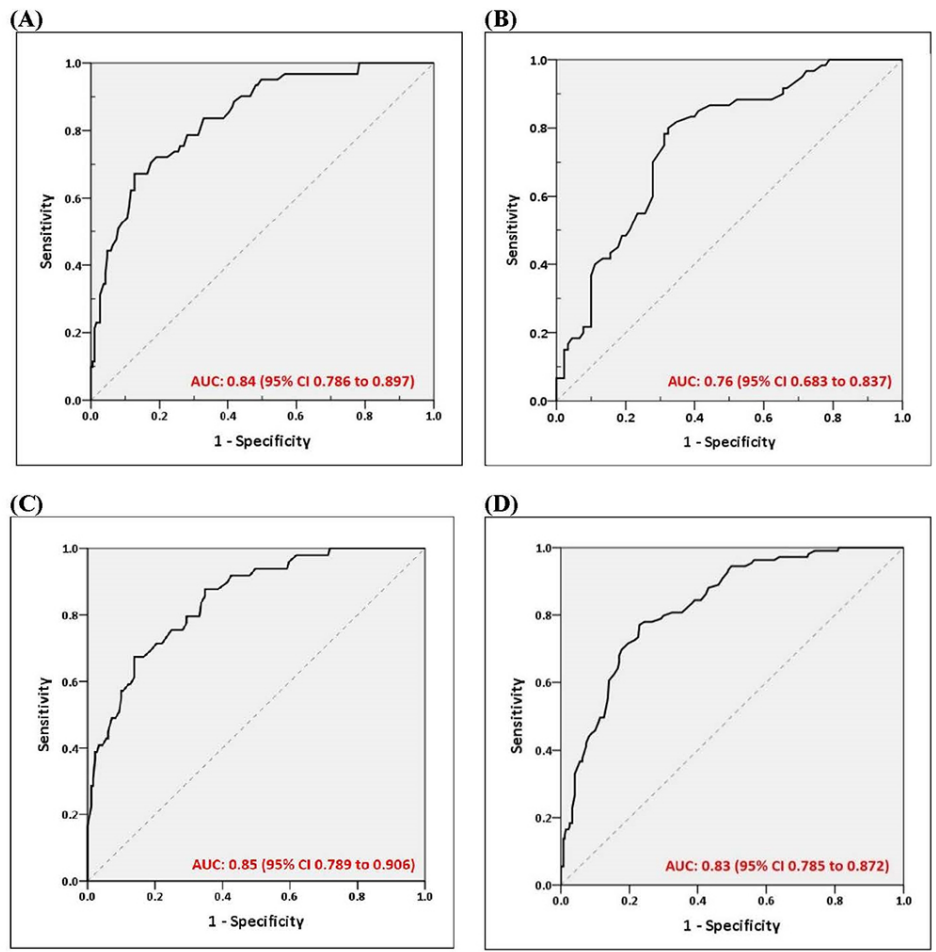


Figure 2

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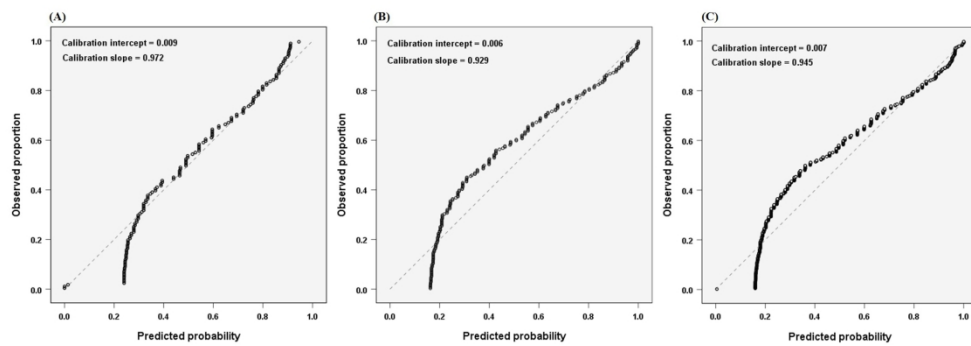


Figure 3

241x90mm (300 x 300 DPI)

TRIPOD Checklist: Prediction Model Validation

Section/Topic	Item	Checklist Item	Page
Title and abstract			
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	2
Introduction			
Background and objectives	3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	4
	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	6
Methods			
Source of data	4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	7
	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	7
Participants	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	7
	5b	Describe eligibility criteria for participants.	7
	5c	Give details of treatments received, if relevant.	
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	8-10
	6b	Report any actions to blind assessment of the outcome to be predicted.	
Predictors	7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	5, 8
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	
Sample size	8	Explain how the study size was arrived at.	
Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	
Statistical analysis methods	10c	For validation, describe how the predictions were calculated.	10
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	10-11
	10e	Describe any model updating (e.g., recalibration) arising from the validation, if done.	
Risk groups	11	Provide details on how risk groups were created, if done.	
Development vs. validation	12	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	10-11
Results			
Participants	13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	12, Fig 1
	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	12
	13c	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	13
Model performance	16	Report performance measures (with CIs) for the prediction model.	13
Model-updating	17	If done, report the results from any model updating (i.e., model specification, model performance).	
Discussion			
Limitations	18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	17
Interpretation	19a	For validation, discuss the results with reference to performance in the development data, and any other validation data.	15-16
	19b	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	17
Implications	20	Discuss the potential clinical use of the model and implications for future research.	17-18
Other information			
Supplementary information	21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	
Funding	22	Give the source of funding and the role of the funders for the present study.	19

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BMJ Open

Validation of a delirium predictive model in patients admitted to surgical intensive care units: a multicenter prospective observational cohort study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-057890.R1
Article Type:	Original research
Date Submitted by the Author:	01-Apr-2022
Complete List of Authors:	Chaiwat, Onuma; Mahidol University Faculty of Medicine Siriraj Hospital, Department of Anesthesiology; Mahidol University Faculty of Medicine Siriraj Hospital, Integrated Perioperative Geriatric Excellent Research Center Chittawatanarat, Kaweesak ; Chiang Mai University Faculty of Medicine, Department of Surgery; Chiang Mai University Faculty of Medicine, Clinical surgical research center Mueankwan, Sirirat ; Chiang Mai University Faculty of Medicine, Surgical critical care unit, Department of Surgery Morakul, Sunthiti ; Mahidol University Faculty of Medicine Ramathibodi Hospital, Department of Anesthesiology Dilokpattanamongkol, Pitchaya ; Mahidol University Faculty of Pharmacy, Department of Pharmacy Thanakiattiwibun, Chayanan ; Mahidol University Faculty of Medicine Siriraj Hospital, Integrated Perioperative Geriatric Excellent Research Center Siriussawakul, Arunotai; Mahidol University Faculty of Medicine Siriraj Hospital, Department of Anesthesiology; Mahidol University Faculty of Medicine Siriraj Hospital, Integrated Perioperative Geriatric Excellent Research Center
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Intensive care
Keywords:	Adult intensive & critical care < ANAESTHETICS, INTENSIVE & CRITICAL CARE, Delirium & cognitive disorders < PSYCHIATRY

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4 1 **Validation of a delirium predictive model in patients admitted to surgical**
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6 2 **intensive care units: a multicenter prospective observational cohort study**
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9 3

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2
3 **17 Abstract**
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7 **18 Objective** To internally and externally validate a delirium predictive model for adult patients
8
9 admitted to intensive care units (ICUs) following surgery.
10

11 **20 Design** A prospective, observational, multicenter study.
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13 **21 Setting** Three university-affiliated teaching hospitals in Thailand.
14

15 **22 Participants** Adults aged over 18 years were enrolled if they were admitted to a surgical ICU
16
17 (SICU) and had the surgery within 7 days before SICU admission.
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19

20 **24 Main outcome measures** Postoperative delirium was assessed using the Thai version of the
21
22 CAM-ICU. The assessments commenced on the first day after the patient's operation and
23
24 continued for 7 days, or until either discharge from the ICU or the death of the patient.
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26

27 Validation was performed of the previously developed delirium predictive model: Age + (5 ×
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29 SOFA) + (15 × benzodiazepine use) + (20 × DM) + (20 × mechanical ventilation) + (20 ×
30
31 modified IQCODE > 3.42).
32
33

34 **30 Results** In all, 380 SICU patients were recruited. Internal validation on 150 patients with the
35
36 mean age of 75 ± 7.5 year resulted in an area under a receiver operating characteristic curve
37
38 (AUROC) of 0.76 (0.683 to 0.837). External validation on 230 patients with the mean age of
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40 57 ± 17.3 year resulted in an AUROC of 0.85 (0.789 to 0.906). The AUROC of all validation
41
42 cohorts was 0.83 (0.785 to 0.872). The optimum cutoff value to discriminate between a high
43
44 and low probability of postoperative delirium in SICU patients was 115. This cutoff offered
45
46 the highest value for Youden's index (0.50), the best AUROC, and the optimum values for
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48 sensitivity (78.9%) and specificity (70.9%).
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52 **38 Conclusions** The model developed by the previous study was able to predict the occurrence
53
54 of postoperative delirium in critically ill surgical patients admitted to SICUs.
55
56

57 **40 Registration:** Thai Clinical Trial Registry (TCTR ID: TCTR20180105001), 05 January 2018
58

59 **41 Keywords:** postoperative delirium, predictive model, surgical intensive care units, validation
60

42 **Strengths and limitations of this study**

- 43 • The developed delirium predictive model consists of 6 risk factors was able to
44 predict the occurrence of postoperative delirium in critically ill surgical patients
- 45 • The internal and external validation demonstrated moderate to good statistical
46 performance, with the AUROC being comparable to that of the development
47 cohort
- 48 • The optimum cutoff value to discriminate between a high and low probability of
49 POD in SICU patients was 115

50

51 BACKGROUND

52 Delirium, a disturbance of consciousness, is both acute and fluctuating. Delirium is an
53 extremely common condition among hospitalized patients. Its incidence varies with the study
54 population, but higher rates are observed among geriatric, postsurgical, intensive care unit
55 (ICU), cardiac surgery, and hip-fracture patients ¹⁻⁴. Postoperative delirium (POD) among
56 patients who have been treated with surgery and anesthesia is typically found during the first 3
57 postoperative days ⁵. Although the POD can be transient, it is linked to poor outcomes. These
58 include long stays in postanesthesia care units (PACUs), ICUs, and hospitals; high medical-
59 complication rates; and raised mortality levels ⁶.

60 Several tools for assessing delirium have been validated. Among those is the Confusion
61 Assessment Method for the ICU (CAM-ICU), which shows high sensitivity and specificity ⁷.
62 The CAM-ICU has been translated into Thai, and it, too, has demonstrated good sensitivity and
63 specificity for critically ill patients ⁸. In Thailand, there are limited data relating to POD as well
64 as delirium among critically ill patients. Muangpaisan *et al.*, 2015 ⁹ reported the incidence of
65 delirium was 22.5% in hip surgery. Their investigation also identified the following risk
66 factors: age, premorbid function, dementia/cognitive impairment, the nonstop administration
67 of nonsteroidal anti-inflammatory drugs, and postoperative sedative use. Another study
68 reported a 44.0% prevalence of delirium among critically ill, old patients at a medical ICU in
69 northeastern Thailand. That work found that the independent factors related to delirium were
70 the use of physical restraints, a history of stroke, and multiple bed changes ¹⁰.

71 Given that delirium can result in poor clinical outcomes, predictions of its occurrence
72 among patients who are at risk of delirium are especially important. During the recent decade,
73 some predictive scoring systems for delirium have been proposed for use with various
74 populations. For instance, the PRE-DELIRC (PREdiction of DELIRium in ICU patients)
75 delirium risk prediction tool was developed for intensive care patients ¹¹. This model utilizes

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3 76 10 parameters. It had an area under a receiver operating characteristic curve (AUROC) of 0.87
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5 77 (95% confidence interval [CI], 0.85 to 0.89). Temporal validation and external validation
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7 78 resulted in an AUROC of 0.89 (0.86–0.92) and 0.84 (0.82–0.87), respectively ¹¹. Another tool,
8
9 79 the Risk Model for Delirium, assesses a number of predisposing risk factors for delirium in hip
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11 80 fracture patients. This model showed good intraclass correlation coefficient (0.77), sensitivity
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13 81 (80.4%), and AUROC (0.73) ¹². Furthermore, Kim *et al* developed the DELirium Prediction
14
15 82 based on Hospital Information (Delphi) system for general surgery patients. Delphi
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17 83 demonstrated good AUROCs for both the developed (0.91) and validated models (0.98) ¹³.
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19 84 Nevertheless, each of the above models was developed for specific application with medical
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21 85 critically ill, general surgical, or particular orthopedic patients, and the scoring systems tend to
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23 86 be overly complicated.

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28 87 The Siriraj Integrated Perioperative Geriatric (SIPG) Excellent Research Center has
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30 88 studied the incidence, risk factors, and predictive scores of POD in critically ill surgical
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32 89 patients. The independent risk factors for delirium identified by a multivariate analysis were
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34 90 age, diabetes mellitus, severity of disease (assessed by the sequential organ failure assessment
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36 91 [SOFA] score), perioperative use of benzodiazepine, mechanical ventilation and dementia
37
38 92 defined by the Thai version of the Modified Informant Questionnaire on Cognitive Decline in
39
40 93 the Elderly (modified IQCODE) scores > 3.42. The following predictive model was created:

$$\begin{aligned} & \text{Age} + (5 \times \text{SOFA}) + (15 \times \text{benzodiazepine use}) + (20 \times \text{DM}) + \\ & (20 \times \text{mechanical ventilation}) + (20 \times \text{modified IQCODE} > 3.42) \end{aligned}$$

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49 96 Its AUROC was 0.84 (95% CI, 0.786–0.897). A cutoff value of 125 demonstrated a sensitivity
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51 97 of 72.1% and a specificity of 80.9 ¹⁴. Thus, we were interested in validating the model. To this
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53 98 end, internal validation was performed at our hospital, while external validation was conducted
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55 99 at 2 other academic hospitals. There has been no previous investigation of a predictive model
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58 100 for POD in patients in surgical ICUs (SICUs). The aim of this study was to validate the use of
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101 the proposed POD predictive scoring tool in SICUs in order to identify patients who tend to
102 develop delirium.
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104 **METHODS**

105 **Design**

106 A prospective, observational, cohort study was conducted. The study was approved by the
107 Siriraj Institutional Review Board of the Faculty of Medicine Siriraj Hospital, Mahidol
108 University, Bangkok, Thailand (Si 623/2017, Chairperson Prof. Chairat Shayakul, M.D.) on
109 20 October 2017; the Committee on Human Rights Related to Research Involving Human
110 Subjects, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand
111 (MURA 2017/574, Chairperson Asst. Prof. Chusak Okascharoen, M.D.) on 27 November
112 2017; and Research Ethics Committee 4 at the Faculty of Medicine, Chiang Mai University,
113 Chiang Mai, Thailand (SUR-2560-05016, Chairperson Emeritus Prof. Panja Kulapongs,
114 M.D.) on 28 November 2017. Written informed consent was obtained from the participants
115 before their entry into the study. The trial was registered with the Thai Clinical Trials
116 Registry (TCTR20180105001).

118 **Study population**

119 The study was conducted on 380 SICU patients at 3 hospitals: Siriraj, Ramathibodi, and
120 Maharaj Nakorn Chiang Mai.

121 The study population comprised patients who were at least 18 years of age and were
122 admitted to a SICU within 7 days of surgery at Siriraj, Ramathibodi, or Maharaj Nakorn Chiang
123 Mai Hospital (Table 1). In addition, patients for the internal validation cohort were 65 years or
124 older and had been admitted to a Siriraj Hospital SICU^{15, 16} for a stay anticipated to exceed 24
125 hours. At all 3 hospitals, we excluded SICU patients who had (1) not undergone any operations;
126 (2) communication problems (unable to communicate in Thai, or having a severe visual or
127 auditory impairment interfering with communication); or (3) a Richmond Agitation Sedation
128 Scale (RASS) score of -4 or -5 during the whole of their ICU stay. A flowchart illustrating the

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3 129 patient selection processes for the development and validation cohorts is presented in Figure 1.
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8 131 **Patient and public involvement**
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10 132 No patient involved.
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15 134 **Measurement instruments**
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17 135 Delirium was assessed using the Thai version of the CAM-ICU (S1). Delirium was identified
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19 136 by the following 4 features: 1) a change or fluctuation in baseline mental status; 2) inattention;
20
21 137 and either 3) an altered level of consciousness; or 4) disorganized thinking¹⁷. The Thai version
22
23 138 has demonstrated satisfactory validity and reliability (specificity, 94.7%; sensitivity, 92.3%)⁸.
24
25 139 As to the level of consciousness, it was assessed by the RASS. It utilizes a 10-point scale
26
27 140 ranging from -5 to +4. The delirium subtypes were recorded as hypoactive (RASS -1 to -3),
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29 141 hyperactive (RASS +1 to +4), and mixed type (hypo- and hyperactive)¹⁸. With regard to
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31 142 dementia, it was evaluated via the Thai version of modified IQCODE (S2). The questionnaire
32
33 143 consists of 32 items, with assessments of patients being made by their caregivers. The optimal
34
35 144 cutoff score for the modified IQCODE is 3.42 (sensitivity, 90%; specificity, 95%; and
36
37 145 accuracy, 92%)¹⁹. Lastly, the severity of illness at SICU admission was evaluated using the
38
39 146 Acute Physiology and Chronic Health Evaluation II (APACHE II) scoring system, and SOFA
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41 147 scores.
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47 148 Patients provided informed consent in writing. Delirium was evaluated at least twice
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49 149 daily (once during the 12 hours from 6.00 AM, and once during the 12 hours after 6.00 PM),
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51 150 and whenever patients developed a mental change. Delirium was screened routinely utilizing a
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53 151 2-step process. Initially, the patients' level of consciousness was assessed using the RASS. If
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55 152 the score was between -3 and +4, the evaluators proceeded to Step 2 (assessment of the patient
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57 153 with the Thai version of CAM-ICU). However, if Step 1 produced a -4 RASS score (responsive
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3 154 only to physical stimulus) or a -5 RASS score (unresponsive to physical and verbal stimulus),
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5 155 Step 2 was not performed. If a patient was found to be sedated in the first step, the dose of the
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8 156 sedative medication was adjusted. The patient was later assessed with the CAM-ICU once a
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10 157 RASS score of -3 or higher was achieved.

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12 158 The second step involved the determination of the patient's delirium level using the Thai
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14 159 version of CAM-ICU, employing standard methodology. The assessments commenced on the
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17 160 first day after the patient's operation and continued for 7 days, or until either discharge from
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19 161 the ICU or the death of the patient. Patients with delirium were further assessed until the CAM-
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21 162 ICU was negative for 24 hours. Thereafter, the ICU attending physician was notified for further
22
23 163 management.

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25

26 165 **Data collection**

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29 166 The predisposing and precipitating factors potentially linked to the onset of delirium were
30
31 167 grouped as preoperative, intraoperative, and postoperative variables. The preoperative risk
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33 168 factors were demographic variables obtained from a review of an individual patient's medical
34
35 169 records and interviews with any proxies. Each patient's cognitive status was measured using
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37 170 the modified IQCODE¹⁹.

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39 171 The intraoperative variables were obtained from anesthetic records. They consisted of
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41 172 the surgical type (abdominal, vascular, orthopedic, urological, gynecological, and head and
42
43 173 neck); admission type (emergency or elective); operation time; intraoperative blood loss;
44
45 174 amount of blood transfused; and total fluid intake. Intraoperative hypotension was deemed to
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47 175 be either a systolic pressure below 90 mmHg or the need to be treated with medications.^{20, 21}
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49 176 Intraoperative hypoxemia was defined as an oxygen saturation (derived from pulse oximetry)
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51 177 of below 90% for any duration.

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53 178 The postoperative variables were primarily obtained from the SICU data records. They
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3 179 were the use of mechanical ventilation, physical restraints, or a Foley's catheter; the presence
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5 180 of sleep deprivation or shock; exposure to psychoactive drugs (benzodiazepines, opioids, and
6
7 181 sedatives); and the presence of coma (indicated by a RASS score of -4 or -5).
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10 182

11 12 183 **Preparation of research team**

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14 184 The clinical researchers administering the Thai CAM-ICU were physicians and nurses who had
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16
17 185 been trained by the principal investigator. To ensure reliability among the assessors, inter-rater
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19 186 reliability scores were calculated. Once their kappa score reached 0.8, the trained physicians
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21 187 and nurses were permitted to perform the Thai CAM-ICU assessments.
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25 26 189 **Internal and external validation**

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28 190 After development of a predictive model from a prospective cohort study that took place
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30 191 between February 2016 and February 2017, we did a second prospective cohort study in the
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32
33 192 same hospital for internal validation of the model between April 2018 and December 2019. In
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35 193 the meantime, we externally validated the predictive model with data from intensive care
36
37 194 surgical patients admitted to 2 other university hospitals in Thailand. They were Ramathibodi
38
39 195 Hospital, Mahidol University, and Maharaj Nakorn Chiang Mai Hospital, Chiang Mai
40
41 196 University. Trained intensive care nurses at those hospitals used the CAM-ICU at least twice
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43
44 197 daily. The validation process was conducted according to the Transparent Reporting of a
45
46 198 multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) Statement²²,
47
48
49 199 a guideline specifically designed for the reporting of studies developing or validating a
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51 200 multivariable prediction model, whether for diagnostic or prognostic purposes.
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55 56 202 **Statistical analysis**

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58 203 The sample size was estimated based on the reported 78% accuracy of development predictive
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3 204 score.¹⁴ Based on the estimated accuracy of 80% ($p=0.80$) and a 4% error ($d = 0.04$), an 5%
4
5 205 alpha ($\alpha = 0.05$), the sample size of 380 cases was calculated.
6

7
8 206 Demographic variables are presented as mean \pm standard deviation or median (interquartile
9
10 207 range [IQR]) for continuous data, and frequency and percentage for categorical data.
11

12 208 In both validation studies, we multiplied regression coefficients for each risk factor in the
13
14 209 predictive model by the observed patients' values. The outcome was a calculated predicted
15
16 210 probability, on which we built a new AUROC. Finally, an ROC curve was plotted to determine
17
18 211 the best cutoff in terms of Youden's index, sensitivity, specificity, and 95% CI. The Youden's
19
20 212 index was the difference between the true and the false positive rates. Maximizing this index
21
22 213 allows an optimal cutoff value to be found from the ROC curve, independently from the
23
24 214 prevalence^{23, 24}. Finally, to examine how well the model was calibrated, we calculated linear
25
26 215 predictor values for each patient of every cohort by using the coefficients from the model. We
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28 216 used these linear predictors in a logistic regression model to test whether the prediction rule
29
30 217 was well calibrated, resulting in a calibration slope and an intercept. A calibration slope of 1
31
32 218 and an intercept of 0 show a perfect calibration^{25, 26}. Statistics were analyzed using PASW
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34 219 Statistics for Windows (version 18; SPSS Inc., Chicago, IL, USA); and MedCalc statistical
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36 220 software (version 17.6; MedCalc Software BVBA, Ostend, Belgium).
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222 RESULTS

223 Patients

224 The patients were enrolled between February 2016 and February 2017¹⁴ for the development
225 cohort, and between April 2018 and December 2019 for the internal and external validation
226 studies. In all, 1,437 SICU patients were excluded for the reasons given in Figure. 1, and 380
227 were recruited. The mean age of the patients in the internal validation cohort was 75.1 ± 7.5
228 years, while the mean for the patients in the external validation cohort was 56.9 ± 17.3 years.
229 The mean age of all of the patients in the 2 validation cohorts was 64.1 ± 16.8 years. More than
230 half of the patients in the validation cohort were males. Details relating to the demographic and
231 intraoperative data, ICU admission, and the medications used are given in Table 2. There was
232 a higher proportion of patients with hypertension, diabetes mellitus (DM), and cardiac disease
233 in the internal validation cohort than the external validation cohort. The incidence of delirium
234 was 40.0%, 21.3%, and 28.7% in the internal, external, and all validation cohorts, respectively,
235 compared with 24.4% in the development cohort. The majority of patients in all cohorts
236 underwent intra-abdominal surgery. The median SOFA score was 4 (IQR 1–6) for all validation
237 cohorts, which was higher than the median of 3 (IQR 2–6) for the development cohort. The
238 percentage of benzodiazepine use in the development cohort (10% vs. 25.2%; Table 2).

239

240 Development study

241 Of the 412 recruited patients, a total of 162 were excluded for the reasons detailed in Figure.
242 1. As a result, 250 patients were enrolled, 61 of whom (24.4%) developed delirium (Table 2).
243 The predictive model was derived from a multiple logistic regression that used significant risk
244 factors. The final formula required 6 factors (2 quantitative factors, and 4 binary factors). The
245 formula of the model was:

$$246 \text{Age} + (5 \times \text{SOFA}) + (15 \times \text{benzodiazepine use}) + (20 \times \text{DM}) +$$

247 (20 × mechanical ventilation) + (20 × modified IQCODE > 3.42)

248 The AUROC was 0.84 (95% CI, 0.786–0.897). The cutoff value of ≥ 125 demonstrated a
249 sensitivity of 72.1% and a specificity of 80.9%¹⁴.

250

251 **Validation study**

252 *Internal validation of predictive model*

253 For the prospective validation study, we recruited 984 consecutive patients who were aged over
254 65 years; however, 834 were subsequently excluded (Figure. 1). Of the remaining 150 patients,
255 60 (40%) developed delirium (Table 2). The internal validation resulted in an AUROC of 0.76
256 (0.683 to 0.837; Figure. 2A), and this AUROC was not significantly different from the AUROC
257 of the developed predictive model ($P = 0.092$), with a calibration slope of 0.972 and an intercept
258 of 0.009 (Figure. 2B).

259

260 *External validation of predictive model*

261 We performed the external validation study on critically ill surgical patients admitted to SICUs
262 at Ramathibodi and Maharaj Nakorn Chiang Mai Hospitals. Of the 833 recruited patients, 603
263 were excluded (Figure. 1). As a result, 230 patients were enrolled: 62 (27%) at Ramathibodi
264 Hospital, and 168 (73%) at Maharaj Nakorn Chiang Mai Hospital. The incidence of delirium
265 in the external validation cohort was 21% (Table 2). The external validation resulted in an
266 AUROC of 0.85 (0.789 to 0.906; Figure. 2C), and it was not significantly different from the
267 AUROC of the developed predictive model ($P = 0.865$), with a calibration slope of 0.929 and
268 an intercept of 0.006 (Figure. 2D).

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270 *Optimal cutoff value of predictive model*

271 The AUROCs of the development, internal, and external validation cohorts were comparable

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3 272 (0.84 for the development cohort, 0.76 for the internal validation cohort, and 0.85 for the
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5 273 external validation cohort). As no differences in prediction existed between the 3 validation
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7 274 studies, we pooled the data of all validation cohorts (n = 380). That revealed that 109 patients
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9 275 (29%) developed delirium (Table 2). Consequently, the AUROC of all of the validation cohorts
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11 276 was 0.83 (0.785 to 0.872; Figure. 2E). The recalibration of all validation study showed a
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13 277 calibration slope of 0.945 and an intercept of 0.007 (Figure 2F). The optimum cutoff value to
14
15 278 discriminate between a high and low probability of POD in SICU patients was 115. This cutoff
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17 279 presented the highest value of Youden's index (0.50), the best AUROC, and the optimum
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19 280 values for sensitivity (78.9%) and specificity (70.9%; Table 3). The last 2 values were similar
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21 281 to the sensitivity (78.8%) and specificity (70.4%) of the development cohort.
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283 DISCUSSION

284 Given the high costs of managing delirium and its consequential complications, it is essential
285 to identify individuals at high risk of developing the condition and to deliver evidenced-based
286 preventive measures. This multicenter-study demonstrated the performance of the internal and
287 external validation of a proposed model¹⁴ that had been developed to predict POD in patients
288 admitted postoperatively to an SICU. It is essential to confirm the predictive performance of
289 the model before its use outside the development setting. The external validation showed
290 moderate to good statistical performance, with the AUROC of the external cohort being
291 comparable to that of the development cohort. In addition, the new cutoff value also
292 demonstrated optimum sensitivity and specificity values that were equivalent to those achieved
293 for the development cohort. However, the performance of the internal validation cohort was
294 not as high as the development and external validation cohort (AUROC, 0.76). This was
295 because the internal validation cohort only included patients aged 65 years or older, resulting
296 in a higher incidence of delirium.

297 Recently, 2 ICU delirium predictive models—the early predictive model for ICU delirium
298 (E-PRE-DELIRIC), and the recalibrated predictive model for ICU delirium (PRE-DELIRIC)
299 have been developed and validated^{11, 27, 28}. These 2 models are currently used in clinical
300 practice and in research to predict the development of delirium in ICUs. The PRE-DELIRIC
301 model consists of 10 predictors that are available during the first 24 hours after admission to
302 an ICU²⁷. The E-PRE-DELIRIC is composed of 9 parameters available at time of ICU
303 admission. Wassenaar *et al.*, 2019²⁹ recently conducted an external validation of both
304 assessment tools, using either the CAM-ICU or the Intensive Care Delirium Screening
305 Checklist for delirium assessment. The researchers reported moderate-to-good statistical
306 performances. Nevertheless, the formulas for those 2 models were quite complicated, using
307 several parameters, and they were developed in a mixed-ICU setting (medical and surgical

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3 308 populations). Given that cognitive impairment (including dementia) and severity of illness have
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5 309 been recognized as strong predictors for delirium in hospitalized patients,^{30, 31} the E-PRE-
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7 310 DELIRIC system included only a history of cognitive impairment but no severity scores. In
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9 311 contrast, the PRE-DELIRIC model included only APACHE II scores, but no information on
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11 312 cognitive impairment.
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14 313 The currently proposed predictive model for POD in critically ill surgical patients has
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16 314 several strengths. Firstly, it was developed specifically for surgical patients, and it
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18 315 demonstrated high accuracy. In addition, it employs only 5 parameters, which makes it
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20 316 relatively easy to calculate. Furthermore, dementia is assessed by both the patient's history and
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22 317 the modified IQCODE assessment tool. A previous study found that the prevalence of dementia
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24 318 among elderly delirious patients was 5 times higher when evaluated by the modified IQCODE
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26 319 tool than when using information obtained solely from history taking³². Consequently, the
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28 320 proposed predictive model was validated in the same hospital and in 2 other academic hospitals.
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30 321 Although we recruited only elderly patients for the internal validation cohort, the AUROC
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32 322 showed an acceptable value. For the external validation cohort in the SICUs of the 2 other
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34 323 hospitals, we performed quality control by determining the inter-rater reliability of CAM-ICU
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36 324 assessment before commencing the study. There were differences in the patient case-mix of
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38 325 the external and development validation samples. In particular, relative to the development
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40 326 group, the external validation cohort had a lower age, a lower percentage of patients with
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42 327 mechanical ventilation, a higher percentage of dementia, and a lower percentage of
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44 328 benzodiazepine use. Despite that, the models' discriminative performance showed the same
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46 329 value (AUROC 0.84 for the development cohort, and 0.85 for the external validation cohort).
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48 330 In short, for the all-validation cohort, the AUROC was approximately the same as that for the
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50 331 development and the external validation cohorts. A score of ≥ 115 was the best cutoff value to
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52 332 predict the occurrence of delirium in SICUs. This cutoff presented the highest value for
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3 333 Youden's index (0.50), the best AUROC, and the optimum values for sensitivity (78.9%) and
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5 334 specificity (70.9%). Additionally, the predictive value depends on a disease's prevalence in the
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7 335 population group that is being diagnosed³³. A good model must have sufficient prevalence,
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9 336 high sensitivity, and high specificity, and it should allow diagnosis before a patient displays
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11 337 symptoms^{33, 34}.
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17 339 **Strengths and limitations**

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19 340 The significant strength of our study is that it was the first multicenter study in Thailand to
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21 341 evaluate the performance of a proposed predictive model for delirium in SICUs. The early
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23 342 prediction of the development of delirium in ICU patients facilitates the implementation of
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25 343 prevention protocols. These interventions can be non-pharmacological (such as cognitive
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27 344 stimulation, early mobilization, and enhanced sleep)^{35, 36} or pharmacological (like the
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29 345 prophylactic administration of dexmedetomidine³⁷ to high-risk patients).
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33 346 Several limitations need to be addressed. Firstly, only the CAM-ICU was used to assess
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35 347 delirium. In the current work, the researchers (physicians and nurses) who evaluated delirium
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37 348 using this tool were well-trained, and their ratings are therefore regarded as accurate. However,
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39 349 other research showed that the accuracies of delirium assessments performed by bedside nurses
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41 350 in daily practice demonstrated lower sensitivity and specificity than our clinical researchers
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43 351 achieved³⁸. The skill level of staff undertaking assessments in a clinical setting may therefore
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45 352 influence the results of the predictive model. In addition, the internal validation cohort only
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47 353 included critically ill elderly patients. The optimum cutoff value that resulted in the best
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49 354 sensitivity and specificity might be different from the all-validation and development cohorts.
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51 355 Moreover, differences in risk factors might affect the predictive model. We did not perform a
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53 356 logistic regression for the validation cohort in order to identify independent risk factors for
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55 357 delirium. This is because the prognostic ability demonstrated by the AUROC of the internal
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3 358 and external validation groups showed moderate-to-good performance. Lastly, the predictive
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5 359 model only used parameters available at the time of SICU admission. Any changes in patients'
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7 360 conditions during their stay can affect the probability of their developing delirium. Our model
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10 361 did not account for such changes.
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14 363 **CONCLUSIONS**

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18 364 The model reported in this study can predict which critically ill surgical patients will develop
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20 365 POD in SICUs. Consequently, high-risk patients can be identified, and both non-
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22 366 pharmacological and pharmacological prevention protocols can be implemented to improve
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24 367 the clinical outcomes. The use of this selective strategy is appropriate in a resource-limited
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26 368 country, in which the administration of a prevention protocol for all critically-ill patients is not
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29 369 viable.
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34
35 385 **Contributions**
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37 386 OC and AS contributed to the design of the study. OC, KC and S. Morakul were involved in
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39 data management and oversaw the project. KC, S. Mueankwan, S. Morakul, PD, contributed
40 387
41 to data collection. CT contributed to data analysis. OC and CT contributed to the
42 388
43 interpretation of the results and drafting the manuscript. All authors read and approved the
44 389
45 final manuscript.
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50 392 **Funding**
51

52 393 This study was supported by the Faculty of Medicine Siriraj Hospital, Mahidol University,
53
54 Thailand (IO: R016132015). The funders had no role in study design, data collection, and
55 394
56 analysis, decision to publish, or preparation of the manuscript.
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45 397 **Competing interests**6
7 398 The authors declare that they have no competing interests.
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12 400 **Data availability statement**13
14 401 The datasets used and analyzed during the current study are available from the corresponding
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16 author on reasonable request.
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21 404 **Ethics statements**22
23 405 **Patient consent for publication**24
25 406 Not applicable.
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30 408 **Ethics approval**31
32 409 This study was conducted according to the ethical standards established by the 1964
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34 Declaration of Helsinki. The study was approved by the Siriraj Institutional Review Board of
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36 the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand (Si
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38 411 623/2017, Chairperson Prof. Chairat Shayakul, M.D.) on 20 October 2017; the Committee on
39
40 412 Human Rights Related to Research Involving Human Subjects, Faculty of Medicine
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42 413 Ramathibodi Hospital, Mahidol University, Bangkok, Thailand (MURA 2017/574,
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44 414 Chairperson Asst. Prof. Chusak Okascharoen, M.D.) on 27 November 2017; and Research
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46 415 Ethics Committee 4 at the Faculty of Medicine, Chiang Mai University, Chiang Mai,
47
48 416 Thailand (SUR-2560-05016, Chairperson Emeritus Prof. Panja Kulapongs, M.D.) on 28
49
50 417 November 2017. Written informed consent was obtained from the participants before their
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52 418 entry into the study. The trial was registered with the Thai Clinical Trials Registry
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54 419 (TCTR20180105001).
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8 423 **Acknowledgements**9
10 424 The authors gratefully acknowledge the patients who generously agreed to participate in this
11
12 425 study, and Assist. Prof. Dr. Chulaluk Komoltri, M.P.H. Biostatistics, for the statistical analyses.
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17 427 **Supplemental file**18
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20 428 S1. Confusion Assessment method for the ICU (CAM-ICU) tool21
22 429 S2. Modified Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) tool
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543 **Table 1.** Characteristics of participating hospitals

Participating hospital	Institution	ICU beds for adults	ICU population	CAM-ICU screenings
Siriraj Hospital	Faculty of Medicine Siriraj Hospital, Mahidol University	14 beds	Surgery	2/day; IRR > 0.8
Ramathibodi Hospital	Faculty of Medicine Ramathibodi Hospital, Mahidol University	12 beds	Surgery	2/day; IRR > 0.8
Maharaj Nakorn Chiang Mai Hospital	Faculty of Medicine, Chiang Mai University	7 beds	Surgery	2/day; IRR not measured

544 Abbreviations: CAM, Confusion Assessment Method; ICU, intensive care unit; IRR, inter-rater reliability
 545 expressed as Cohen's κ

546

547 **Table 2.** Characteristics of patients in development and validation groups

Variable	Development (n = 250)	Internal validation (n = 150)	External validation (n = 230)	All validation (n = 380)
Demographic data				
Age (years)	64.2 ± 16.4	75.1 ± 7.5	56.9 ± 17.3	64.1 ± 16.8
Sex; male	121 (48.4%)	84 (56.0%)	128 (55.7%)	212 (55.8%)
Comorbidities				
Hypertension	155 (62.0%)	101 (67.3%)	109 (47.4%)	210 (55.3%)
DM	63 (25.2%)	41 (27.3%)	49 (21.3%)	90 (23.7%)
Cardiac disease	64 (25.6%)	37 (24.7%)	33 (14.3%)	70 (18.4%)
ESRD or CKD stage 4–5	34 (13.6%)	30 (20.0%)	75 (32.6%)	105 (27.6%)
Modified IQCODE score ≥ 3.42	16 (6.4%)	20 (13.3%)	27 (11.7%)	47 (12.4%)
Current alcohol consumption	17 (6.8%)	12 (8.0%)	41 (17.8%)	53 (13.9%)
Incidence of delirium	61 (24.4%)	60 (40.0%)	49 (21.3%)	109 (28.7%)
Type of delirium				
Hypoactive	44 (72%)	16 (26.7%)	26 (53.1%)	42 (38.5%)
Hyperactive	9 (15%)	17 (28.3%)	6 (12.2%)	23 (21.1%)
Mixed	8 (13%)	27 (45%)	17 (34.7%)	44 (40.4%)
Intraoperative data				
Emergency surgery	108 (43.2%)	64 (42.7%)	73 (31.7%)	137 (36.1%)
Type of surgery				
Vascular	52 (20.8%)	43 (28.7%)	26 (11.3%)	69 (18.2%)
Intra-abdominal	88 (35.2%)	79 (52.7%)	81 (35.2%)	160 (42.1%)
Orthopedic	29 (11.6%)	8 (5.3%)	10 (4.3%)	18 (4.7%)
Gynecological	26 (10.4%)	1 (0.7%)	4 (1.7%)	5 (1.3%)
Other	55 (22.0%)	19 (12.7%)	109 (47.4%)	128 (33.7%)
Hypoxia	10 (4.0%)	8 (5.3%)	2 (0.9%)	10 (2.6%)
Intraoperative hypotension	196 (78.4%)	127 (84.7%)	93 (40.4%)	220 (57.9%)
ICU admission				
Sepsis	61 (24.4%)	39 (26.0%)	30 (13.0%)	69 (18.2%)
APACHE II score	9 (6–11)	14 (11–19)	12 (8–17)	12 (9–17)
SOFA score	3 (2–6)	4 (3–6)	4 (1–6)	4 (2–6)
Mechanical ventilation	185 (74.0%)	126 (84.0%)	153 (66.5%)	279 (73.4%)
Medication				
Benzodiazepine	63 (25.2%)	19 (12.7%)	19 (8.3%)	38 (10.0%)
Opioid	244 (97.6%)	140 (93.3%)	203 (88.3%)	343 (90.3%)
Outcomes				
Duration of mechanical ventilation (days)	1 (0–4)	3 (1–7)	1 (0–3)	2 (1–4)
Nosocomial infection in ICU	29 (11.6%)	41 (27.3%)	4 (1.7%)	45 (11.8%)
ICU length of stay (days)	3 (2–5)	5 (3–10)	3 (3–6)	4 (3–7)
ICU mortality	9 (3.6%)	5 (3.3%)	5 (2.2%)	10 (2.6%)
Hospital length of stay (days)	16 (10–29)	20 (13–34)	16 (13–27)	18 (13–29)
Hospital mortality	26 (10.4%)	25 (16.7%)	13 (5.7%)	38 (10.0%)

548

549 Data are presented as mean ± SD, median (IQR), or n (%).

550 Abbreviations: APACHE II score, Acute Physiology and Chronic Health Evaluation II score; CKD, chronic

551 kidney disease; DM, diabetes mellitus; ESRD, end state renal disease; Modified IQCODE, Modified Informant

552 Questionnaire on Cognitive Decline in the Elderly; SOFA score, Sequential Organ Failure Assessment score

Table 3. Cutoff values of the Delirium Prediction Score

Cutoff value	Development (n = 250)		J	Internal validation (n = 150)		J	External validation (n = 230)		J	All validation (n = 380)		J
	Sensitivity (95% CI)	Specificity (95% CI)		Sensitivity (95% CI)	Specificity (95% CI)		Sensitivity (95% CI)	Specificity (95% CI)		Sensitivity (95% CI)	Specificity (95% CI)	
≥ 100	95.1% (86.3–99.0)	50.3% (42.9–57.6)	0.45	100.0% (94.0–100.0)	21.1% (13.2–31.0)	0.21	87.8% (75.2–95.4)	64.6% (57.2–71.6)	0.50	94.5% (88.4–98.0)	50.2% (44.1–56.3)	0.45
≥ 105	90.2% (79.8–96.3)	56.1% (48.7–63.3)	0.46	96.7% (88.5–99.6)	27.8% (18.9–38.2)	0.25	79.6% (65.7–89.8)	66.7% (59.5–73.7)	0.44	89.0% (81.6–94.2)	53.9% (47.7–59.9)	0.43
≥ 110	83.6% (71.9–91.9)	63.0% (55.7–69.9)	0.47	90.0% (79.5–96.2)	34.4% (24.7–45.2)	0.24	75.5% (61.1–86.7)	75.1% (68.2–81.3)	0.50	83.5% (75.2–89.9)	61.6% (55.6–67.4)	0.45
≥ 115	78.7% (66.3–88.1)	70.4% (63.3–76.8)	0.49	86.7% (75.4–94.1)	50.0% (39.3–60.7)	0.37	69.4% (54.6–81.8)	81.2% (74.8–86.7)	0.50	78.90% (70.0–86.1)	70.9% (65.1–76.2)	0.50
≥ 120	75.4% (62.7–85.5)	74.1% (67.2–80.2)	0.50	83.3% (71.5–91.7)	60.0% (49.1–70.2)	0.47	61.2% (46.2–74.8)	86.2% (80.3–90.9)	0.47	73.3% (64.1–81.4)	77.5% (72.1–82.3)	0.50
≥ 125	72.1% (59.2–82.9)	81.0% (74.6–86.3)	0.53	78.3% (65.8–87.9)	68.9% (58.3 to 78.2)	0.47	55.1% (40.2–69.3)	90.1% (84.7–94.0)	0.44	67.9% (58.3–76.5)	83.0% (78.0–87.3)	0.50
≥ 130	67.2% (54.0–78.7)	87.3% (81.7–91.7)	0.54	61.7% (48.2–73.9)	72.2% (61.8 to 81.2)	0.34	46.9% (32.5–61.7)	93.4% (88.7–96.5)	0.47	55.1% (45.2–64.6)	86.4% (81.7–90.2)	0.42

Abbreviation: J, Youden's index

Figure legends

Figure 1. Flowchart of development and validation studies

Figure 2. Receiver operating characteristic (ROC) curves and calculated areas under the curve (AUC), and Calibration plot of pooled data;

(A and B) Internal validation study of the delirium predictive score

(C and D) External validation study of the delirium predictive score

(E and F) All validation study of the delirium predictive score

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Figure 1. Flowchart of development and validation studies

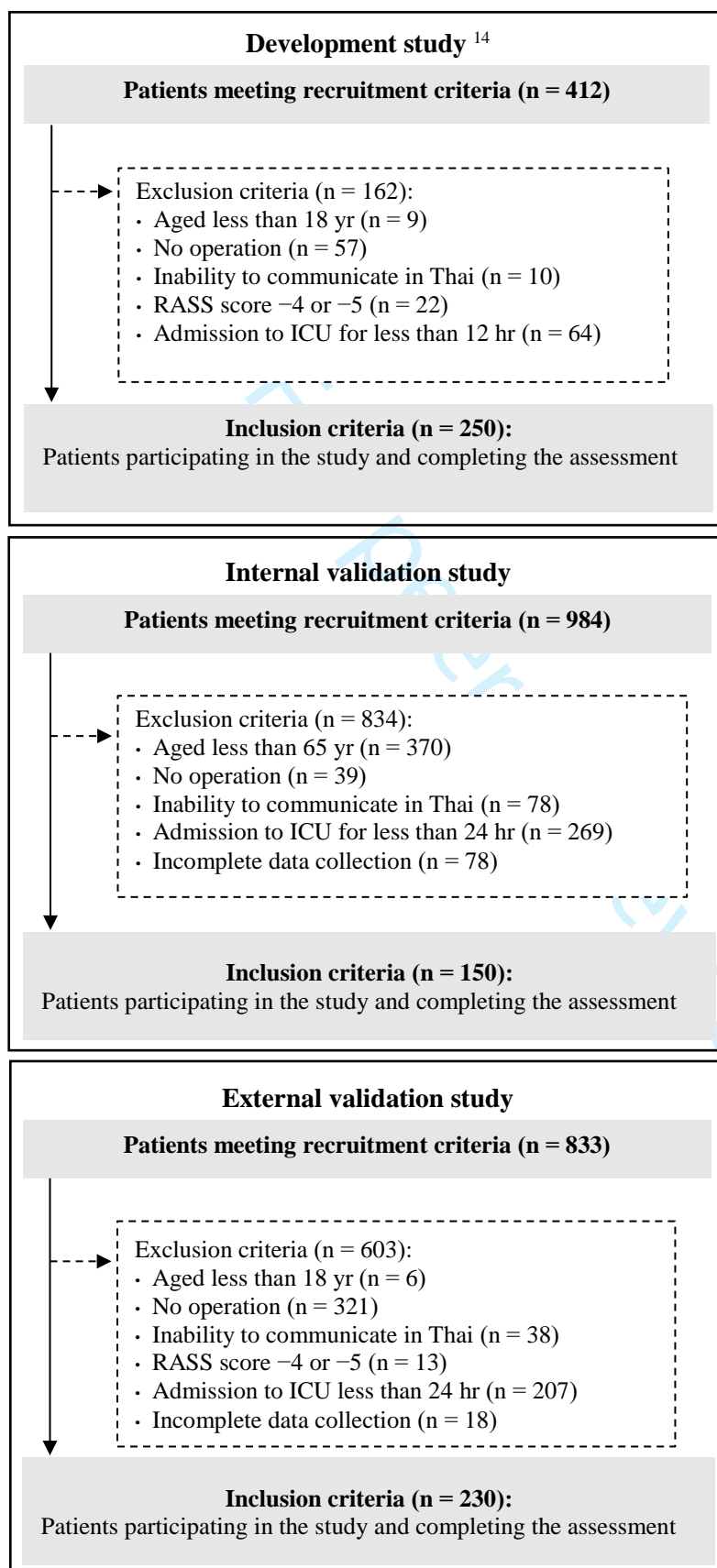
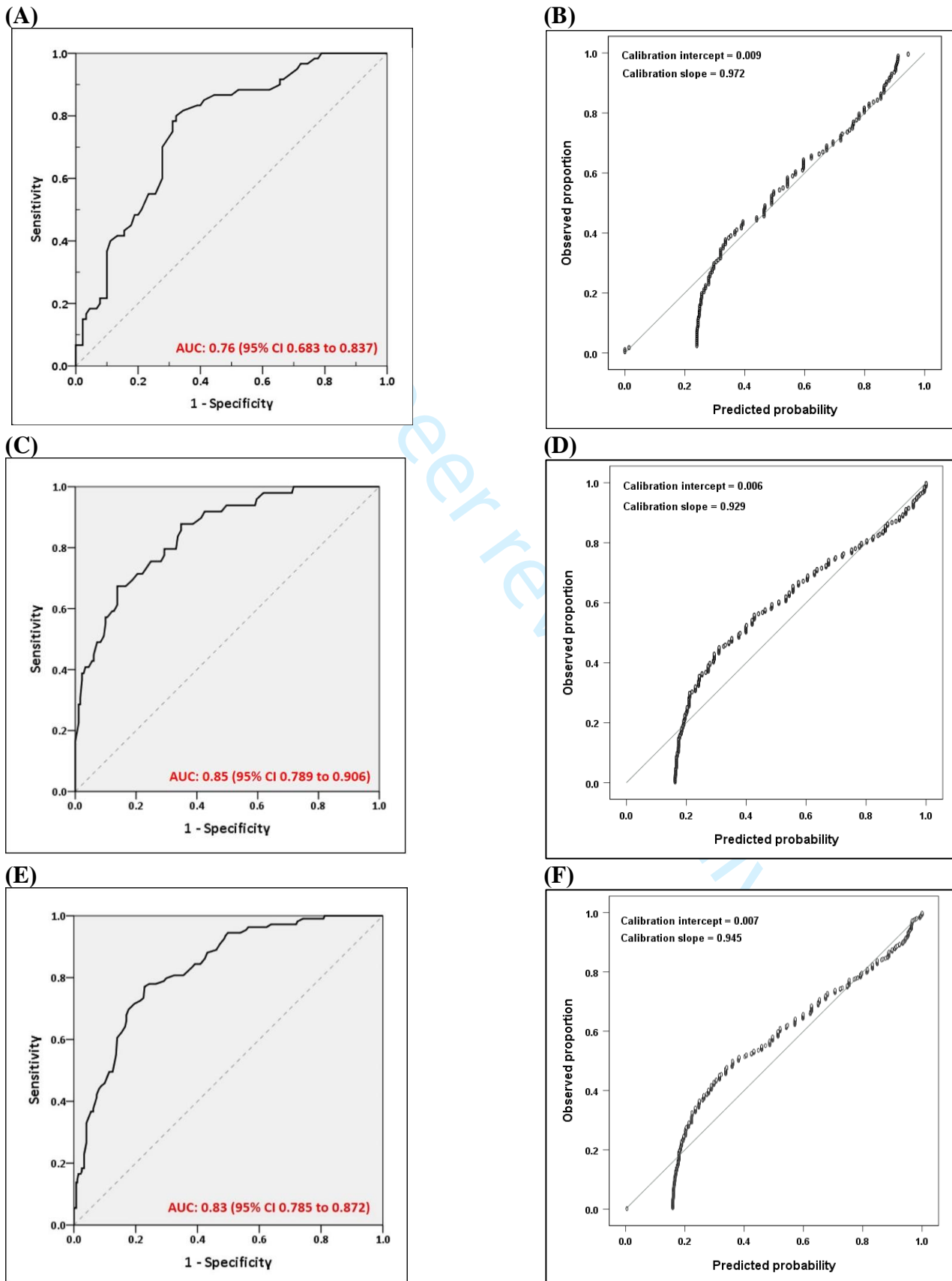


Figure 2. Receiver operating characteristic (ROC) curves and calculated areas under the curve (AUC), and Calibration plot of pooled data;

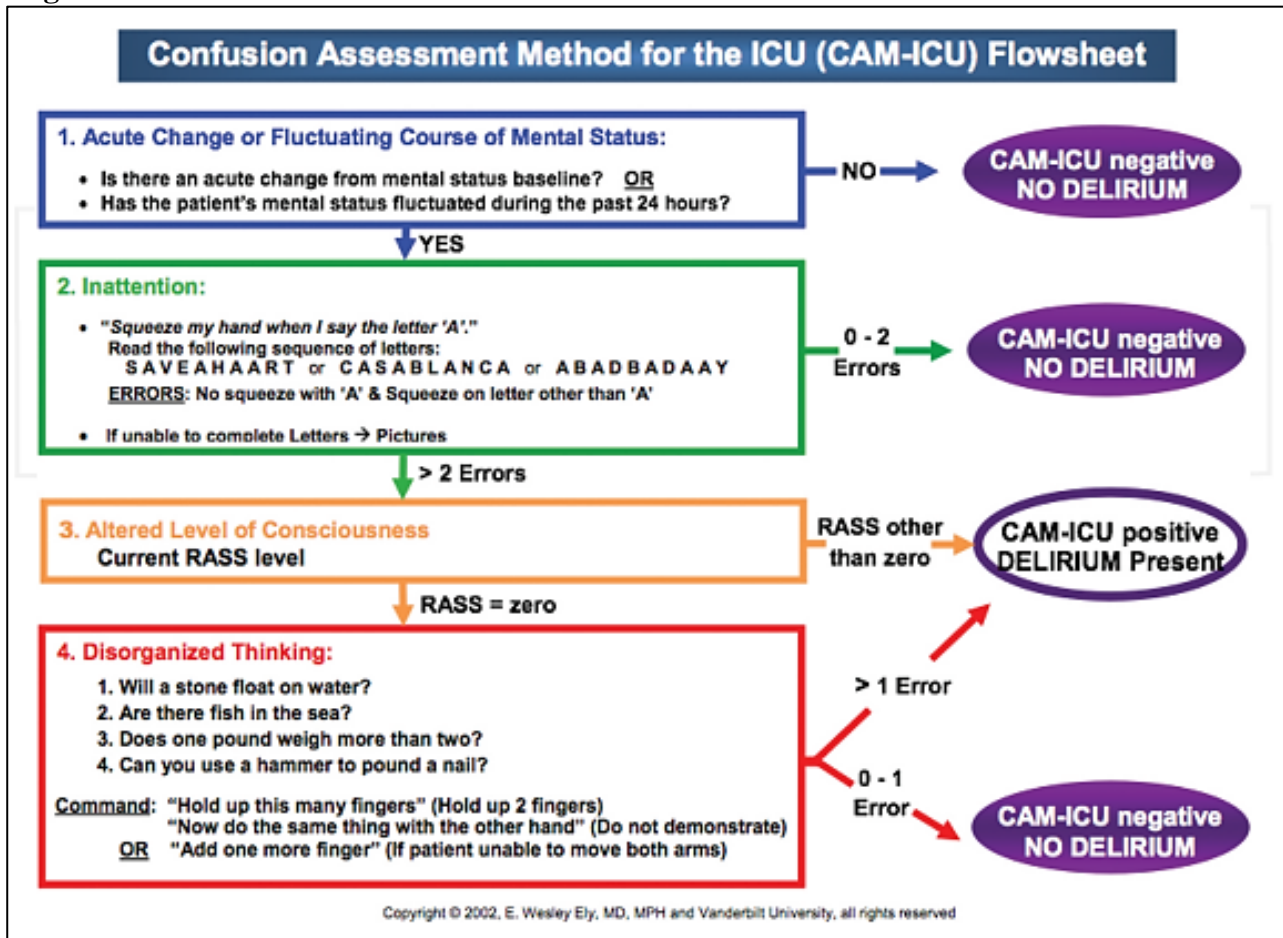
- (A and B) Internal validation study of the delirium predictive score
 (C and D) External validation study of the delirium predictive score
 (E and F) All validation study of the delirium predictive score



Supplemental file

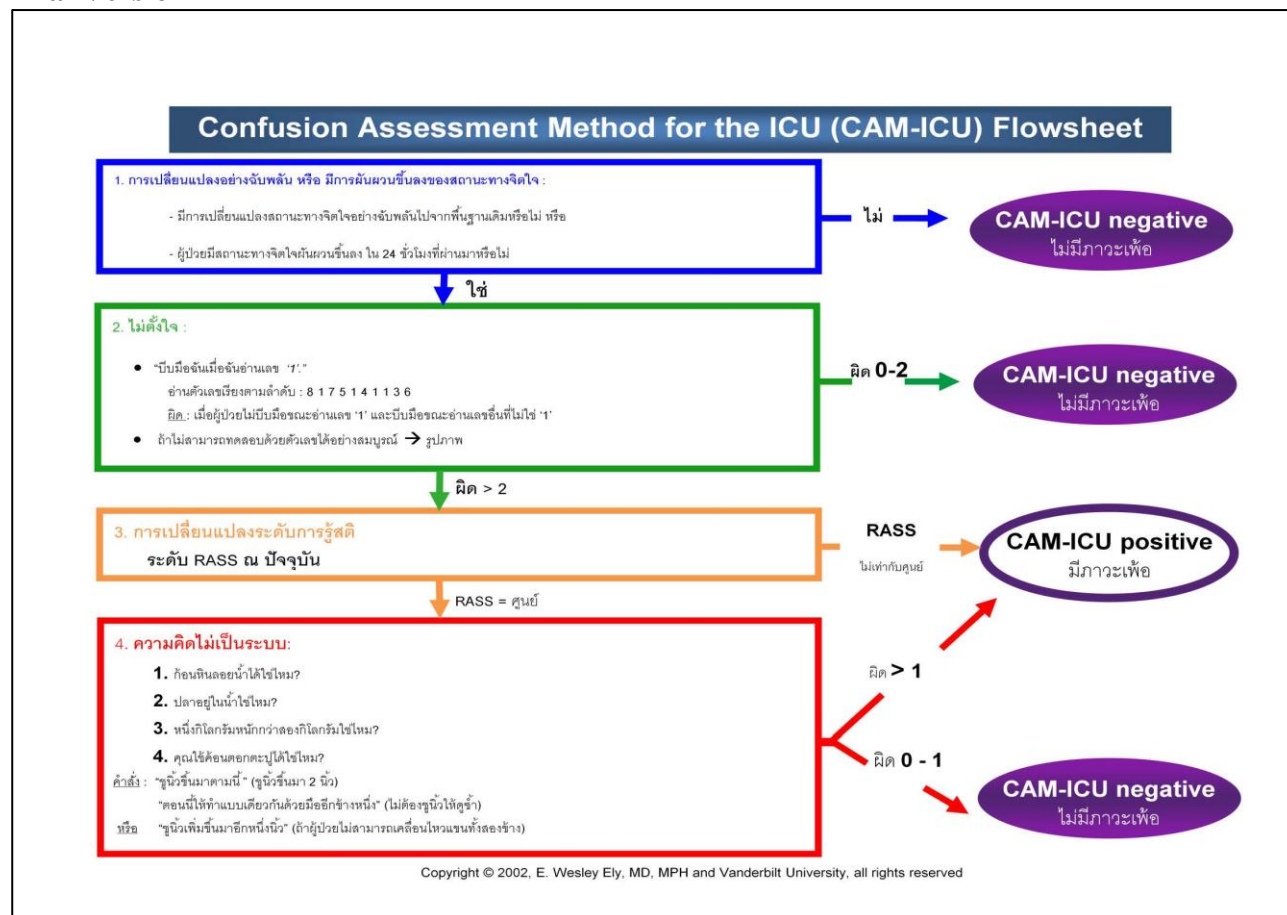
S1. Confusion Assessment method for the ICU (CAM-ICU) tool

English Version



Ely EW, Margolin R, Francis, J, et al. Evaluation of delirium in critically ill patients: Validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). *Crit Care Med* 2001;29:1370–9. [https://doi:10.1097/00003246-200107000-00012](https://doi.org/10.1097/00003246-200107000-00012).

Thai Version



Pipanmekaporn T, Wongpakaran N, Mueankwan S, et al. Validity and reliability of the Thai version of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). *Clin Interv Aging* 2014;9:879–85. <https://doi:10.2147/CIA.S62660>.

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Supplemental file

S2. Modified Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) tool

English version

Items	Comparing the elder's change with the previous 10 years				
	1 Much improve	2 A bit improve	3 Not much change	4 A bit worse	5 Much worse
1. Recognizing the faces of family and friends					
2. Remembering the names of family and friends					
3. Remembering things about family and friends eg, occupations, birthdays, addresses					
4. Remembering things that have happened recently					
5. Recall conversations a few day later					
6. Forgetting what he/she want to say in the middle of a conversation					
7. Remembering his/her address and telephone number					
8. Remembering what day and month it is					
9. Remembering where things are usually kept					
10. Remembering where to find things which have been put in a different place from usual					
11. Remembering things that happened to him/her when he/she was young					
12. Remembering things he/she learned when he/she was young					
13. Knowing about important historical events of the past					
14. Adjusting to any change in his/her day-to-day					
15. Knowing how to work familiar machines around the house					
16. Learning to use a new gadget or machines around the house					
17. Learning the new things that in general					
18. Understanding the meaning of unusual words					
19. Understanding magazine or newspaper articles					
20. Following a story in a book or on TV					
21. Contacting with friends or for business purposes					
22. Making decisions on everyday matters					
23. Handing money for shopping					
24. Handing financial matters					
25. Handing other everyday arithmetic problems, eg knowing how much food to buy, knowing a period of time for doing activity					
26. Using his/her intelligence to understand what's going on and to reason things through					
27. Able to sing or pray the used one					
28. Selecting appropriate instrument					
29. Keep speak repeating					
30. Carrying out daily activities					
31. Traveling to familiar place					
32. Working ability					

Thai Version

	การเปลี่ยนแปลงระหว่าง 10 ปีที่แล้วกับปัจจุบัน				
	1 ดีขึ้นมาก	2 ดีขึ้นเล็กน้อย	3 ไม่เปลี่ยนแปลง	4 แย่ลงเล็กน้อย	5 แย่ลงมาก
1. ความจำเกี่ยวกับหน้าตาคนในครอบครัวหรือญาติ					
2. ความจำเกี่ยวกับชื่อคนในครอบครัวหรือญาติ					
3. ความจำในรายละเอียดของคนในครอบครัวหรือญาติเกี่ยวกับอาชีพที่อยู่					
4. ความจำในเหตุการณ์ที่เกิดขึ้นเมื่อ 2-3 วันที่ผ่านมา					
5. ความจำในเรื่องที่สนทนาไปเมื่อ 2-3 วันที่ผ่านมา					
6. พุดคุยอย่างต่อเนื่องโดยไม่ลืมสิ่งที่จะพูด					
7. จำได้ว่าตอนนี้พักอาศัยอยู่ที่ไหน					
8. จำได้ว่าวันนี้เป็น วัน เดือน อะไร					
9. ความจำเกี่ยวกับที่ประจำที่ใช้เก็บของในบ้าน					
10. จำได้ว่าวางของไว้ที่ไหน					
11. จำเหตุการณ์เกี่ยวกับคนในวัยเด็ก					
12. จำสิ่งที่ตนได้เรียนรู้ในวัยเด็ก					
13. ทราบเหตุการณ์ที่สำคัญในอดีต					
14. ความสามารถในการปรับตัวเข้ากับการเปลี่ยนแปลงในชีวิตประจำวัน					
15. สามารถใช้เครื่องมือที่คุ้นเคยภายในบ้าน					
16. สามารถเรียนรู้การใช้เครื่องมือ เครื่องใช้ใหม่ๆ ในบ้าน					
17. สามารถเรียนรู้สิ่งใหม่ ๆ ทั่ว ๆ ไป					
18. สามารถเข้าใจความหมายของคำแปลก ๆ					
19. สามารถเข้าใจบทความในหนังสือพิมพ์หรือนิตยสาร					
20. สามารถติดตามเรื่องราวต่างๆ ในวิทยุ หรือโทรทัศน์					
21. สามารถติดต่อลูกหลาน ญาติหรือกิจธุระต่างๆ ไป					
22. ความสามารถในการตัดสินใจเรื่องต่าง ๆ ในชีวิตประจำวัน					
23. ความสามารถในการใช้จ่าย					
24. ความสามารถในการจัดสรรเรื่องเงิน					
25. สามารถประมาณได้ว่าจะใช้สิ่งของประมาณเท่าไร เช่น จะซื้ออาหารเท่าไร หรือระยะเวลาที่ใช้ในการทำกิจกรรมต่างๆ เช่น ใช้เวลาในการเดินทางเท่าไร					
26. สามารถที่จะเข้าใจในสิ่งที่เกิดขึ้น พร้อมกับให้เหตุผลในสิ่งนั้นได้					
27. สามารถร้องเพลงที่เคยร้อง หรือ สวดมนต์ที่เคยสวด					
28. สามารถเลือกใช้เครื่องมือเครื่องใช้ต่าง ๆ ได้อย่างเหมาะสมกับงาน					
29. การพูดจาหรือถามซ้ำๆ					
30. สามารถปฏิบัติกิจวัตรประจำวันของตนเอง					
31. สามารถเดินทางไป-กลับสถานที่ที่คุ้นเคยได้โดยลำพัง					
32. สามารถทำงานที่เคยทำ					

Siri S, Okanurak K, Chansirikanjana S, et al. Modified Informant Questionnaire on Cognitive decline in the Elderly (IQCODE) as a screening test for dementia for Thai elderly. *Southeast Asian J Trop Med Public Health* 2006;37:587-94.

BMJ Open

Validation of a delirium predictive model in patients admitted to surgical intensive care units: a multicenter prospective observational cohort study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-057890.R2
Article Type:	Original research
Date Submitted by the Author:	29-May-2022
Complete List of Authors:	Chaiwat, Onuma; Mahidol University Faculty of Medicine Siriraj Hospital, Department of Anesthesiology; Mahidol University Faculty of Medicine Siriraj Hospital, Integrated Perioperative Geriatric Excellent Research Center Chittawatanarat, Kaweesak ; Chiang Mai University Faculty of Medicine, Department of Surgery; Chiang Mai University Faculty of Medicine, Clinical surgical research center Mueankwan, Sirirat ; Chiang Mai University Faculty of Medicine, Surgical critical care unit, Department of Surgery Morakul, Sunthiti ; Mahidol University Faculty of Medicine Ramathibodi Hospital, Department of Anesthesiology Dilokpattanamongkol, Pitchaya ; Mahidol University Faculty of Pharmacy, Department of Pharmacy Thanakiattiwibun, Chayanan ; Mahidol University Faculty of Medicine Siriraj Hospital, Integrated Perioperative Geriatric Excellent Research Center Siriussawakul, Arunotai; Mahidol University Faculty of Medicine Siriraj Hospital, Department of Anesthesiology; Mahidol University Faculty of Medicine Siriraj Hospital, Integrated Perioperative Geriatric Excellent Research Center
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Intensive care
Keywords:	Adult intensive & critical care < ANAESTHETICS, INTENSIVE & CRITICAL CARE, Delirium & cognitive disorders < PSYCHIATRY

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4 1 **Validation of a delirium predictive model in patients admitted to surgical**
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6 2 **intensive care units: a multicenter prospective observational cohort study**
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1
2
3 17 **Abstract**
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7 18 **Objective** To internally and externally validate a delirium predictive model for adult patients
8
9 19 admitted to intensive care units (ICUs) following surgery.
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11 20 **Design** A prospective, observational, multicenter study.
12

13 21 **Setting** Three university-affiliated teaching hospitals in Thailand.
14

15 22 **Participants** Adults aged over 18 years were enrolled if they were admitted to a surgical ICU
16 23 (SICU) and had the surgery within 7 days before SICU admission.
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19 24 **Main outcome measures** Postoperative delirium was assessed using the Thai version of the
20 25 CAM-ICU. The assessments commenced on the first day after the patient's operation and
21 26 continued for 7 days, or until either discharge from the ICU or the death of the patient.
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23

24 27 Validation was performed of the previously developed delirium predictive model: Age + (5 ×
25 28 SOFA) + (15 × benzodiazepine use) + (20 × DM) + (20 × mechanical ventilation) + (20 ×
26 29 modified IQCODE > 3.42).
27
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29 30 **Results** In all, 380 SICU patients were recruited. Internal validation on 150 patients with the
30 31 mean age of 75 ± 7.5 year resulted in an area under a receiver operating characteristic curve
31 32 (AUROC) of 0.76 (0.683 to 0.837). External validation on 230 patients with the mean age of
32 33 57 ± 17.3 year resulted in an AUROC of 0.85 (0.789 to 0.906). The AUROC of all validation
33 34 cohorts was 0.83 (0.785 to 0.872). The optimum cutoff value to discriminate between a high
34 35 and low probability of postoperative delirium in SICU patients was 115. This cutoff offered
35 36 the highest value for Youden's index (0.50), the best AUROC, and the optimum values for
36 37 sensitivity (78.9%) and specificity (70.9%).
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39 38 **Conclusions** The model developed by the previous study was able to predict the occurrence
40 39 of postoperative delirium in critically ill surgical patients admitted to SICUs.
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43 40 **Registration:** Thai Clinical Trial Registry (TCTR ID: TCTR20180105001), 05 January 2018
44
45

46 41 **Keywords:** postoperative delirium, predictive model, surgical intensive care units, validation
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42 **Strengths and limitations of this study**

- 43 • The developed delirium predictive model consists of 6 risk factors was able to
44 predict the occurrence of postoperative delirium in critically ill surgical patients
- 45 • The internal and external validation demonstrated moderate to good statistical
46 performance, with the AUROC being comparable to that of the development
47 cohort
- 48 • The optimum cutoff value to discriminate between a high and low probability of
49 POD in SICU patients was 115

50

51 BACKGROUND

52 Delirium, a disturbance of consciousness, is both acute and fluctuating. Delirium is an
53 extremely common condition among hospitalized patients. Its incidence varies with the study
54 population, but higher rates are observed among geriatric, postsurgical, intensive care unit
55 (ICU), cardiac surgery, and hip-fracture patients ¹⁻⁴. Postoperative delirium (POD) among
56 patients who have been treated with surgery and anesthesia is typically found during the first 3
57 postoperative days ⁵. Although the POD can be transient, it is linked to poor outcomes. These
58 include long stays in postanesthesia care units (PACUs), ICUs, and hospitals; high medical-
59 complication rates; and raised mortality levels ⁶.

60 Several tools for assessing delirium have been validated. Among those is the Confusion
61 Assessment Method for the ICU (CAM-ICU), which shows high sensitivity and specificity ⁷.
62 The CAM-ICU has been translated into Thai, and it, too, has demonstrated good sensitivity and
63 specificity for critically ill patients ⁸. In Thailand, there are limited data relating to POD as well
64 as delirium among critically ill patients. Muangpaisan *et al.*, 2015 ⁹ reported the incidence of
65 delirium was 22.5% in hip surgery. Their investigation also identified the following risk
66 factors: age, premorbid function, dementia/cognitive impairment, the nonstop administration
67 of nonsteroidal anti-inflammatory drugs, and postoperative sedative use. Another study
68 reported a 44.0% prevalence of delirium among critically ill, old patients at a medical ICU in
69 northeastern Thailand. That work found that the independent factors related to delirium were
70 the use of physical restraints, a history of stroke, and multiple bed changes ¹⁰.

71 Given that delirium can result in poor clinical outcomes, predictions of its occurrence
72 among patients who are at risk of delirium are especially important. During the recent decade,
73 some predictive scoring systems for delirium have been proposed for use with various
74 populations. For instance, the PRE-DELIRC (PREdiction of DELIRium in ICU patients)
75 delirium risk prediction tool was developed for intensive care patients ¹¹. This model utilizes

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3 76 10 parameters. It had an area under a receiver operating characteristic curve (AUROC) of 0.87
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5 77 (95% confidence interval [CI], 0.85 to 0.89). Temporal validation and external validation
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7 78 resulted in an AUROC of 0.89 (0.86–0.92) and 0.84 (0.82–0.87), respectively ¹¹. Another tool,
8
9 79 the Risk Model for Delirium, assesses a number of predisposing risk factors for delirium in hip
10
11 80 fracture patients. This model showed good intraclass correlation coefficient (0.77), sensitivity
12
13 81 (80.4%), and AUROC (0.73) ¹². Furthermore, Kim *et al* developed the DELirium Prediction
14
15 82 based on Hospital Information (Delphi) system for general surgery patients. Delphi
16
17 83 demonstrated good AUROCs for both the developed (0.91) and validated models (0.98) ¹³.
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19 84 Nevertheless, each of the above models was developed for specific application with medical
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21 85 critically ill, general surgical, or particular orthopedic patients, and the scoring systems tend to
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23 86 be overly complicated.

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28 87 The Siriraj Integrated Perioperative Geriatric (SIPG) Excellent Research Center has
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30 88 studied the incidence, risk factors, and predictive scores of POD in critically ill surgical
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32 89 patients. The independent risk factors for delirium identified by a multivariate analysis were
33
34 90 age, diabetes mellitus, severity of disease (assessed by the sequential organ failure assessment
35
36 91 [SOFA] score), perioperative use of benzodiazepine, mechanical ventilation and dementia
37
38 92 defined by the Thai version of the Modified Informant Questionnaire on Cognitive Decline in
39
40 93 the Elderly (modified IQCODE) scores > 3.42. The following predictive model was created:

$$94 \quad \text{Age} + (5 \times \text{SOFA}) + (15 \times \text{benzodiazepine use}) + (20 \times \text{DM}) +$$
$$95 \quad (20 \times \text{mechanical ventilation}) + (20 \times \text{modified IQCODE} > 3.42)$$

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49 96 Its AUROC was 0.84 (95% CI, 0.786–0.897). A cutoff value of 125 demonstrated a sensitivity
50
51 97 of 72.1% and a specificity of 80.9 ¹⁴. Thus, we were interested in validating the model. To this
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53 98 end, internal validation was performed at our hospital, while external validation was conducted
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55 99 at 2 other academic hospitals. There has been no previous investigation of a predictive model
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58 100 for POD in patients in surgical ICUs (SICUs). The aim of this study was to validate the use of
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3 101 the proposed POD predictive scoring tool in SICUs in order to identify patients who tend to
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5 102 develop delirium.
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For peer review only

104 **METHODS**

105 **Design**

106 A prospective, observational, cohort study was conducted. The study was approved by the
107 Siriraj Institutional Review Board of the Faculty of Medicine Siriraj Hospital, Mahidol
108 University, Bangkok, Thailand (Si 623/2017, Chairperson Prof. Chairat Shayakul, M.D.) on
109 20 October 2017; the Committee on Human Rights Related to Research Involving Human
110 Subjects, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand
111 (MURA 2017/574, Chairperson Asst. Prof. Chusak Okascharoen, M.D.) on 27 November
112 2017; and Research Ethics Committee 4 at the Faculty of Medicine, Chiang Mai University,
113 Chiang Mai, Thailand (SUR-2560-05016, Chairperson Emeritus Prof. Panja Kulapongs,
114 M.D.) on 28 November 2017. Written informed consent was obtained from the participants
115 before their entry into the study. The trial was registered with the Thai Clinical Trials
116 Registry (TCTR20180105001).

118 **Study population**

119 The study was conducted on 380 SICU patients at 3 hospitals: Siriraj, Ramathibodi, and
120 Maharaj Nakorn Chiang Mai.

121 The study population comprised patients who were at least 18 years of age and were
122 admitted to a SICU within 7 days of surgery at Siriraj, Ramathibodi, or Maharaj Nakorn Chiang
123 Mai Hospital (Table 1). In addition, patients for the internal validation cohort were 65 years or
124 older and had been admitted to a Siriraj Hospital SICU^{15, 16} for a stay anticipated to exceed 24
125 hours. At all 3 hospitals, we excluded SICU patients who had (1) not undergone any operations;
126 (2) communication problems (unable to communicate in Thai, or having a severe visual or
127 auditory impairment interfering with communication); or (3) a Richmond Agitation Sedation
128 Scale (RASS) score of -4 or -5 during the whole of their ICU stay. A flowchart illustrating the

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3 129 patient selection processes for the development and validation cohorts is presented in Figure 1.
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8 131 **Patient and public involvement**
9

10 132 No patient involved.
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15 134 **Measurement instruments**
16

17 135 Delirium was assessed using the Thai version of the CAM-ICU (S1). Delirium was identified
18
19 136 by the following 4 features: 1) a change or fluctuation in baseline mental status; 2) inattention;
20
21 137 and either 3) an altered level of consciousness; or 4) disorganized thinking¹⁷. The Thai version
22
23 138 has demonstrated satisfactory validity and reliability (specificity, 94.7%; sensitivity, 92.3%)⁸.
24
25 139 As to the level of consciousness, it was assessed by the RASS. It utilizes a 10-point scale
26
27 140 ranging from -5 to +4. The delirium subtypes were recorded as hypoactive (RASS -1 to -3),
28
29 141 hyperactive (RASS +1 to +4), and mixed type (hypo- and hyperactive)¹⁸. With regard to
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31 142 dementia, it was evaluated via the Thai version of modified IQCODE (S2). The questionnaire
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33 143 consists of 32 items, with assessments of patients being made by their caregivers. The optimal
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35 144 cutoff score for the modified IQCODE is 3.42 (sensitivity, 90%; specificity, 95%; and
36
37 145 accuracy, 92%)¹⁹. Lastly, the severity of illness at SICU admission was evaluated using the
38
39 146 Acute Physiology and Chronic Health Evaluation II (APACHE II) scoring system, and SOFA
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41 147 scores.
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47 148 Patients provided informed consent in writing. Delirium was evaluated at least twice
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49 149 daily (once during the 12 hours from 6.00 AM, and once during the 12 hours after 6.00 PM),
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51 150 and whenever patients developed a mental change. Delirium was screened routinely utilizing a
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53 151 2-step process. Initially, the patients' level of consciousness was assessed using the RASS. If
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55 152 the score was between -3 and +4, the evaluators proceeded to Step 2 (assessment of the patient
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57 153 with the Thai version of CAM-ICU). However, if Step 1 produced a -4 RASS score (responsive
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3 154 only to physical stimulus) or a -5 RASS score (unresponsive to physical and verbal stimulus),
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5 155 Step 2 was not performed. If a patient was found to be sedated in the first step, the dose of the
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7 156 sedative medication was adjusted. The patient was later assessed with the CAM-ICU once a
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9 157 RASS score of -3 or higher was achieved.

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12 158 The second step involved the determination of the patient's delirium level using the Thai
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14 159 version of CAM-ICU, employing standard methodology. The assessments commenced on the
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16 160 first day after the patient's operation and continued for 7 days, or until either discharge from
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18 161 the ICU or the death of the patient. Patients with delirium were further assessed until the CAM-
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20 162 ICU was negative for 24 hours. Thereafter, the ICU attending physician was notified for further
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22 163 management.
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27 28 165 **Data collection**

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30 166 The predisposing and precipitating factors potentially linked to the onset of delirium were
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32 167 grouped as preoperative, intraoperative, and postoperative variables. The preoperative risk
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34 168 factors were demographic variables obtained from a review of an individual patient's medical
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36 169 records and interviews with any proxies. Each patient's cognitive status was measured using
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38 170 the modified IQCODE ¹⁹.

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42 171 The intraoperative variables were obtained from anesthetic records. They consisted of
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44 172 the surgical type (abdominal, vascular, orthopedic, urological, gynecological, and head and
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46 173 neck); admission type (emergency or elective); operation time; intraoperative blood loss;
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48 174 amount of blood transfused; and total fluid intake. Intraoperative hypotension was deemed to
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50 175 be either a systolic pressure below 90 mmHg or the need to be treated with medications.^{20, 21}
51
52 176 Intraoperative hypoxemia was defined as an oxygen saturation (derived from pulse oximetry)
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54 177 of below 90% for any duration.

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58 178 The postoperative variables were primarily obtained from the SICU data records. They
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3 179 were the use of mechanical ventilation, physical restraints, or a Foley's catheter; the presence
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5 180 of sleep deprivation or shock; exposure to psychoactive drugs (benzodiazepines, opioids, and
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7 181 sedatives); and the presence of coma (indicated by a RASS score of -4 or -5).
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10 182

11 12 183 **Preparation of research team**

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14 184 The clinical researchers administering the Thai CAM-ICU were physicians and nurses who had
15
16 185 been trained by the principal investigator. To ensure reliability among the assessors, inter-rater
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18 186 reliability scores were calculated. Once their kappa score reached 0.8, the trained physicians
19
20 187 and nurses were permitted to perform the Thai CAM-ICU assessments.
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25 26 189 **Internal and external validation**

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28 190 After development of a predictive model from a prospective cohort study that took place
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30 191 between February 2016 and February 2017, we did a second prospective cohort study in the
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32 192 same hospital for internal validation of the model between April 2018 and December 2019. In
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34 193 the meantime, we externally validated the predictive model with data from intensive care
35
36 194 surgical patients admitted to 2 other university hospitals in Thailand. They were Ramathibodi
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38 195 Hospital, Mahidol University, and Maharaj Nakorn Chiang Mai Hospital, Chiang Mai
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40 196 University. Trained intensive care nurses at those hospitals used the CAM-ICU at least twice
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42 197 daily. The validation process was conducted according to the Transparent Reporting of a
43
44 198 multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) Statement²²,
45
46 199 a guideline specifically designed for the reporting of studies developing or validating a
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48 200 multivariable prediction model, whether for diagnostic or prognostic purposes.
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54 55 56 202 **Statistical analysis**

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58 203 The sample size was estimated based on the reported 78% accuracy of development predictive
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3 204 score.¹⁴ Based on the estimated accuracy of 80% ($p=0.80$) and a 4% error ($d = 0.04$), an 5%
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5 205 alpha ($\alpha = 0.05$), the sample size of 380 cases was calculated. The sample size calculation was
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8 206 estimated using PASS V.14 (NCSS, Kaysville, Utah, USA).
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10 207 Demographic variables are presented as mean \pm standard deviation or median (interquartile
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12 208 range [IQR]) for continuous data, and frequency and percentage for categorical data.
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14 209 In both validation studies, we multiplied regression coefficients for each risk factor in the
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16 210 predictive model by the observed patients' values. The outcome was a calculated predicted
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18 211 probability, on which we built a new AUROC. Finally, an ROC curve was plotted to determine
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20 212 the best cutoff in terms of Youden's index, sensitivity, specificity, and 95% CI. The Youden's
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22 213 index was the difference between the true and the false positive rates. Maximizing this index
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24 214 allows an optimal cutoff value to be found from the ROC curve, independently from the
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26 215 prevalence^{23, 24}. Finally, to examine how well the model was calibrated, we calculated linear
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28 216 predictor values for each patient of every cohort by using the coefficients from the model. We
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30 217 used these linear predictors in a logistic regression model to test whether the prediction rule
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32 218 was well calibrated, resulting in a calibration slope and an intercept. A calibration slope of 1
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34 219 and an intercept of 0 show a perfect calibration^{25, 26}. Statistics were analyzed using PASW
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36 220 Statistics for Windows (version 18; SPSS Inc., Chicago, IL, USA); and MedCalc statistical
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38 221 software (version 17.6; MedCalc Software BVBA, Ostend, Belgium).
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223 RESULTS

224 Patients

225 The patients were enrolled between February 2016 and February 2017¹⁴ for the development
226 cohort, and between April 2018 and December 2019 for the internal and external validation
227 studies. In all, 1,437 SICU patients were excluded for the reasons given in Figure. 1, and 380
228 were recruited. The mean age of the patients in the internal validation cohort was 75.1 ± 7.5
229 years, while the mean for the patients in the external validation cohort was 56.9 ± 17.3 years.
230 The mean age of all of the patients in the 2 validation cohorts was 64.1 ± 16.8 years. More than
231 half of the patients in the validation cohort were males. Details relating to the demographic and
232 intraoperative data, ICU admission, and the medications used are given in Table 2. There was
233 a higher proportion of patients with hypertension, diabetes mellitus (DM), and cardiac disease
234 in the internal validation cohort than the external validation cohort. The incidence of delirium
235 was 40.0%, 21.3%, and 28.7% in the internal, external, and all validation cohorts, respectively,
236 compared with 24.4% in the development cohort. The majority of patients in all cohorts
237 underwent intra-abdominal surgery. The median SOFA score was 4 (IQR 1–6) for all validation
238 cohorts, which was higher than the median of 3 (IQR 2–6) for the development cohort. The
239 percentage of benzodiazepine use in the development cohort (10% vs. 25.2%; Table 2).

240

241 Development study

242 Of the 412 recruited patients, a total of 162 were excluded for the reasons detailed in Figure.
243 1. As a result, 250 patients were enrolled, 61 of whom (24.4%) developed delirium (Table 2).
244 The predictive model was derived from a multiple logistic regression that used significant risk
245 factors. The final formula required 6 factors (2 quantitative factors, and 4 binary factors). The
246 formula of the model was:

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$$\text{Age} + (5 \times \text{SOFA}) + (15 \times \text{benzodiazepine use}) + (20 \times \text{DM}) +$$

248 (20 × mechanical ventilation) + (20 × modified IQCODE > 3.42)

249 The AUROC was 0.84 (95% CI, 0.786–0.897). The cutoff value of ≥ 125 demonstrated a
250 sensitivity of 72.1% and a specificity of 80.9%¹⁴.

251

252 **Validation study**

253 *Internal validation of predictive model*

254 For the prospective validation study, we recruited 984 consecutive patients who were aged over
255 65 years; however, 834 were subsequently excluded (Figure. 1). Of the remaining 150 patients,
256 60 (40%) developed delirium (Table 2). The internal validation resulted in an AUROC of 0.76
257 (0.683 to 0.837; Figure. 2A), and this AUROC was not significantly different from the AUROC
258 of the developed predictive model ($P = 0.092$), with a calibration slope of 0.972 and an intercept
259 of 0.009 (Figure. 2B).

260

261 *External validation of predictive model*

262 We performed the external validation study on critically ill surgical patients admitted to SICUs
263 at Ramathibodi and Maharaj Nakorn Chiang Mai Hospitals. Of the 833 recruited patients, 603
264 were excluded (Figure. 1). As a result, 230 patients were enrolled: 62 (27%) at Ramathibodi
265 Hospital, and 168 (73%) at Maharaj Nakorn Chiang Mai Hospital. The incidence of delirium
266 in the external validation cohort was 21% (Table 2). The external validation resulted in an
267 AUROC of 0.85 (0.789 to 0.906; Figure. 2C), and it was not significantly different from the
268 AUROC of the developed predictive model ($P = 0.865$), with a calibration slope of 0.929 and
269 an intercept of 0.006 (Figure. 2D).

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271 *Optimal cutoff value of predictive model*

272 The AUROCs of the development, internal, and external validation cohorts were comparable

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3 273 (0.84 for the development cohort, 0.76 for the internal validation cohort, and 0.85 for the
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5 274 external validation cohort). As no significant differences in prediction existed between the 3
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7 275 validation studies, we pooled the data of all validation cohorts (n = 380). That revealed that
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9 276 109 patients (29%) developed delirium (Table 2). Consequently, the AUROC of all of the
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11 277 validation cohorts was 0.83 (0.785 to 0.872; Figure. 2E). The recalibration of all validation
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13 278 study showed a calibration slope of 0.945 and an intercept of 0.007 (Figure 2F). The optimum
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15 279 cutoff value to discriminate between a high and low probability of POD in SICU patients was
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17 280 115. This cutoff presented the highest value of Youden's index (0.50), the best AUROC, and
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19 281 the optimum values for sensitivity (78.9%) and specificity (70.9%; Table 3). The last 2 values
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21 282 were similar to the sensitivity (78.8%) and specificity (70.4%) of the development cohort.
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284 DISCUSSION

285 Given the high costs of managing delirium and its consequential complications, it is essential
286 to identify individuals at high risk of developing the condition and to deliver evidenced-based
287 preventive measures. This multicenter-study demonstrated the performance of the internal and
288 external validation of a proposed model ¹⁴ that had been developed to predict POD in patients
289 admitted postoperatively to an SICU. It is essential to confirm the predictive performance of
290 the model before its use outside the development setting. The external validation showed
291 moderate to good statistical performance, with the AUROC of the external cohort being
292 comparable to that of the development cohort. In addition, the new cutoff value also
293 demonstrated optimum sensitivity and specificity values that were equivalent to those achieved
294 for the development cohort. However, the performance of the internal validation cohort was
295 not as high as the development and external validation cohort (AUROC, 0.76). This was
296 because the internal validation cohort only included patients aged 65 years or older, resulting
297 in a higher incidence of delirium.

298 Recently, 2 ICU delirium predictive models-the early predictive model for ICU delirium
299 (E-PRE-DELIRIC), and the recalibrated predictive model for ICU delirium (PRE-DELIRIC)
300 have been developed and validated ^{11, 27, 28}. These 2 models are currently used in clinical
301 practice and in research to predict the development of delirium in ICUs. The PRE-DELIRIC
302 model consists of 10 predictors that are available during the first 24 hours after admission to
303 an ICU ²⁷. The E-PRE-DELIRIC is composed of 9 parameters available at time of ICU
304 admission. Wassenaar *et al.*, 2019 ²⁹ recently conducted an external validation of both
305 assessment tools, using either the CAM-ICU or the Intensive Care Delirium Screening
306 Checklist for delirium assessment. The researchers reported moderate-to-good statistical
307 performances. Nevertheless, the formulas for those 2 models were quite complicated, using
308 several parameters, and they were developed in a mixed-ICU setting (medical and surgical

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3 309 populations). Given that cognitive impairment (including dementia) and severity of illness have
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5 310 been recognized as strong predictors for delirium in hospitalized patients,^{30, 31} the E-PRE-
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7 311 DELIRIC system included only a history of cognitive impairment but no severity scores. In
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9 312 contrast, the PRE-DELIRIC model included only APACHE II scores, but no information on
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11 313 cognitive impairment.
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14 314 The currently proposed predictive model for POD in critically ill surgical patients has
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16 315 several strengths. Firstly, it was developed specifically for surgical patients, and it
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18 316 demonstrated high accuracy. In addition, it employs only 5 parameters, which makes it
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20 317 relatively easy to calculate. Furthermore, dementia is assessed by both the patient's history and
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22 318 the modified IQCODE assessment tool. A previous study found that the prevalence of dementia
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24 319 among elderly delirious patients was 5 times higher when evaluated by the modified IQCODE
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26 320 tool than when using information obtained solely from history taking³². Consequently, the
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28 321 proposed predictive model was validated in the same hospital and in 2 other academic hospitals.
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30 322 Although we recruited only elderly patients for the internal validation cohort, the AUROC
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32 323 showed an acceptable value. For the external validation cohort in the SICUs of the 2 other
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34 324 hospitals, we performed quality control by determining the inter-rater reliability of CAM-ICU
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36 325 assessment before commencing the study. There were differences in the patient case-mix of
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38 326 the external and development validation samples. In particular, relative to the development
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40 327 group, the external validation cohort had a lower age, a lower percentage of patients with
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42 328 mechanical ventilation, a higher percentage of dementia, and a lower percentage of
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44 329 benzodiazepine use. Despite that, the models' discriminative performance showed the same
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46 330 value (AUROC 0.84 for the development cohort, and 0.85 for the external validation cohort).
47
48 331 In short, for the all-validation cohort, the AUROC was approximately the same as that for the
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50 332 development and the external validation cohorts. A score of ≥ 115 was the best cutoff value to
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52 333 predict the occurrence of delirium in SICUs. This cutoff presented the highest value for
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3 334 Youden's index (0.50), the best AUROC, and the optimum values for sensitivity (78.9%) and
4
5 335 specificity (70.9%). Additionally, the predictive value depends on a disease's prevalence in the
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7 336 population group that is being diagnosed³³. A good model must have sufficient prevalence,
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9 337 high sensitivity, and high specificity, and it should allow diagnosis before a patient displays
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11 338 symptoms^{33, 34}.

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16 17 340 **Strengths and limitations**

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19 341 The significant strength of our study is that it was the first multicenter study in Thailand to
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21 342 evaluate the performance of a proposed predictive model for delirium in SICUs. The early
22
23 343 prediction of the development of delirium in ICU patients facilitates the implementation of
24
25 344 prevention protocols. These interventions can be non-pharmacological (such as cognitive
26
27 345 stimulation, early mobilization, and enhanced sleep)^{35, 36} or pharmacological (like the
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29 346 prophylactic administration of dexmedetomidine³⁷ to high-risk patients).

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33 347 Several limitations need to be addressed. Firstly, only the CAM-ICU was used to assess
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35 348 delirium. In the current work, the researchers (physicians and nurses) who evaluated delirium
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37 349 using this tool were well-trained, and their ratings are therefore regarded as accurate. However,
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39 350 other research showed that the accuracies of delirium assessments performed by bedside nurses
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41 351 in daily practice demonstrated lower sensitivity and specificity than our clinical researchers
42
43 352 achieved³⁸. The skill level of staff undertaking assessments in a clinical setting may therefore
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45 353 influence the results of the predictive model. In addition, the internal validation cohort only
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47 354 included critically ill elderly patients. The optimum cutoff value that resulted in the best
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49 355 sensitivity and specificity might be different from the all-validation and development cohorts.
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51 356 Moreover, differences in risk factors might affect the predictive model. We did not perform a
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53 357 logistic regression for the validation cohort in order to identify independent risk factors for
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55 358 delirium. This is because the prognostic ability demonstrated by the AUROC of the internal
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3 359 and external validation groups showed moderate-to-good performance. Lastly, the predictive
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5 360 model only used parameters available at the time of SICU admission. Any changes in patients'
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7 361 conditions during their stay can affect the probability of their developing delirium. Our model
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9 362 did not account for such changes.
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14 364 **CONCLUSIONS**

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18 365 The model reported in this study can predict which critically ill surgical patients will develop
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20 366 POD in SICUs. Consequently, high-risk patients can be identified, and both non-
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22 367 pharmacological and pharmacological prevention protocols can be implemented to improve
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24 368 the clinical outcomes. The use of this selective strategy is appropriate in a resource-limited
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26 369 country, in which the administration of a prevention protocol for all critically-ill patients is not
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28 370 viable.
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34
35 386 **Contributions**
36

37 387 OC and AS contributed to the design of the study. OC, KC and S. Morakul were involved in
38
39 data management and oversaw the project. KC, S. Mueankwan, S. Morakul, PD, contributed
40 388
41 to data collection. CT contributed to data analysis. OC and CT contributed to the
42 389
43 interpretation of the results and drafting the manuscript. All authors read and approved the
44 390
45 final manuscript.
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50
51 393 **Funding**
52

53 394 This study was supported by the Faculty of Medicine Siriraj Hospital, Mahidol University,
54
55 Thailand (IO: R016132015). The funders had no role in study design, data collection, and
56 395
57 analysis, decision to publish, or preparation of the manuscript.
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45 398 **Competing interests**6
7
8 399 The authors declare that they have no competing interests.
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12 401 **Data availability statement**13
14 402 The datasets used and analyzed during the current study are available from the corresponding
15
16
17 403 author on reasonable request.
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22 405 **Ethics statements**23
24 406 **Patient consent for publication**25
26 407 Not applicable.
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29 40830
31 409 **Ethics approval**32
33 410 This study was conducted according to the ethical standards established by the 1964
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35
36 411 Declaration of Helsinki. The study was approved by the Siriraj Institutional Review Board of
37
38 412 the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand (Si
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40 413 623/2017, Chairperson Prof. Chairat Shayakul, M.D.) on 20 October 2017; the Committee on
41
42 414 Human Rights Related to Research Involving Human Subjects, Faculty of Medicine
43
44 415 Ramathibodi Hospital, Mahidol University, Bangkok, Thailand (MURA 2017/574,
45
46 416 Chairperson Asst. Prof. Chusak Okascharoen, M.D.) on 27 November 2017; and Research
47
48 417 Ethics Committee 4 at the Faculty of Medicine, Chiang Mai University, Chiang Mai,
49
50 418 Thailand (SUR-2560-05016, Chairperson Emeritus Prof. Panja Kulapongs, M.D.) on 28
51
52 419 November 2017. Written informed consent was obtained from the participants before their
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54 420 entry into the study. The trial was registered with the Thai Clinical Trials Registry
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56 421 (TCTR20180105001).
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8 424 **Acknowledgements**
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10 425 The authors gratefully acknowledge the patients who generously agreed to participate in this
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12 426 study, and Assist. Prof. Dr. Chulaluk Komoltri, M.P.H. Biostatistics, for the statistical analyses.
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17 428 **Supplemental file**
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20 429 S1. Confusion Assessment method for the ICU (CAM-ICU) tool
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22 430 S2. Modified Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) tool
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544 **Table 1.** Characteristics of participating hospitals

Participating hospital	Institution	ICU beds for adults	ICU population	CAM-ICU screenings
Siriraj Hospital	Faculty of Medicine Siriraj Hospital, Mahidol University	14 beds	Surgery	2/day; IRR > 0.8
Ramathibodi Hospital	Faculty of Medicine Ramathibodi Hospital, Mahidol University	12 beds	Surgery	2/day; IRR > 0.8
Maharaj Nakorn Chiang Mai Hospital	Faculty of Medicine, Chiang Mai University	7 beds	Surgery	2/day; IRR not measured

545 Abbreviations: CAM, Confusion Assessment Method; ICU, intensive care unit; IRR, inter-rater reliability
 546 expressed as Cohen's κ

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548 **Table 2.** Characteristics of patients in development and validation groups

Variable	Development (n = 250)	Internal validation (n = 150)	External validation (n = 230)	All validation (n = 380)
Demographic data				
Age (years)	64.2 ± 16.4	75.1 ± 7.5	56.9 ± 17.3	64.1 ± 16.8
Sex; male	121 (48.4%)	84 (56.0%)	128 (55.7%)	212 (55.8%)
Comorbidities				
Hypertension	155 (62.0%)	101 (67.3%)	109 (47.4%)	210 (55.3%)
DM	63 (25.2%)	41 (27.3%)	49 (21.3%)	90 (23.7%)
Cardiac disease	64 (25.6%)	37 (24.7%)	33 (14.3%)	70 (18.4%)
ESRD or CKD stage 4–5	34 (13.6%)	30 (20.0%)	75 (32.6%)	105 (27.6%)
Modified IQCODE score ≥ 3.42	16 (6.4%)	20 (13.3%)	27 (11.7%)	47 (12.4%)
Current alcohol consumption	17 (6.8%)	12 (8.0%)	41 (17.8%)	53 (13.9%)
Incidence of delirium	61 (24.4%)	60 (40.0%)	49 (21.3%)	109 (28.7%)
Onset of delirium (days)	1 (1 – 2)	2 (1 – 4)	1 (1 – 1)	1 (1 – 3)
Type of delirium				
Hypoactive	44 (72%)	16 (26.7%)	26 (53.1%)	42 (38.5%)
Hyperactive	9 (15%)	17 (28.3%)	6 (12.2%)	23 (21.1%)
Mixed	8 (13%)	27 (45%)	17 (34.7%)	44 (40.4%)
Intraoperative data				
Emergency surgery	108 (43.2%)	64 (42.7%)	73 (31.7%)	137 (36.1%)
Type of surgery				
Vascular	52 (20.8%)	43 (28.7%)	26 (11.3%)	69 (18.2%)
Intra-abdominal	88 (35.2%)	79 (52.7%)	81 (35.2%)	160 (42.1%)
Orthopedic	29 (11.6%)	8 (5.3%)	10 (4.3%)	18 (4.7%)
Gynecological	26 (10.4%)	1 (0.7%)	4 (1.7%)	5 (1.3%)
Other	55 (22.0%)	19 (12.7%)	109 (47.4%)	128 (33.7%)
Hypoxia	10 (4.0%)	8 (5.3%)	2 (0.9%)	10 (2.6%)
Intraoperative hypotension	196 (78.4%)	127 (84.7%)	93 (40.4%)	220 (57.9%)
ICU admission				
Sepsis	61 (24.4%)	39 (26.0%)	30 (13.0%)	69 (18.2%)
APACHE II score	9 (6 – 11)	14 (11 – 19)	12 (8 – 17)	12 (9 – 17)
SOFA score	3 (2 – 6)	4 (3 – 6)	4 (1 – 6)	4 (2 – 6)
Mechanical ventilation	185 (74.0%)	126 (84.0%)	153 (66.5%)	279 (73.4%)
Medication				
Benzodiazepine	63 (25.2%)	19 (12.7%)	19 (8.3%)	38 (10.0%)
Opioid	244 (97.6%)	140 (93.3%)	203 (88.3%)	343 (90.3%)
Outcomes				
Duration of mechanical ventilation (days)	1 (0 – 4)	3 (1 – 7)	1 (0 – 3)	2 (1 – 4)
Nosocomial infection in ICU	29 (11.6%)	41 (27.3%)	4 (1.7%)	45 (11.8%)
ICU length of stay (days)	3 (2 – 5)	5 (3 – 10)	3 (3 – 6)	4 (3 – 7)
ICU mortality	9 (3.6%)	5 (3.3%)	5 (2.2%)	10 (2.6%)
Hospital length of stay (days)	16 (10 – 29)	20 (13 – 34)	16 (13 – 27)	18 (13 – 29)
Hospital mortality	26 (10.4%)	25 (16.7%)	13 (5.7%)	38 (10.0%)

549

550 Data are presented as mean ± SD, median (IQR), or n (%).

551 Abbreviations: APACHE II score, Acute Physiology and Chronic Health Evaluation II score; CKD, chronic
552 kidney disease; DM, diabetes mellitus; ESRD, end state renal disease; Modified IQCODE, Modified Informant
553 Questionnaire on Cognitive Decline in the Elderly; SOFA score, Sequential Organ Failure Assessment score

Table 3. Cutoff values of the Delirium Prediction Score

Cutoff value	Development (n = 250)		J	Internal validation (n = 150)		J	External validation (n = 230)		J	All validation (n = 380)		J
	Sensitivity (95% CI)	Specificity (95% CI)		Sensitivity (95% CI)	Specificity (95% CI)		Sensitivity (95% CI)	Specificity (95% CI)		Sensitivity (95% CI)	Specificity (95% CI)	
≥ 100	95.1% (86.3–99.0)	50.3% (42.9–57.6)	0.45	100.0% (94.0–100.0)	21.1% (13.2–31.0)	0.21	87.8% (75.2–95.4)	64.6% (57.2–71.6)	0.5	94.5% (88.4–98.0)	50.2% (44.1–56.3)	0.45
≥ 105	90.2% (79.8–96.3)	56.1% (48.7–63.3)	0.46	96.7% (88.5–99.6)	27.8% (18.9–38.2)	0.25	79.6% (65.7–89.8)	66.7% (59.5–73.7)	0.4	89.0% (81.6–94.2)	53.9% (47.7–59.9)	0.43
≥ 110	83.6% (71.9–91.9)	63.0% (55.7–69.9)	0.47	90.0% (79.5–96.2)	34.4% (24.7–45.2)	0.24	75.5% (61.1–86.7)	75.1% (68.2–81.3)	0.5	83.5% (75.2–89.9)	61.6% (55.6–67.4)	0.45
≥ 115	78.7% (66.3–88.1)	70.4% (63.3–76.8)	0.49	86.7% (75.4–94.1)	50.0% (39.3–60.7)	0.37	69.4% (54.6–81.8)	81.2% (74.8–86.7)	0.5	78.90% (70.0–86.1)	70.9% (65.1–76.2)	0.50
≥ 120	75.4% (62.7–85.5)	74.1% (67.2–80.2)	0.50	83.3% (71.5–91.7)	60.0% (49.1–70.2)	0.47	61.2% (46.2–74.8)	86.2% (80.3–90.9)	0.4	73.3% (64.1–81.4)	77.5% (72.1–82.3)	0.50
≥ 125	72.1% (59.2–82.9)	81.0% (74.6–86.3)	0.53	78.3% (65.8–87.9)	68.9% (58.3 to 78.2)	0.47	55.1% (40.2–69.3)	90.1% (84.7–94.0)	0.4	67.9% (58.3–76.5)	83.0% (78.0–87.3)	0.50
≥ 130	67.2% (54.0–78.7)	87.3% (81.7–91.7)	0.54	61.7% (48.2–73.9)	72.2% (61.8 to 81.2)	0.34	46.9% (32.5–61.7)	93.4% (88.7–96.5)	0.4	55.1% (45.2–64.6)	86.4% (81.7–90.2)	0.42

Abbreviation: J, Youden's index

Figure legends

Figure 1. Flowchart of development and validation studies

Figure 2. Receiver operating characteristic (ROC) curves and calculated areas under the curve (AUC), and Calibration plot of pooled data;

(A and B) Internal validation study of the delirium predictive score

(C and D) External validation study of the delirium predictive score

(E and F) All validation study of the delirium predictive score

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Figure 1. Flowchart of development and validation studies

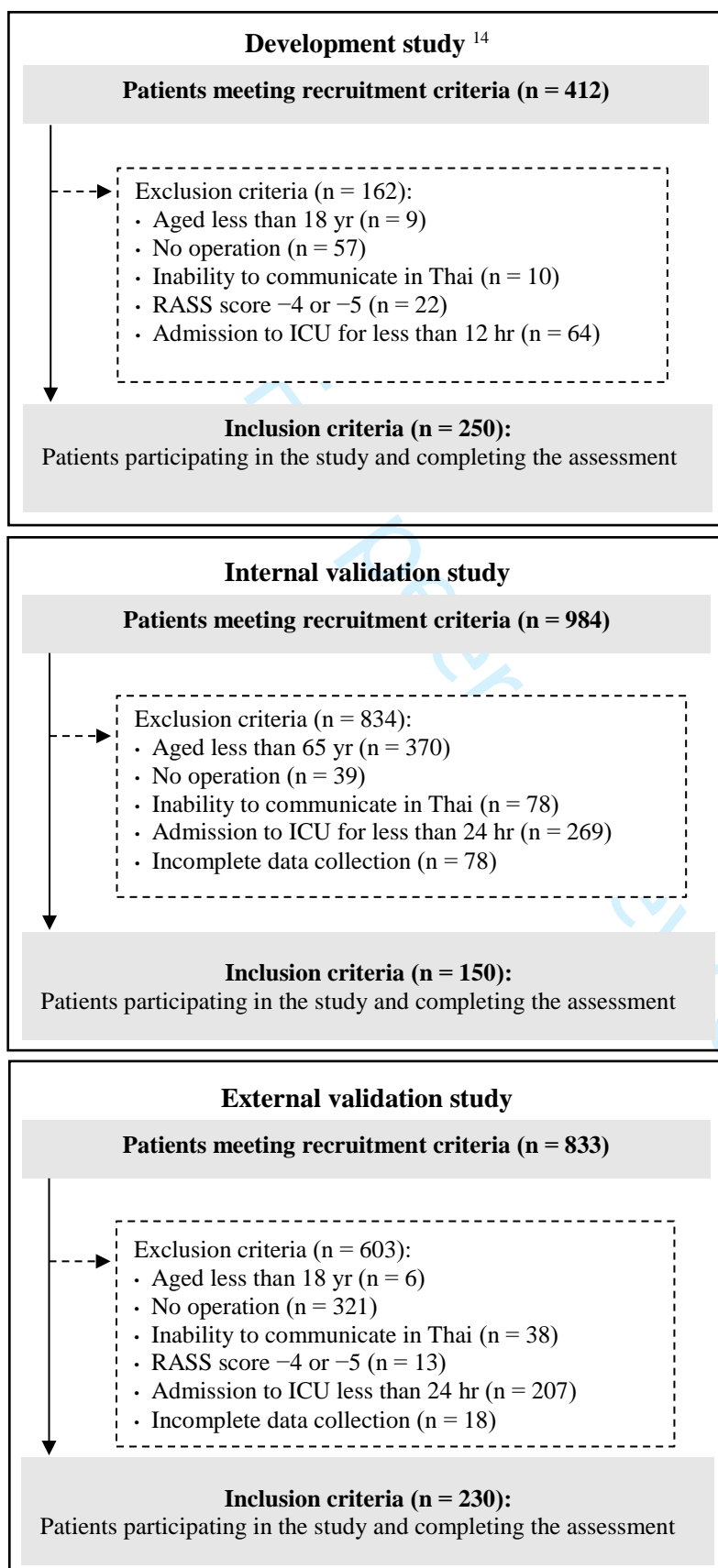


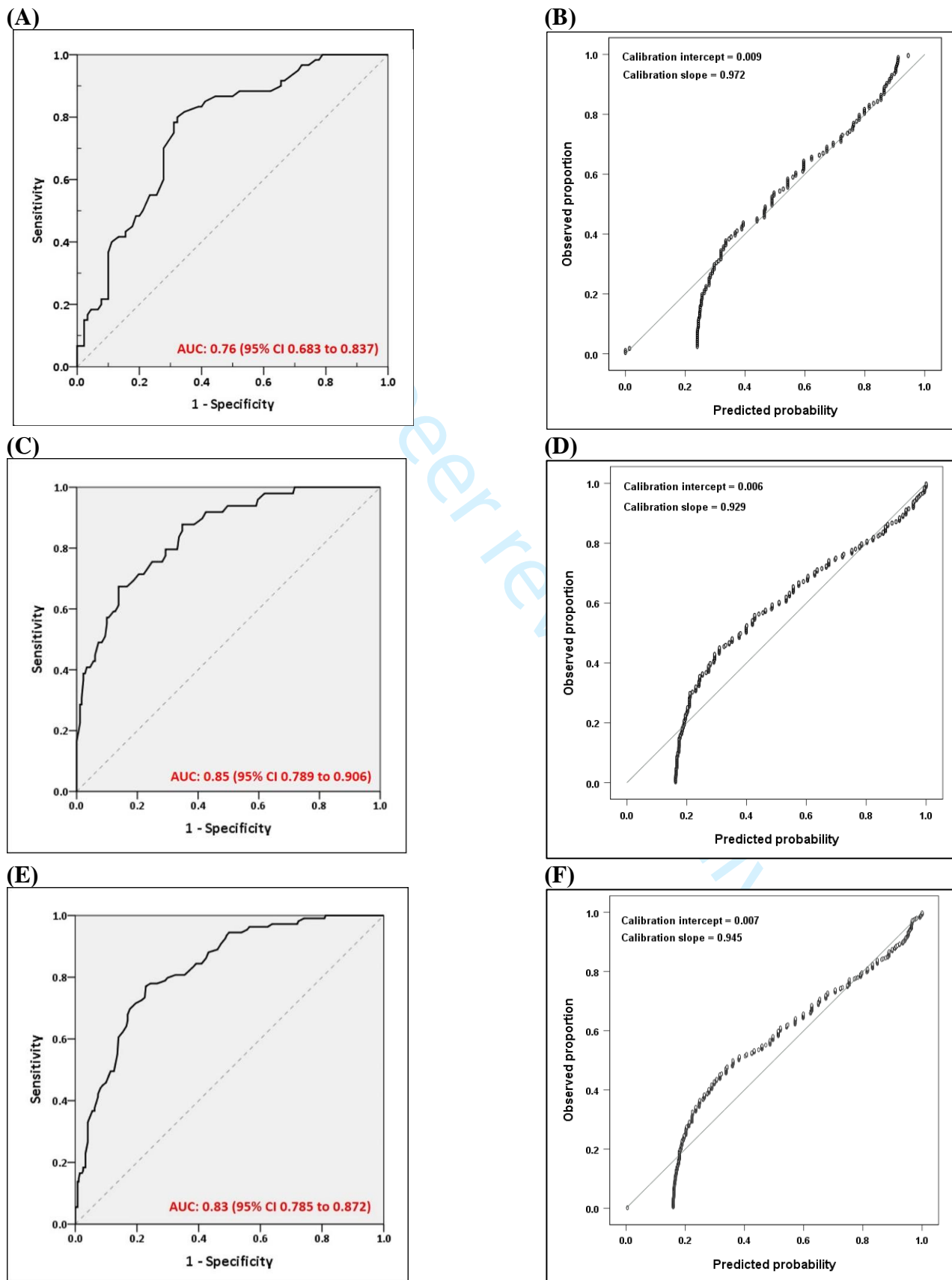
Figure 2. Receiver operating characteristic (ROC) curves and calculated areas under the curve (AUC),

and Calibration plot of pooled data;

(A and B) Internal validation study of the delirium predictive score

(C and D) External validation study of the delirium predictive score

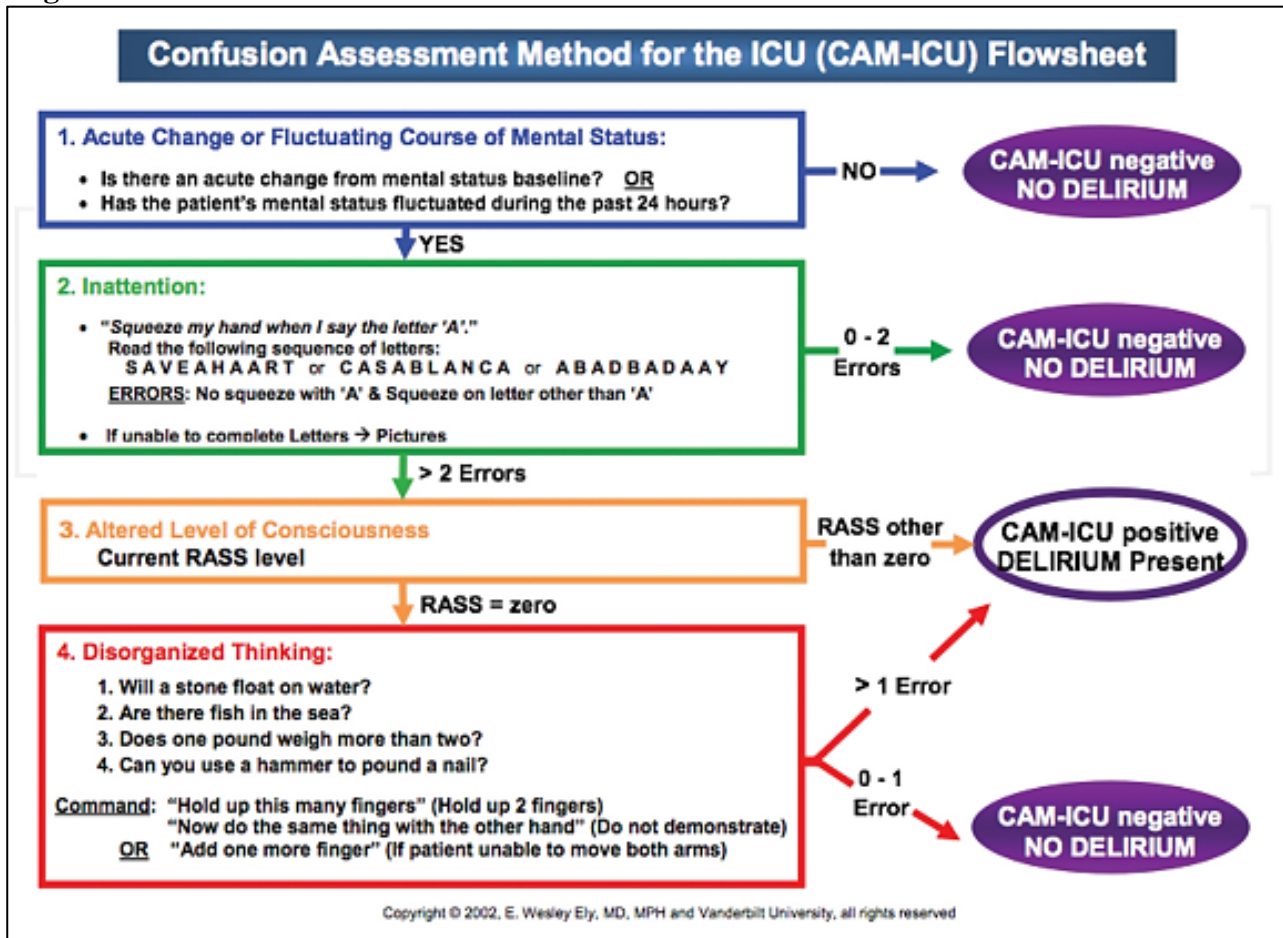
(E and F) All validation study of the delirium predictive score



Supplemental file

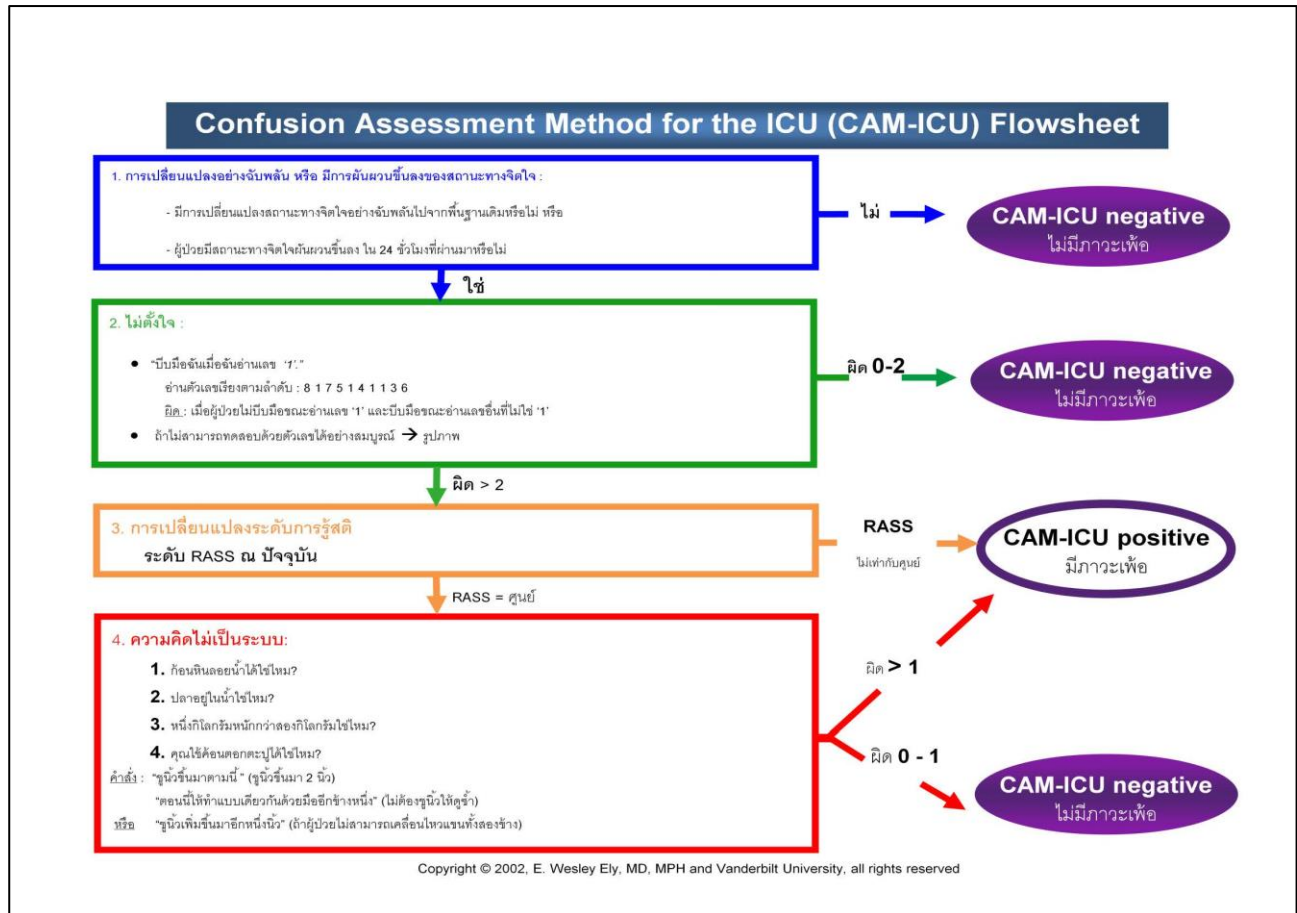
S1. Confusion Assessment method for the ICU (CAM-ICU) tool

English Version



Ely EW, Margolin R, Francis, J, et al. Evaluation of delirium in critically ill patients: Validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). *Crit Care Med* 2001;29:1370–9. [https://doi:10.1097/00003246-200107000-00012](https://doi.org/10.1097/00003246-200107000-00012).

Thai Version



Pipanmekaporn T, Wongpakaran N, Mueankwan S, et al. Validity and reliability of the Thai version of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). *Clin Interv Aging* 2014;9:879–85. <https://doi:10.2147/CIA.S62660>.

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Supplemental file

S2. Modified Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) tool

English version

Items	Comparing the elder's change with the previous 10 years				
	1 Much improve	2 A bit improve	3 Not much change	4 A bit worse	5 Much worse
1. Recognizing the faces of family and friends					
2. Remembering the names of family and friends					
3. Remembering things about family and friends eg, occupations, birthdays, addresses					
4. Remembering things that have happened recently					
5. Recall conversations a few day later					
6. Forgetting what he/she want to say in the middle of a conversation					
7. Remembering his/her address and telephone number					
8. Remembering what day and month it is					
9. Remembering where things are usually kept					
10. Remembering where to find things which have been put in a different place from usual					
11. Remembering things that happened to him/her when he/she was young					
12. Remembering things he/she learned when he/she was young					
13. Knowing about important historical events of the past					
14. Adjusting to any change in his/her day-to-day					
15. Knowing how to work familiar machines around the house					
16. Learning to use a new gadget or machines around the house					
17. Learning the new things that in general					
18. Understanding the meaning of unusual words					
19. Understanding magazine or newspaper articles					
20. Following a story in a book or on TV					
21. Contacting with friends or for business purposes					
22. Making decisions on everyday matters					
23. Handing money for shopping					
24. Handing financial matters					
25. Handing other everyday arithmetic problems, eg knowing how much food to buy, knowing a period of time for doing activity					
26. Using his/her intelligence to understand what's going on and to reason things through					
27. Able to sing or pray the used one					
28. Selecting appropriate instrument					
29. Keep speak repeating					
30. Carrying out daily activities					
31. Traveling to familiar place					
32. Working ability					

Thai Version

	การเปลี่ยนแปลงระหว่าง 10 ปีที่แล้วกับปัจจุบัน				
	1 ดีขึ้นมาก	2 ดีขึ้นเล็กน้อย	3 ไม่เปลี่ยนแปลง	4 แย่ลงเล็กน้อย	5 แย่ลงมาก
1. ความจำเกี่ยวกับหน้าตาคนในครอบครัวหรือญาติ					
2. ความจำเกี่ยวกับชื่อคนในครอบครัวหรือญาติ					
3. ความจำในรายละเอียดของคนในครอบครัวหรือญาติเกี่ยวกับอาชีพที่อยู่					
4. ความจำในเหตุการณ์ที่เกิดขึ้นเมื่อ 2-3 วันที่ผ่านมา					
5. ความจำในเรื่องที่สนทนาไปเมื่อ 2-3 วันที่ผ่านมา					
6. พุดคุยอย่างต่อเนื่องโดยไม่ลืมสิ่งที่จะพูด					
7. จำได้ว่าตอนนี้พักอาศัยอยู่ที่ไหน					
8. จำได้ว่าวันนี้เป็น วัน เดือน อะไร					
9. ความจำเกี่ยวกับที่ประจำที่ใช้เก็บของในบ้าน					
10. จำได้ว่าวางของไว้ที่ไหน					
11. จำเหตุการณ์เกี่ยวกับคนในวัยเด็ก					
12. จำสิ่งที่ตนได้เรียนรู้ในวัยเด็ก					
13. ทราบเหตุการณ์ที่สำคัญในอดีต					
14. ความสามารถในการปรับตัวเข้ากับการเปลี่ยนแปลงในชีวิตประจำวัน					
15. สามารถใช้เครื่องมือที่คุ้นเคยภายในบ้าน					
16. สามารถเรียนรู้การใช้เครื่องมือ เครื่องใช้ใหม่ๆ ในบ้าน					
17. สามารถเรียนรู้สิ่งใหม่ ๆ ทั่ว ๆ ไป					
18. สามารถเข้าใจความหมายของคำแปลก ๆ					
19. สามารถเข้าใจบทความในหนังสือพิมพ์หรือนิตยสาร					
20. สามารถติดตามเรื่องราวต่างๆ ในวิทยุ หรือโทรทัศน์					
21. สามารถติดต่อลูกหลาน ญาติหรือกิจธุระต่างๆ ไป					
22. ความสามารถในการตัดสินใจเรื่องต่าง ๆ ในชีวิตประจำวัน					
23. ความสามารถในการใช้จ่าย					
24. ความสามารถในการจัดสรรเรื่องเงิน					
25. สามารถประมาณได้ว่าจะใช้สิ่งของประมาณเท่าไร เช่น จะซื้ออาหารเท่าไร หรือระยะเวลาที่ใช้ในการทำกิจกรรมต่างๆ เช่น ใช้เวลาในการเดินทางเท่าไร					
26. สามารถที่จะเข้าใจในสิ่งที่เกิดขึ้น พร้อมกับให้เหตุผลในสิ่งนั้นได้					
27. สามารถร้องเพลงที่เคยร้อง หรือ สวดมนต์ที่เคยสวด					
28. สามารถเลือกใช้เครื่องมือเครื่องใช้ต่าง ๆ ได้อย่างเหมาะสมกับงาน					
29. การพูดจาหรือถามซ้ำๆ					
30. สามารถปฏิบัติกิจวัตรประจำวันของตนเอง					
31. สามารถเดินทางไป-กลับสถานที่ที่คุ้นเคยได้โดยลำพัง					
32. สามารถทำงานที่เคยทำ					

Siri S, Okanurak K, Chansirikanjana S, et al. Modified Informant Questionnaire on Cognitive decline in the Elderly (IQCODE) as a screening test for dementia for Thai elderly. *Southeast Asian J Trop Med Public Health* 2006;37:587-94.