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Development and validation of a dynamic delirium prediction rule in patients admitted to the Intensive Care Units (DYNAMIC-ICU): A prospective cohort study

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ABSTRACT

Background: Delirium is one of the most common cognitive complications among patients admitted to the intensive care units (ICU).
Objective: To develop and validate a **DYNA**mic deliriu**M** pred**IC**tion rule for **ICU** patients (DYNAMIC-ICU) and to stratify patients into different risk levels among patients in various types of ICUs.
Design: Prospective cohort study.
Setting and participants: A total of 560 (median age of 66 years, 62.5% male) consecutively enrolled patients from four ICUs were included in the study. The patients were randomly assigned into either the derivation (n = 336, 60%) or the validation (n = 224, 40%) cohort by stratified randomization based on delirium/non-delirium and types of ICU.
Methods: The simplified Chinese version of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) was used to assess delirium until patients were discharged from the ICUs. Potential predisposing, disease-related, and iatrogenic and environmental risk factors as well as data on patients' outcomes were collected prospectively.
Results: Of the enrolled patients, 20.2% and 20.5% developed delirium in the derivation and validation cohorts, respectively. Predisposing factors (history of chronic diseases, hearing deficits), disease-related factors (infection, higher APACHE II scores at admission), and iatrogenic and environmental factors (the use of sedatives and analgesics, indwelling catheter, and sleep disturbance) were identified as independent predictors of delirium. Points were assigned to each predictor according to their odds ratio to create a prediction rule which was internally validated based on total scores and by bootstrapping (AUCs of 0.907 [95% CI 0. 871 -0.944], 0.888 [95% CI 0.845-0.932], and 0.874 [95% CI 0.828-0.920]), respectively. The total score of the DYNAMIC-ICU ranged from 0 to 33 and patients were divided into low risk (0–9), moderate risk (10–17), high risk (18–33) groups in developing delirium according to their total score with incidence of delirium at 2.8%, 16.8% and 75.9% in the derivation group, respectively. The DYNAMIC-ICU and its performance of risk level stratification were further validated in the validation cohort (AUC = 0.900 [95% CI 0.858-0.941]). The all-cause mortality was increased and the length of hospital stay was prolonged dramatically with the increase of delirium risk levels in both derivation ($p = 0.034$, $p < 0.001$) and validation cohorts ($p < 0.001$, $p < 0.001$).
Conclusions: Seven predictors for ICU delirium were identified to create DYNAMIC-ICU, which could well stratify ICU patients into three different delirium risk levels, tailor risk level changes, and predict in-hospital outcomes by a dynamic assessment approach.

What is already known about the topic?

- Delirium is one of the most common cognitive complications among patients admitted to ICU settings with incidences varying from 19% to 80% depending on different patient populations. It is,

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however, highly preventable and reversible through adequate interventions based on risk factors and risk levels.
- There are existing delirium prediction rules developed for elderly people and ICU patients. Moreover, prediction rules for delirium were also developed based on preoperative factors among patients who underwent cardiac surgery.
- All delirium prediction rule developed in previous studies are static models and the independent predictors identified and included in previously developed ICU delirium prediction rules are predominantly patients' predisposing factors and disease-related factors.

What this paper adds

- A prediction rule was developed using parameters that were dynamic in nature. It could well stratify patients from various ICU settings into three different risk levels in developing delirium and in-hospital outcomes dynamically.
- Besides patients' predisposing factors and disease-related factors, the current prediction rule identified and included environmental factors which were not included in previously developed ICU delirium prediction rules.
- This study identified two independent predictive factors, hearing deficits and sleep deprivation, which has extended the previous work in addressing ICU delirium prediction rule. The predictors included in the current prediction rule may provide insights of underlying pathophysiology of ICU delirium.

1. Introduction

Delirium is a cognitive disorder characterized by a fluctuating process of disorganized thinking or altered level of consciousness (Girard et al., 2008; van den Boogaard et al., 2012,2014). Delirium occurs frequently among critically ill patients who are admitted to the intensive care unit (ICU) (Girard et al., 2008). The incidence of delirium in ICU patients (ICU delirium) has been reported as varying from 19% to 80% depending on different patient population studied (Ely et al., 2003; Eizadi-Mood et al., 2014; van den Boogaard et al., 2010; Wang et al., 2013). ICU patients who have developed delirium are predisposed to adverse short term outcomes, such as increased risk of in-hospital mortality and prolonged ICU and hospital stays (Ely et al., 2001, 2004; Salluh et al., 2015; Zhang et al., 2013a,b). Delirium can also result in significant long term consequences, such as cognitive and functional impairments, even permanent brain damage if the delirium is not well managed, therefore resulting in decreased quality of life (Carrasco et al., 2014; Girard et al., 2008; Ouimet et al., 2007; Pandharipande et al., 2013; Salluh et al., 2015; Trogrlić et al., 2015).

Delirium, as shown in previous studies, is highly preventable and reversible in its early stage with interventions that target risk factors categorized as predisposing factors, diseased related factors, and iatrogenic and environmental factors (Ely et al., 2001; Trogrlić et al., 2015; Zhang et al., 2013a,b). The most commonly recommended preventive and early management interventions are often targeting at the iatrogenic and environmental factors, such as the ABCDEF bundle: Awakening and Breathing, Coordination, Delirium monitoring/management, Early exercise/mobility, and Family empowerment (Bounds et al., 2016; Morandi et al., 2017; Yang et al., 2014; Zhang et al., 2013a,b). ABCDEF bundle has been proved as an effective measure in preventing delirium occurrence as well as reducing the severity and duration of delirium once it occurs. Patients with various risk factors or with different risk levels respond differently to the interventions(O'Mahony et al., 2011; Popp and Arlt, 2012; Zhang et al., 2013a,b). Therefore, a prediction rule, which is based on presenting delirium risk factors and classifies ICU patients into different risk levels in developing delirium, can assist health care providers to determine the possibility of delirium occurrence and select appropriate preventive measures (Kobayashi et al., 2013).

Several delirium prediction rules have been developed to predict potential high risk patients in developing delirium, and most of which do not include all three types of delirium risk factors and do not classify patients into different risk levels (Kennedy et al., 2014; Oldenbeuving et al., 2014). Although, Carrasco et al. (2014) created a delirium predictive scoring system for elderly patients who were admitted to the general medical wards, the authors did not stratify patients into different risk levels for developing delirium based on the risk scores. Rudolph et al. (2009) developed a delirium prediction rule based on preoperative factors among patients who underwent cardiac surgery and aimed to predict the occurrence of postoperative delirium. However, the study population was limited to patients with cardiac surgery, and the rules developed may not be applicable to other types of ICU patients or general ICU patients. van den Boogaard et al. (2012) conducted a study to develop and validate an ICU delirium prediction rule through a multinational study; however, this prediction rule only has a sensitivity of 46.2% and 30.0% in identifying high-risk and very high-risk patients.

All the prediction rules developed in previous studies are static models that do not take into account the changes in patients' health status or risk factors during their ICU stay (Carrasco et al., 2014; Kennedy et al., 2014; Oldenbeuving et al., 2014; Rudolph et al., 2009; van den Boogaard et al., 2012). Delirium is the result of cumulative or additive effect of all risk factors that may present at times, or come and go prior to the onset of delirium. Therefore, the risk level of ICU patients to develop delirium during their ICU stay should be predicted by all risk factors that present prior to the occurrence of delirium (Hales and Yudofsky, 2003; van den Boogaard et al., 2012). In achieving this goal, a delirium risk prediction rule which allows ICU nurses or physicians to assess ICU patients' delirium risk in a dynamic manner is needed.

The current study was aimed to develop and validate an ICU delirium risk dynamic prediction rule (**DYNA**mic deliriu**M** pred**IC**tion rule for **ICU** patients, DYNAMIC-ICU**)** which can be used in various ICU settings to stratify patients into different risk levels in developing delirium. Our secondary aim was to examine the correlations of predicted delirium risk levels with adverse in-hospital outcomes to further verify the accuracy of the DYNAMIC-ICU in predicting the risk level stratification.

2. Method

2.1. Study setting

This prospective cohort study was conducted among adult patients admitted to the following ICU settings: General Surgical Intensive Care Unit (SICU), Thoracic Vascular Surgery Intensive Care Unit (TVICU), Cardiac Intensive Care Unit (CCU), and Respiratory Intensive Care Unit (RICU), in a university-affiliated tertiary hospital in Beijing, China. Patients who were admitted to these settings between January 2009 and January 2010 were consecutively recruited to the study. The study was approved by the institutional review board (Approval number: 2010SY27). Written informed consent was obtained from patients or their surrogates at the time of enrollment.

2.2. Participants

Patients who were aged 18 years old or above, admitted to the four ICUs after surgery or for receiving intensive medical care, and

were expected to stay in the ICUs for at least 24 h or longer were included in this study.

Patients were excluded from the study if they: (1) reported a history of severe dementia, psychosis or serious neurologic disease such as hemorrhagic or ischemic stroke and pulmonary encephalopathy; (2) were comatose or heavily sedated after admission; (3) died before developing delirium during the first 2 days after ICU admission; (4) had difficulties in communication because of aphasia or inability to speak and understand Mandarin; or (5) refused to participate in the study.

2.3. Assessment for delirium

Using the simplified Chinese version of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU), Patients were assessed for delirium twice a day at around 7 A M and 7 PM until they were discharged from the ICUs, by one of the two well-trained nursing researchers (Kappa coefficient of 0.92). The simplified Chinese version of CAM-ICU has been tested for its validity and reliability among ICU patients in Mainland China, with a sensitivity, specificity, and inter-rater reliability of 91.8% to 93.4%, 87.7% to 90.8%, and 0.92, respectively (Wang et al., 2013). CAM-ICU assesses four features of delirium including "acute onset of changes or fluctuations in the course of mental status" (feature 1), "inattention" (feature 2), "disorganized thinking" (feature 3), and "altered level of consciousness" (feature 4) (Ely et al., 2001; Wang et al., 2013). The level of consciousness was assessed using the Richmond Agitation Sedation Scale (RASS) (Ely et al., 2003; Sessler et al., 2002) and results were used to determine the presence or absence of feature 1 and 3, as well as to determine whether or not the patient needed further assessment on feature 2 or/and feature 4. A score of -4 or lower against RASS was defined as coma or heavily sedated among patients using sedatives and they were assessed later (Girard et al., 2008). Delirium was determined when either feature 3 or 4 being positive in addition to positive findings for both feature 1 and 2. The first positive delirium assessment result was used both for prediction rule construction and validation.

2.4. Assessment of risk factors

Possible risk factors related to delirium were categorized into three groups: patients' predisposing factors, disease-related factors, and iatrogenic and environmental factors. Patient's predisposing factors, including baseline demographic data, history of chronic diseases (respiratory diseases, cardiac diseases, diabetes mellitus and hypertension) and delirium, history of alcohol drinking or abuse, visual and hearing deficits were obtained at admission. Data were collected from the patients or their caregivers if the patients could not provide relevant information themselves, as well as through review of patients' medical records. The cognitive status was also assessed with the Mini Mental State Examination (MMSE) and the scores were explained based on patient's educational level (Folstein et al., 1975). The total MMSE score is ranged between 0–30 with an interpretation of the higher the score, the better the cognitive function.

Disease-related information was collected after patients were enrolled in the study. Types of surgery and the duration (including cardiac, vascular, thoracic or abdominal surgeries, as well as interventional procedures) were collected postoperatively if applicable. The severity of illness at admission was assessed using the Acute Physiology and Chronic Health Evaluation II (APACHE II), which has been validated and reported with a high sensitivity and specificity in the Chinese population (Li et al., 2008). The APACHE II score determines the severity of illness based upon 12 physiologic measurements such as hypoxemia, and abnormal laboratory values such as the level of hemoglobin. The APACHE II has a maximum score of 71, the higher the APACHE II score, the more severe the patient's condition (Knaus et al., 1985). Because some parameters such as the heart rate and respiratory rate were measured at multiple times during the first 24 h of ICU admission, the most abnormal values of all multiple measured parameters were used to calculate the APACHE II score in this study. Infection was defined as fever with an axillary temperature of 37.5 °C or above after ruling out absorptive fever, or having a positive blood, urine, or sputum culture. Conditions such as the presence of pain were assessed daily until the patient was discharged from ICUs. Pain was assessed using the Numeric Pain Rating Scale (NPRS) (Hawker et al., 2011; Jensen and Mcfarland, 1993), with 0 as no pain at all and 10 as the most severe pain ever experienced.

Data about iatrogenic and environmental factors including mechanical ventilation, the use of sedatives or analgesics, restraint, indwelling catheter (for 24 h or longer), as well as sleep disturbance were collected daily until patients were discharged from the ICUs. Sleep disturbance was assessed using the self-report Richards-Campbell Sleep Questionnaire (RCSQ) and defined when a score was 25 or lower (Chen et al., 2016; Richards et al., 2000).

In order to develop a dynamic prediction rule and take into account the dynamic changes in patients' health status and risk factors, as well as their cumulative effect on the onset of delirium during their ICU stay, we collected data on all potential disease-related factors and iatrogenic and environmental predictors daily. In developing and validating the DYNAMIC-ICU, we used the most abnormal values on those repeat measured potential risk factors on the days prior to the development of delirium for patients who developed delirium (first positive result), or during the ICU stay for those who did not develop delirium.

2.5. In-hospital outcomes

The in-hospital outcomes such as the declining of cognitive status (decline in MMSE scores at discharge), all-cause in-hospital mortality, and the length of ICU and hospital stay were collected until patient was discharged from the hospital. Complications or adverse incidents such as development of pressure ulcer, gastric aspiration, and accidental tube removal were also collected, and only incidents that occurred after the onset of delirium were included in analysis for the delirium group.

2.6. Statistical analysis

According to the rule in logistic regression (Vittinghoff and Mcculloch, 2007), we needed at least five patients with delirium for each variable to be included in the model (Kennedy et al., 2014; Martinez et al., 2012). Our study had 13 candidate variables for model building and seven variables for model validating. Assuming a prevalence of delirium of 20%, we need at least 325 patients for the derivation cohort and 175 for the validation cohort with a total of 500 patients. We enrolled 682 patients in the study and 560 were included in the final analysis. A stratified randomization based on delirium, non-delirium and types of ICU admission was used to divide 60% of consecutively recruited patients into the derivation cohort (336 patients) and 40% into the validation cohort (224 patients) using computer generated random numbers. Therefore, the sample size for both derivation and validation cohort were adequate for model development and validation. Continuous variables were expressed as means and standard deviation for normally distributed variables and median with interquartile range for non-normally distributed data. Categorical variables were expressed using proportions or percentages.

To compare the differences in patients' characteristics and possible delirium risk factors between derivation and validation

cohorts, patients were divided into delirious or non-delirious groups in the derivation cohort, Student *t* test or Mann-Whitney rank-sum tests were used for continuous variables where appropriate. Chi-square test or Chi-square test for $r \times k$ contingency table were conducted for categorical variables and partitioning Chi-square test for $r \times k$ contingency table was used if there was a difference to determine which cells contributed to the significant differences found.

For the prediction rule derivation, candidate covariates (with $p \leq 0.10$ in univariate analysis or considered as clinically relevant) were entered into the backward stepwise multiple logistic regression for modeling to identify the independent predictors of ICU delirium (Fine et al., 1997). Odds ratios (OR) and their 95% confidence interval (CI) were used to assess the independent contribution of the predictors. The Hosmer-Lemeshow test was performed to assess the goodness of fit of all models. In order to develop a prediction rule which is easy to use in the clinical settings, continuous variables, such as the APACHE II score, were dichotomized using a cut-off point determined by the receiver operating characteristics curve (ROC) if they remained in the model, and remodeled again as categorical variables.

We estimated the predictive ability of the model using the area under the ROC (AUC). Bootstrapping techniques were used to adjust for overfitting that is for overly optimistic estimates of the regression coefficients of the risk factors in the model, sampling for 1000 times.

Points were assigned to each predictor according to their OR values and summated to create an ICU delirium risk score. Rules in identifying subjects as low, moderate, or high risk of developing delirium were created based on the proportion of patients who developed delirium with different ranges of total risk scores. The prediction rule was validated for delirium prediction in the validation cohort using logistic regression, and its AUC was calculated. The ICU delirium risk score was then calculated for each patient in the validation cohort based on the established rule. Patients were grouped into different risk levels according to their risk scores. We compared the proportions of subjects who were delirious in each risk level within each cohort. If there were differences found, the proportions of delirium in each risk level in the validation cohort were compared with the corresponding risk level in the derivation cohort using Chi-square test for $r \times k$ contingency table and partitioning Chi-square test for $r \times k$ contingency table.

To assess the predictive value of the established rule for clinical outcomes, stratified comparisons were performed in terms of the length of ICU and hospital stay, all-cause mortality and cognitive changes at discharge among low, moderate, and high risk groups in both derivation and validation cohorts using Wilcoxon rank test or Fishers Exact Tests. Data were missing at random, mean imputation technique was used to impute data applying the mean value of the study sample for the delirium or non-delirium group (van den Boogaard et al., 2012). In the derivation and validation cohorts, a total of 11.6% of the MMSE scores were missing and imputed. All statistical analyses were conducted using SPSS 21.0 (IBM Corp, Armonk, NY), and *a priori* of 0.05, two-tailed, was set to detect any significant findings. Bootstrap analyses were conducted using R 3.3.1.

3. Results

3.1. Characteristics of the participants

In total, 682 patients were admitted consecutively to the four ICUs during the study period. As shown in Fig. 1, 560 patients were

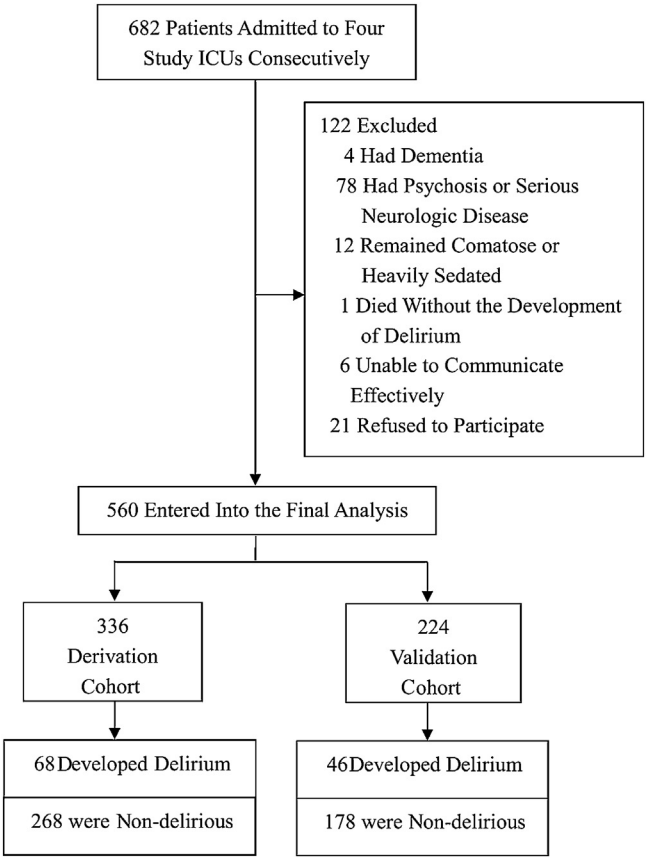

Fig. 1. Flow Diagram of Patients in Study Cohorts.

included for the final analysis with a median age of 66 years (range 20–92 years), and 62.5% being male. The mean follow-up time was 18.0 ± 13.0 days (range 2-201 days). Patients were then randomly divided into derivation (n = 336) and validation cohorts (n = 224) by stratified randomization based on delirium/non-delirium as well as the types of ICU admission.

The characteristics of the participants and group differences between the derivation and validation cohorts were presented in Table 1. The proportion of patients who were identified as delirious was 20.2% (n = 68) in the derivation group and 20.5% (n = 46) in the validation group. In both derivation and validation cohorts, the incidences of ICU delirium in SICU, TVICU, CCU, RICU were 23.1% vs 23.6%, 25.5% vs 25.8%, 10.9% vs 10.3%, and 45.5% vs 50.0%, respectively. The incidence of delirium and the types of ICU admission were not significantly different between the two cohorts. There were also no significant differences between the derivation and the validation cohorts in terms of demographic and study variables included in this study, such as age, gender, history of chronic diseases, the APACHE II score, and the MMSE score.

3.2. Development of prediction model

In the derivation cohort (n = 336), the results comparing patients' characteristics between the delirium and non-delirium groups were shown in Table 2. The median age of patients in the delirium group (76 years, range 41–92 years) was older than those in the non-delirium group (65 years, range 20–89 years, p = 0.005). Patients in the delirium group tended to have lower education levels and presented with higher rates on history of chronic diseases, long-term medication, visual and hearing deficits, the use of sedatives or analgesics, mechanical ventilation, restraint, indwelling catheter, and sleep disturbance than those without delirium. The cognitive level measured by the MMSE was lower among patients in the delirium group than those in the non-delirium group (p = 0.008).

Since the APACHE II score already incorporated the contributions from age, fever, hypoxemia, and abnormal laboratory values such as the levels of hemoglobin, serum potassium, and serum sodium, therefore, only the APACHE II score was used for modeling. With a total of 13 potential predictors included for the multiple logistic regression modeling, seven variables (history of chronic diseases, hearing deficits, infection, higher APACHE II score, use of sedative and analgesic drugs, indwelling catheter and sleep disturbance) remained in the final model (Table 2, model 1).

ROC analysis of the APACHE II score was performed and a cut-off point of 7.5 was selected based on its optimal sensitivity and specificity. The APACHE II scores were then dichotomized and remodeled as categorical variable. The goodness of fit of the model was 0.544 with an AUC of 0.907 (95% CI 0. 871–0.944; Fig. 2 A). Bootstrap analysis revealed an AUC of 0.874 (95% CI 0.828–0.920).

3.3. Development of the DYNAMIC-ICU

As shown in Table 2, we assigned points to each predictor based on their OR values in the model, which resulted in the total score of the model as ranging from 0 to 33. Internal validation of the model based on the total scores in the derivation dataset revealed an AUC of 0.888 (95% CI 0.845-0.932, Fig. 2B).

As shown in Fig. 2C, patients were stratified into three different risk levels in developing delirium according to their total risk

Table 1
Descriptive Analysis for Derivation Cohort and Validation Cohort.

Variables	Derivation Cohort (n = 336)	Validation Cohort (n = 224)	*p* value
Predispose factors			
Age (years)	68.5 (20-92)	69.0 (22-90)	0.959
Gender (Male)	202 (60.1)	148 (66.1)	0.181
Education level (Below primary school)	141 (39.2)	82 (36.6)	0.364
History of chronic diseases	220 (65.5)	146 (65.2)	1.000
Smoking	118 (35.1)	96 (42.9)	0.076
Alcohol	47 (14.0)	34 (15.2)	0.714
Current use of medications, Sedatives	6 (1.8)	5 (2.2)	0.761
History of long-term medication	187 (55.7)	123 (54.9)	0.863
Number of drugs more than 3	102 (30.4)	62 (27.7)	0.844
History of delirium	2 (0.6)	0	–
Visual deficits	56 (16.7)	40 (17.9)	0.732
Hearing deficits	32 (9.5)	21 (9.4)	1.000
MMSE when admission	25.0 (11-30)	25.0 (14-30)	0.412
Type of ICU			0.997
SICU	108 (32.1)	72 (32.1)	
TVICU	98 (29.2)	66 (29.5)	
CCU	119 (35.4)	78 (34.8)	
RICU	11 (3.3)	8 (3.6)	
Disease-related factors			
Surgery	198 (58.9)	139 (62.1)	0.067
General anesthesia	160 (47.6)	122 (54.5)	0.121
Surgical time	1.0 (0-12)	2.0 (0-8.5)	0.199
Infection	50 (14.9)	29 (12.9)	0.538
APACHE II	6.0 (0-22)	7.0 (0-59)	0.091
Pain	0 (0-10)	0 (0-10)	0.439
Iatrogenic and environmental factors			
Use of sedatives or analgesics	134 (39.9)	76 (33.9)	0.181
Mechanical ventilation	100 (29.8)	71 (31.7)	0.640
Duration of ventilation	0 (0-648)	15.5 (0-984)	0.642
Restraint	98 (29.2)	68 (30.4)	0.777
Indwelling catheter	195 (58.0)	129 (57.6)	0.931
Sleep disturbance	55 (16.4)	39 (17.4)	0.818
Follow-up time	18 (3-96)	19 (2-201)	0.823

Abbreviation: MMSEmini-mental state examination; ICUintensive care unit; SICUgeneral surgery intensive care unit; TVICUthoracic vascular surgery intensive care unit; CCUcardiac intensive care unit; RICUrespiratory intensive care unit; APACHE IIacute physiology and chronic health evaluation.

Table 2
Univariate and Multiple Logistic Regression of ICU Delirium Risk Factors and Points Assigned for DYNAMIC-ICU.

Univariate analysis			
Variables	Derivation Cohort		
	Delirium Group (n = 68)	Non-Delirium Group (n = 268)	*p* value
Predispose factors			
Age	76 (41-92)	65 (20-89)	0.005
History of chronic diseases	57 (83.8)	163 (60.8)	< 0.001
History of long-term medication	50 (73.5)	137 (51.1)	0.001
Visual deficits	22 (32.4)	34 (12.7)	< 0.001
Hearing deficits	20 (29.4)	12 (4.5)	< 0.001
MMSE when admission	23 (15-30)	26 (11-30)	0.008
Type of ICU			0.005
SICU	25 (23.1)	83 (76.9)	
TVICU	25 (25.5)	73 (74.5)	
CCU	13 (10.9)	106 (89.1)	
RICU	5 (45.5)	6 (54.5)	
Disease-related factors			
Infection	27 (39.7)	23 (8.6)	< 0.001
APACHE II	10 (3-22)	6 (0-18)	< 0.001
Iatrogenic and environmental factors			
Use of sedatives or analgesics	46 (67.6)	88 (32.8)	< 0.001
Mechanical ventilation	37 (54.4)	63 (23.5)	< 0.001
Restraint	34 (50.0)	64 (23.9)	< 0.001
Indwelling catheter	58 (85.3)	137 (51.1)	< 0.001
Sleep disturbance	37 (32.5)	57 (12.8)	< 0.001

Multiple Logistic model and points assigned					
Variables	Wald	OR	95%CI	*p* value	Points assigned for DYNAMIC-ICU
Hearing deficits	12.58	9.18	2.70 - 31.23	< 0.001	9
Indwelling catheter	14.91	7.96	2.78 - 22.79	< 0.001	8
Infection	8.77	4.10	1.61 - 10.42	0.003	4
Use of sedatives or analgesics	6.58	2.75	1.27 - 5.95	0.010	3
Sleep disturbance	4.91	2.89	1.13 - 7.39	0.027	3
History of chronic diseases	5.75	3.14	1.23 - 7.99	0.016	3
APACHE II	7.87	3.20	1.42 - 7.20	0.005	3
Total					33

Abbreviation: MMSE, mini-mental state examination; ICU, intensive care unit; SICU, general surgery intensive care unit; TVICU, thoracic vascular surgery intensive care unit; CCU, cardiac intensive care unit; RICU, respiratory intensive care unit; APACHE II, acute physiology and chronic health evaluation; CI, confidence interval; Points assigned to each predictor based on their OR values.

scores: low risk (0–9), moderate risk (10–17), and high risk (18–33), with the incidence rates of delirium at 2.8%, 16.8%, and 75.9% ($p < 0.001$), respectively, in the derivation cohort.

3.4. Validation of the DYNAMIC-ICU

Fig. 2D shows the results of the multivariate logistic regression using the seven predictors in the validation cohort with the AUC value of 0.900 (95% CI 0.858-0.941). As shown in Fig. 2C, after the patients were grouped into low, moderate and high risk groups according to their risk scores, the incidence of delirium increased gradually (7.3%, 19.0% and 63.9%, respectively, $p < 0.001$). No significant differences were detected at the corresponding risk levels between the validation and the derivation cohorts ($p = 0.507$).

3.5. Association of risk levels with in-hospital outcomes

As shown in Table 3, all-cause mortality increased dramatically and significantly along with the elevation of ICU delirium risk levels in both derivation ($p = 0.034$) and validation cohorts ($p < 0.001$). Trends of prolonged lengths of ICU and hospital stay were observed as patients' risk for developing delirium increased in both the derivation ($p < 0.001$) and validation cohorts ($p < 0.001$). Additionally, a trend of declining cognitive function was found in two cohorts along with increased risk levels. Pressure ulcer (1.1%), gastric aspiration (0.2%), and tube removal behaviors (1.4%) were not analyzed because their prevalence was all below 5%.

4. Discussion

In this prospective cohort study of patients from four ICU settings, delirium was quite common, with RICU patients having the highest incidence rate (45.5% to 50.0%). We identified a total of seven predictors that were independently associated with the development of ICU delirium with two predisposing factors (history of chronic diseases and hearing deficits), two disease-related factors (infection and severity of the diseases indicated by the APACHE II score), and three iatrogenic and environmental factors (the use of sedatives or analgesics, indwelling catheter, and sleep disturbance). We then developed the DYNAMIC-ICU with seven predictors for predicting ICU delirium in the derivation cohort and then validated it. The DYNAMIC-ICU had a good performance in both derivation and validation cohorts with the C statistic at 0.907 and 0.900, respectively. With a possible total score of 0 to 33, the DYNAMIC-ICU clearly classified ICU patients into three different risk levels (low risk: 0–9, moderate risk: 10–17, and high risk: 18–33), with the incidence for developing delirium increasing from 2.8%, 16.8%, to 75.9% for each level change. The DYNAMIC-ICU could also well predict hospital outcomes, with the higher the risk levels, the worse the in-hospital outcomes, which in turn, further confirms the good performance of the DYNAMIC-ICU.

Our DYNAMIC-ICU has face validity because four of the predictors in our prediction rule, the APACHE II score, infection, the use of sedatives or analgesics, and the use of indwelling catheter have been reported as independent predictors in previous prediction models (Oldenbeuving, 2014; Pendlebury et al., 2017;

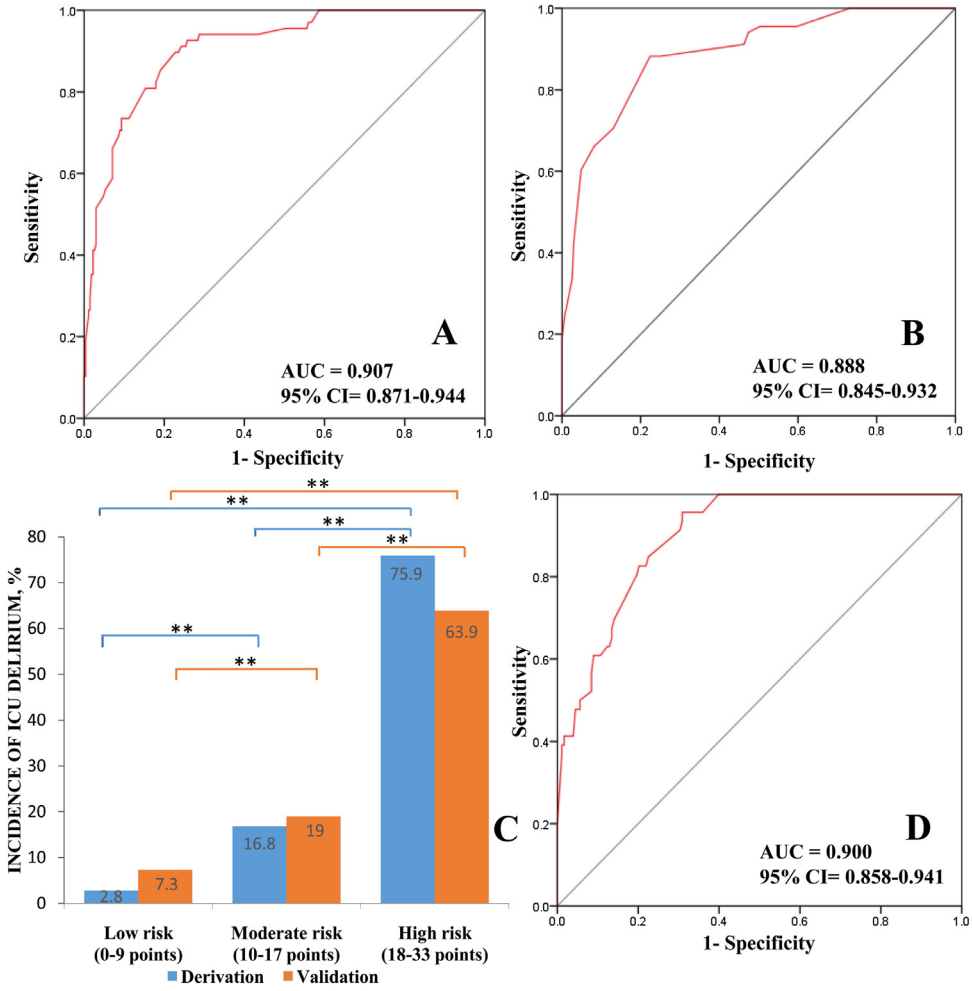

Fig. 2. ROCs of the Prediction Model and the DYNAMIC-ICU.
A: ROC based on 7 risk factors in the derivation dataset; B: ROC based on total scores in the derivation dataset; C: Performance of the rule in derivation cohort and validation cohort; D: ROC based on 7 risk factors in the validation dataset.
CI, confidence interval; $^{**}p < 0.001$

Inouye et al., 1993; Inouye and Charpentier, 1996). To the best of our knowledge, the identification of the additional predictors, hearing deficits and sleep disturbance, has extended the previous work in addressing ICU delirium prediction rule. Both hearing deficits and sleep disturbance have long been proposed as risk factors for delirium, but none of them have previously been included in a delirium prediction model or prediction rule (Girard et al., 2008; Inouye and Charpentier, 1996; Inouye et al., 2014; Maldonado, 2015).

The DYNAMIC-ICU established in the current study may potentially contribute to the understanding of the underlying pathophysiology of delirium. Several predictors (hearing deficits, the use of sedatives or analgesics, indwelling catheter, and sleep disturbance) that were included in the DYNAMIC-ICU are

Table 3
In-hospital Outcomes Predicted by the DYNAMIC-ICU.

Variables	Low risk (0-9)	Moderate risk (10-17)	High risk (18-33)	p value
All Cause Mortality (%, number of delirium/total)				
Derivation cohort	1.4% (2/145)^{l}	5.8% (8/137)*	9.3% (5/54)	0.034
Validation cohort	1.8% (2/109)¶	3.8% (3/79)	22.2% (8/36)†	< 0.001
Length of ICU stay				
Derivation cohort	3.45 ± 0.18¶	5.20 ± 0.45*	8.54 ± 0.89‡	< 0.001
Validation cohort	3.22 ± 0.20¶	5.20 ± 0.63*	8.91 ± 1.78†	< 0.001
Length of hospital stay				
Derivation cohort	13.95 ± 0.72¶	23.41 ± 0.92**	27.11 ± 2.00	< 0.001
Validation cohort	15.68 ± 1.32¶	25.58 ± 1.67*	30.85 ± 5.55	< 0.001
Declining of MMSE scores				
Derivation cohort	0.48 ± 0.19¶	0.21 ± 0.16	−1.90 ± 0.56‡	< 0.001
Validation cohort	0.19 ± 0.14¶	0.30 ± 0.20	−1.91 ± 0.78‡	< 0.001

$^{*}p < 0.05$. $^{**}p < 0.001$ compared with low risk group; $^{†}p < 0.05$. $^{‡}p < 0.001$ compared with moderate risk group; $^{l}p < 0.05$. $^{¶}p < 0.001$ compared with high risk group, by ANOVA or partitioning Chi-square test for r×k contingency table.

potentially associated with either hypo-stimulation or hyper-stimulation of the central nervous system (CNS). It has been proposed that one of the underlying mechanisms of delirium is the imbalance of intra-cerebral neurotransmitter, namely, the imbalance of acetylcholine (ACh) and dopamine or reduced intro-cerebral ACh levels (Girard et al., 2008; Maldonado, 2015). The use of sedatives or analgesics has been demonstrated to inhibit the release of intra-cerebral ACh (Maldonado, 2013; Trzepacz, 1994). Patients with hearing deficits are less likely to interact with the environment, which might in turn result in reduced stimulation transmitted to the CNS and lead to reduced release of ACh in the brain (Picciotto et al., 2012; Tang et al., 2014). The use of indwelling catheters keeps the bladder empty, which may result in a constant stimulation of the bladder mechanoreceptors by the catheter tip. The stimuli received by the bladder mechanoreceptors are transmitted to the CNS and first increase the release of ACh in the brain (de Groat, 1997, 2006) and a depletion of ACh might result after a prolonged stimulation and over releasing of ACh (Gibson and Peterson, 1981). Sleep disturbances might have the same underlying pathogenesis as the indwelling catheter. Further studies are needed to explore the underlying mechanism of those predictors in relation to the onset of delirium.

Our DYNAMIC-ICU, to the best of our knowledge, has the highest predictive value of stratifying ICU patients into different levels of risk in delirium development with the C statistic of 0.907 based on seven risk factors and 0.888 based on total risk scores of seven factors in the derivation cohort and 0.900 in the validation cohort (Rudolph et al., 2009; van den Boogaard et al., 2012, 2014; Wassenaar et al., 2015). Several reasons may explain these findings. Three categories of ICU delirium risk factors have been proposed. They are patient's predisposing factors, disease-related factors, and iatrogenic and environmental factors. Risk factors have cumulative effects on the development of ICU delirium, the more risk factors a patient has, the higher the risk is (Ely et al., 2004; Kennedy et al., 2014). The DYNAMIC-ICU includes at least two risk factors from each category, while none of the ICU delirium prediction rules developed in previous studies included iatrogenic and environmental factors (van den Boogaard et al., 2012, 2014; Wassenaar et al., 2015). Secondly, besides patient's predisposing factors, other risk factors often change dynamically during the ICU stay. The DYNAMIC-ICU allows ICU nurses and physicians to assess patients' risk factors daily and uses the most abnormal values of the predictors to predict the daily risk levels in developing delirium. ICU delirium prediction rules identified in previous studies only collected the predictor values immediately after ICU admission (Wassenaar et al., 2015) or within 24 h after ICU admission (van den Boogaard et al., 2012), which limits the possibility of accounting for changes in patients' health status and risk factors, and including potential iatrogenic and environmental factors in those models.

There are several strengths in the current study. The derivation and validation of the DYNAMIC-ICU were established among patients from four different ICU settings, which has a much broader application in predicting delirium in various ICU settings. More importantly, we aggressively identified and verified all the possible predictors including predisposing, disease-related, and iatrogenic and environmental factors. We took into account the dynamic nature in changes of health status and risk factors among patients in the ICUs, and used the most abnormal values on study variables prior to the onset of delirium to reflect the cumulative effects of the existing risk factors for ICU delirium. This method supports the necessity of dynamically assessing risk factors to predict the delirium risk levels daily or more often. Meanwhile, the DYNAMIC-ICU well stratifies patients into different risk levels for developing delirium and worsening of in-hospital outcomes. The DYNAMIC-ICU will therefore assist ICU nurses and physicians to initiate tailored preventive or therapeutic measures. Finally, we applied mean imputation and bootstrap resampling procedures to augment data for deriving predictors in our prediction rule. These advanced statistical methods may minimize the effects of missing data and limit model overfitting to ensure more stable variables to be included for prediction rule establishment and validation (Austin and Tu, 2004; van den Boogaard et al., 2012). Although the health status of ICU patients and risk factors for ICU delirium are constantly changing during their ICU stay, using the DYNAMIC-ICU, nurses or physicians can reasonably discover patients who are subject to develop delirium while assessing patients in their daily practice. Once risk factors are identified, timely preventive intervention to reduce the occurrence of ICU delirium should be implemented. Providing effective measures to reduce the severity and duration of delirium should follow once it occurred.

This study also has some potential limitations. First, the sample sizes were relatively small in the derivation and validation cohorts for establishing prediction rule, however, bootstrap resampling was used to limit model overfitting. Secondly, this DYNAMIC-ICU for ICU delirium was developed in one hospital, which may limit the generalizability of the findings and its application in other settings. Multicenter external validation studies are needed to further validate the DYNAMIC-ICU. Thirdly, in order to better differentiate patients with delirium from dementia, we excluded patients with severe dementia, resulting in the mean MMSE scores of ICU patients in our study being higher compared with previous studies. The mean APACHE II scores in our study were also lower compared with other studies. These two facts may contribute to the lower incidence of ICU delirium in the current study, and may limit the generalizability of the findings to patient populations with severe dementia and those with more severe conditions. Fourthly, although the APACHE II score is identified as an important independent predictor in previous studies, further studies in developing dynamic prediction rule should consider the use of Sequential Organ Failure Assessment (SOFA) which could collect dynamic parameters for developing delirium.

5. Conclusion

Seven cogent risk factors for ICU delirium were identified in our study, including history of chronic diseases, hearing deficits, infection, higher APACHE II scores, the use of sedatives and analgesics, indwelling catheter, and sleep disturbance, that were potential predictors categorized into patients' predisposing factors, disease-related factors, and iatrogenic and environmental factors. The DYNAMIC-ICU established in our study could well stratify ICU patients into three different delirium risk levels, with the risk of ICU delirium in moderate and high risk groups increased by 5 and 27 folds when compared with low risk group, which supports the idea that dynamic assessments could tailor the changes of delirium risk levels of ICU patients during their ICU stay. This DYNAMIC-ICU could also well predict in-hospital outcomes that are closely related to delirium, which further confirms its good performance. Therefore, the DYNAMIC-ICU could probably provide physicians and nurses with a dynamic tool to tailor preventive or therapeutic interventions according to patients' risk levels in ICU settings.

Conflicts of interest

All authors disclose no conflict of interest.

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