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Comparison of the effectiveness of delirium evaluation tools in intensive care patients: pre-deliric versions 1 and 2, E-pre-deliric and ICDSC

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Abstract. – OBJECTIVE: This study's objective was to compare the effectiveness of the delirium prediction model (pre-deliric) and the early prediction model (E-pre-deliric) in delirium prediction in an intensive care unit (ICU) according to the Intensive Care Delirium Screening Checklist (ICDSC). Our aim was to determine these models' usability and cut-off values for ICU patients.

PATIENTS AND METHODS: We classified the studied patients based on their highest ICDSC scores (tested twice daily) during ICU hospitalization. ICDSC scores of 4 or higher indicated positive results for delirium, whereas a score of 0 represented a negative result. We recorded the patients' demographic and clinical details and characteristics and calculated their E-pre-deliric and pre-deliric version 1 and version 2 scores. To evaluate the effectiveness of the models, we used receiver operating characteristic (ROC) curve analysis.

RESULTS: Two hundred fifty patients (55.6% males, mean age 60.6±18.7 years) participated in this study. Their mean Acute Physiology and Chronic Health Evaluation II (APACHE-II) score was 17.0±9.1. Delirium was more common in men, patients of older ages, those with high APACHE-II scores, those who had undergone urgent admissions, those with histories of trauma, those with high urea or creatinine values and those who had undergone sedation or mechanical ventilation. Compared to patients who did not develop delirium, those who did had longer ICU stays and hospital stays, as well as greater mortality risk. The cutoff values for the patients' pre-deliric version 1, pre-deliric version 2 and E-pre-deliric scores were 38% [area under ROC (AUROC)=1], 22% (AUROC=1) and 28% (AUROC=1), respectively.

CONCLUSIONS: This study is the first to compare the pre-deliric and E-pre-deliric prediction models. These models' validity and reliability were acceptable. They were clinically useful, and we identified their cut-off values. These models provide options for early detection of delirium and are easily applicable in the ICU.

Key Words:
Delirium, Mortality, Pre-deliric, E-pre-deliric, Critical care.

Abbreviations

APACHE-II: Acute Physiology and Chronic Health Evaluation II, AUROC: Area Under Receiver Operator Characteristics Curve, CAM-ICU: Confusion Evaluation Scale in the Intensive Care Unit, CPR: Cardiopulmonary Resuscitation, DSM: Diagnostic and Statistical Manual of Mental Disorders, E-pre-deliric: Early Prediction Model, ICDSC: Intensive Care Delirium Screening Checklist, ICDSC: Intensive Care Delirium Screening Checklist, ICU: Intensive Care Unit, MV: Mechanical Ventilation, Pre-deliric: Delirium Prediction Model, ROC: Receiver Operator Characteristics Curve.

Introduction

Delirium is a type of acute organic brain dysfunction that often occurs in intensive care unit (ICU) patients[1]. Delirium is characterized by a series of signs and symptoms, including fluctuating cognition, abnormal motor behavior, and emotional and sleep-wake cycle disturbances caused by varying underlying etiologies[2]. Delirium has been found[3,4] to have negative consequences in both the short term and the long term. The negative outcomes of delirium include prolonged ICU stays[5], significant and long-term dependence on mechanical ventilation (MV)[6], increased morbidity and mortality[6], and functional[7] and cognitive[5] disabilities requiring frequent hospital admissions.

Delirium's incidence in the ICU ranges from 11% to 87%[8,9]. Despite its high frequency and association with increased morbidity and mortality, delirium remains underdiagnosed in the ICU[10]. Additionally, standard clinical evaluations are

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insufficient for delirium diagnosis[11]. Therefore, delirium screening is recommended for all ICU[12].

The gold standard of delirium diagnosis is a clinical diagnosis using both the patient's history and an examination, and it follows the criteria of the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)[13]. However, using these criteria, a diagnosis of delirium in the ICU can be made only by trained psychiatrists. Therefore, the diagnosis process is prolonged, delaying delirium diagnoses in the ICU[14]. The development of internationally accepted assessment tools will enable the onset and progression of delirium in the ICU to be detected and managed without the need for psychiatric consultations[15]. The Intensive Care Delirium Screening Checklist (ICDSC), based on criteria from the DSM-4, is an internationally proven delirium screening tool, and it has the advantage of diagnosing subsyndromal delirium[16]. Structured delirium screenings facilitate early treatment[6,17] and promote the identification of patients developing delirium[11]. Along with adequate treatment, early detection and prevention of delirium are critical. Predictive models developed to identify high-risk patients enable early intervention. The delirium prediction (pre-deliric) version 1[18], pre-deliric version 2[19] and early prediction (E-pre-deliric)[20] models were developed based on risk factors for delirium in ICU patients and calibrated using the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU).

In this study, we used ICDSC criteria to diagnose delirium, and we compared these diagnoses to results from the pre-deliric version 1, pre-deliric version 2 and E-pre-deliric models patients to determine these models' usability, reliability, and cut-off values.

Patients and Methods

Study Design and Settings

This prospective observational study was performed from November 2017 to June 2019 in a 21-bed ICU of the Department of Anesthesiology and Reanimation of Trakya University's Faculty of Medicine (ClinicalTrials ID NCT03934645). All participants (conscious patients and their first-degree relatives, as well as the first-degree relatives of unconscious patients) provided informed consent.

Ethics

The Ethical Committee of the Trakya University Medical Faculty in Edirne, Turkey (Chairperson Prof. Ülfet Vatansever Özbek) provided ethical approval for this study (TÜTF-BAEK 2017/263) on 25 October 2017. All procedures followed were in accordance with the (institutional and national) ethical standards of the committee and the 1975 Declaration of Helsinki (revised in 2008).

Study Population

We followed up on all patients eligible for the study and admitted to the ICU over the 20-month study period. The study's exclusion criteria included staying in the ICU for less than 24 hours, being under 18 years old, having mental limitations such as Alzheimer's disease or dementia, having severe aphasia (unintelligible speech), being pregnant, being in a coma during the ICU stays (Richmond Sedation Agitation Scale[21]: −4/−5), developing symptoms of delirium within one's first 24 hours in the ICU (ICDSC>3 in first 24 hours), completing less than 80% of the ICDSC during one's ICU stay and scoring 1-3 points (scores indicating subsyndromal delirium) on the ICDSC during one's ICU stay.

Delirium Screening

ICU medical staff evaluated the patients for delirium using the ICDSC twice daily (once during the day, from 08:00 to 20:00, and once at night, from 20:00 to 08:00) during their ICU stays. We classified the patients according to the highest ICDSC scores they received during their ICU stays. The patient received a delirium diagnosis if they achieved an ICDSC score of 4 or more points. Patients diagnosed with delirium, according to their ICDSC scores, underwent psychiatric consultations, and we finalized their delirium according to DSM-5' criteria. If a patient achieved a score of zero during their hospitalization, they were not diagnosed with delirium. Scores of 1, 2 and 3 indicated subsyndromal delirium, and we excluded patients with such scores from the study.

Data Collection

We recorded each patient's age, gender, clinical diagnosis, history of chronic systemic disease, admission category (elective or emergent), Acute Physiology and Chronic Health Evaluation II (APACHE-II) score (used to predict hospital mortality)22 and trauma history at the time of their ICU admission. Additionally, we noted any requirement for cardiopulmonary resuscitation (CPR), sedation or mechanical ventilator treatment before ICU admission or during hospitalization. We also recorded the presence of medical devices

such as endotracheal tubes, nasogastric tubes or catheters and patients' attempts to remove these devices, swearing, grumbling, loud shouting, and violence during their ICU stays. Finally, we included patients' total ICU stay lengths, total number of days in the hospital, and mortality, if it occurred, in the patients' case report forms.

We calculated the patients' E-pre-deliric scores based on nine criteria: age in years, cognitive dysfunction, alcohol addiction, blood urea nitrogen, hospital admission category, urgency, mean arterial pressure, corticosteroid use and respiratory failure. These criteria were evaluated upon patients' admission to the ICU[20].

We used the following 10 criteria to calculate the patients' pre-deliric version 1 and version 2 scores: age in years, APACHE-II score (calculated 24 hours after ICU admission), urgency, hospital admission category, presence of infection requiring antibiotics, coma, use of sedatives, total administered morphine over 24 hours, urea level and presence of metabolic acidosis. These scores were evaluated at the end of a patient's first day in the ICU[18,19].

Sample Size

Following the power analysis, we evaluated the literature[16,18,19,23-25] and determined that 250 cases should be included in the study at a power level of 85% and a significance level of 5%.

Statistical Analysis

We conducted the statistical analysis for this study using SPSS for Windows, version 19.0 (IBM Inc., Armonk, NY, USA) and MedCalc version 14.12.0 (MedCalc Software, Ostend, Belgium). After using the single-sample Shapiro-Wilk test to check the measurable data's normal distribution, we used Student's *t*-test to compare the normally distributed groups. To evaluate non-normally distributed data, we used the Mann-Whitney U test.

For qualitative data, we used Pearson's χ^2 test and the two-sample Kolmogorov-Smirnov test. To evaluate the diagnostic tests, we used receiver operator characteristic (ROC) curve analysis. Arithmetic mean ± standard deviation and median (min-max) are provided for descriptive statistics. We set a two-sided significance limit of $p<.05$ for all statistics.

Results

During the study period, 1,597 patients were hospitalized in the ICU. This total includes patients hospitalized in the ICU more than once. In total, 458 patients met the inclusion criteria and provided informed consent. These patients were screened for delirium. Of them, 208 (45.4%) had ICDSC scores of 1, 2 or 3, thus indicating subsyndromal delirium and resulting in their exclusion from the study. We included the remaining 250 patients in the study. Figure 1 indicates the number of excluded patients, the reasons for their exclusion and the final study cohort.

The patients' mean age was 60.6 (±18.7) years, and 55.6% of the study cohort was male. Patients who had undergone emergency admissions constituted 59.2% of the cohort, 15.6% of whom had a history of trauma. The patients' mean urea concentration was 62.8 (±52.3) mg/dL, and their mean creatinine value was 1.29 (±1.21) mg/dL. Eighty-nine patients (35.6%) received sedative drugs during their ICU stays. Two hundred twenty patients (88%) underwent mechanical ventilator treatment at some point during their ICU stays.

Table I shows the demographic and clinical data for the entire cohort, both patients diagnosed with delirium and those in whom delirium did not occur. Delirium was more common in male patients, older patients, those with urgent admissions, those

Table I. Demographic characteristics of patients in the groups.

Variable	All (n=250)	No Delirium (ND) (n=125)	Clinical Delirium (CD) (n=125)	*p* (ND *vs.* CD)
Age, years - mean (±SD)	60.6 (±18.7)	54.3 (±18.3)	66.8 (±17.1)	***p*<.001**
Male/Female - %	55.6/44.4	44.8/55.2	66.4/33.6	***p*=.001**
APACHE-II - mean (±SD)	17.0 (±9.1)	10.5 (±4.4)	23.5 (±7.9)	***p*<.001**
Urgent/Elective - %	59.2/40.8	50.4/49.6	68/32	***p*=.005**
Trauma history - n / %	39/15.6	12/9.6	27/21.6	***p*=.009**
Urea concentration mg/dL - mean (±SD)	62.8 (±52.3)	40.1 (±27.8)	85.6 (±60.6)	***p*<.001**
Creatinine mg/dL - mean (±SD)	1.29 (±1.21)	0.87 (±0.72)	1.71 (±1.44)	***p*<.001**
Use of sedatives - n/%	89/35.6	8/6.4	81/64.8	***p*<.001**
Use of mechanical ventilation - n/%	220/88	97/77.6	123/98.4	***p*<.001**

with histories of trauma, those with high urea or creatinine values and those who underwent sedation or mechanical ventilation. The patients' mean APACHE-II score was 17.0 (±9.1), and delirium was more common in patients with high scores.

The patients' mean ICU stay length was 11.1 days. Patients diagnosed with clinical delirium underwent significantly longer stays than those without delirium in both the ICU (16.6 days vs. 5.5 days; $p<.001$) and the hospital in general (31.8 vs. 24.2 days; $p<.001$; see Figure 2).

In terms of mortality, 177 (70.8%) of the observed patients recovered and were discharged, whereas 73 patients (29.2%) died. When the 177 discharged patients were evaluated, 65 (36.7%) were diagnosed with clinical delirium, whereas 112 (63.3%) were not. Delirium was detected in 60 (82.2%) of the 73 patients who died; of these, 47 (64.3%) died in the ICU. We observed a significant ($p<.001$) correlation between mortality and the development of delirium.

ROC analysis for the prediction models showed that they were effective in detecting delirium in the studied ICU patients. The pre-deliric version 1 prediction score cut-off value was 38% (AUROC=1; Figure 3); that for pre-deliric version 2 was 22% (AUROC=1; Figure 4), and that for E-pre-deliric was 28% (AUROC=1; Figure 5). Upon evaluating these prediction models, although their delirium-distinguishing powers were similar, the ICU doctors stated that the E-pre-deliric prediction model was most useful in the ICU because its score is calculated at the time of admission, it requires fewer data than the other models and its score can be calculated in less time than those of the other models.

Discussion

Delirium is a multifactorial disease that is common in ICU patients. Despite its prevalence, delirium often goes undetected by both doctors and

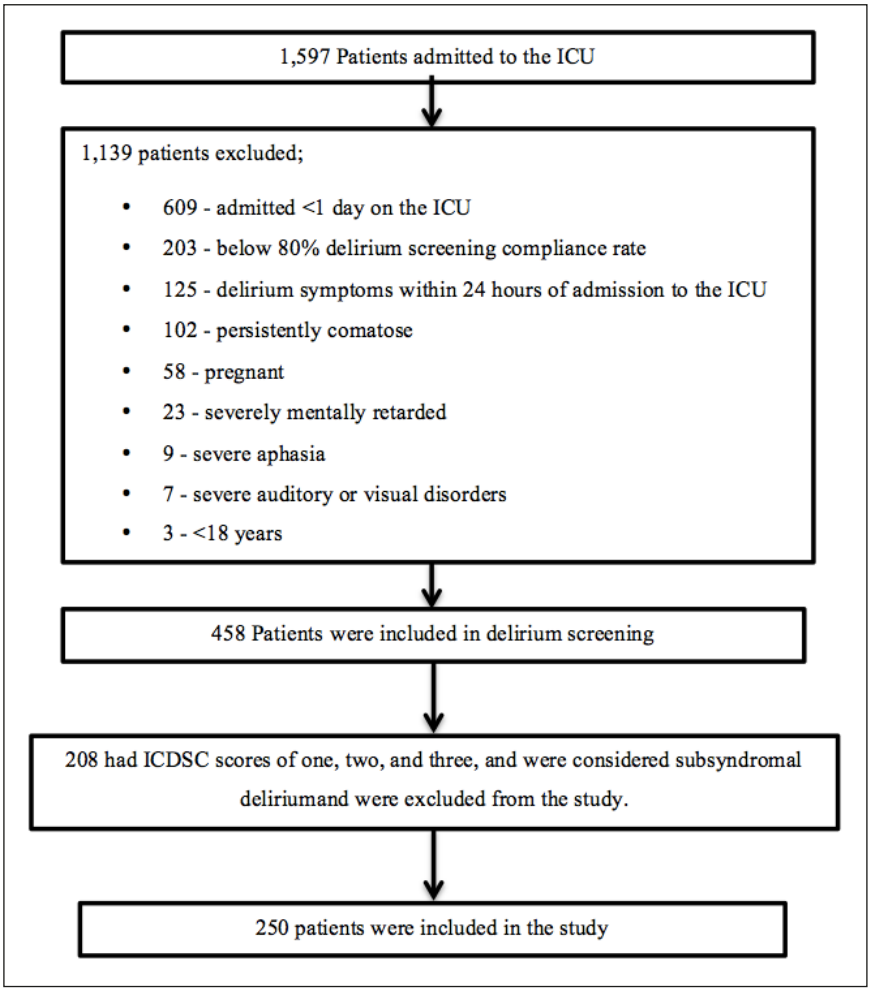


Figure 1. Flowchart of inclusion.

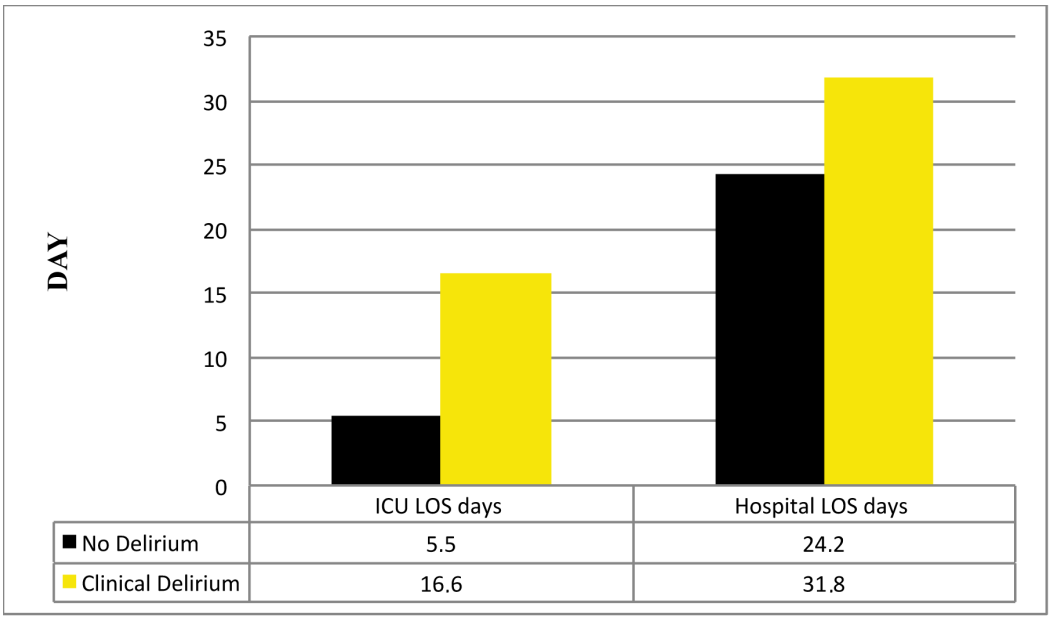
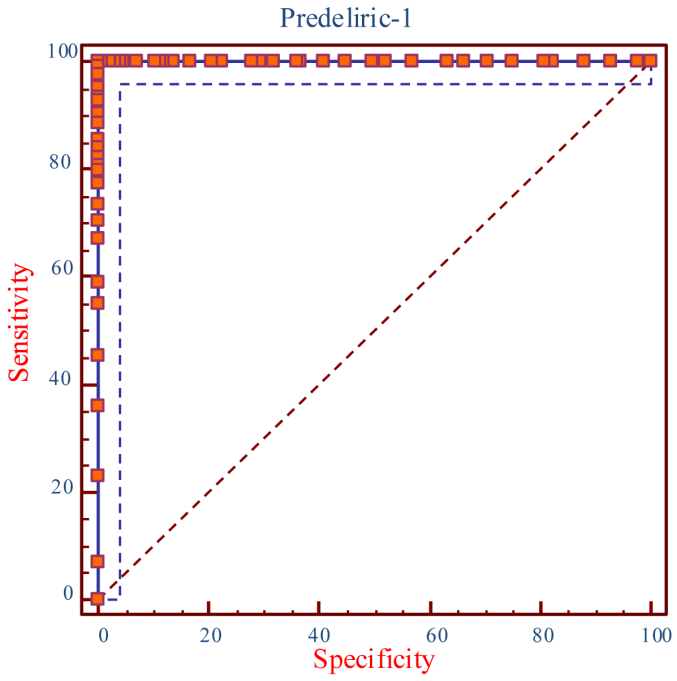


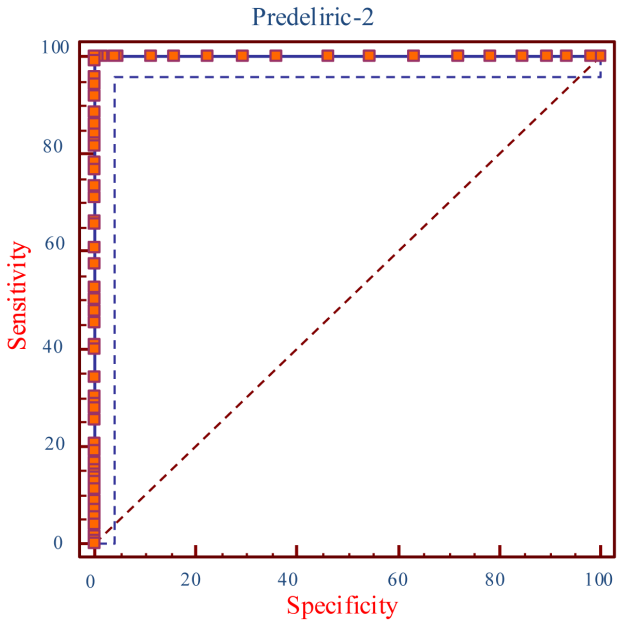
Figure 2. Distribution of patient groups according to mean length of stay (LOS) in ICU/Hospital.

nurses[26]. The development of tools for delirium screening and evaluation has, to some degree, facilitated the recognition of clinical delirium. However, few tools are currently available in the evaluation and screening of delirium in the ICU[9]. In 2001, Bergeron et al[27] devised the ICDSC, which comprises eight items, for ICU use. The ICDSC's sensitivity is 99%, and its specificity is



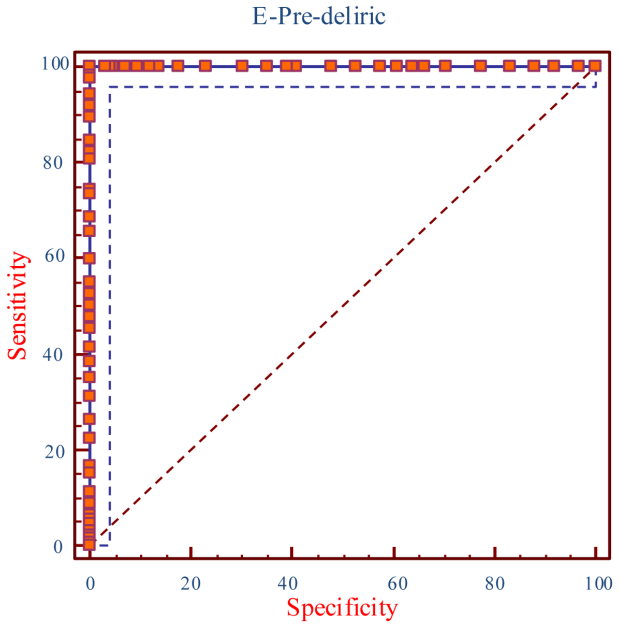
Area under curve	*p*-value	95% confidence interval
1	**<0.0001**	0.985 - 1.000

Figure 3. ROC curve for Pre-deliric version-1 score.



Area under curve	*p*-value	95% confidence interval
1	**<0.0001**	0.985 - 1.000

Figure 4. ROC curve for Pre-deliric version-2 score.



Area under curve	*p*-value	95% confidence interval
1	**<0.0001**	0.985 - 1.000

Figure 5. ROC curve for E-Pre-deliric score.

64% (AUC=0.9017). Chanques et al[28] demonstrated that the ICDSC and the CAM-ICU are valid tools for the diagnosis of delirium according to criteria from the DSM-5, which is the most current neuropsychological standard reference currently available. The ICDSC can be used by ICU nurses or other health personnel without psychiatry training in delirium screening in the ICU[27,29]. Investigator reliability has been found[29] to be over 94% among intensive care doctors and nurses. Because of the ICDSC's advantages, we chose it for delirium screening and applied by resident doctors in the current study.

In 2012, van den Boogaard et al[18] created the first pre-deliric model (pre-deliric version 1), which estimates delirium with a value of 0-100 using data from the first 24 hours of ICU admission. In this model, four different risk groups are defined (a score of 50% or greater indicates high-risk delirium; AUROC=0.85)[18]. Later, van den Boogaard et al[19] revised the pre-deliric prediction model for international use in 2014 (pre-deliric version 2). The parameters used in this forecasting model are the same (with a score of 50% or greater indicating high-risk delirium; AUROC=0.77). In our study, the pre-deliric version 1 model's cutoff score was 38% (with a score above 68% indicating high-risk delirium; AUROC=1). For the pre-deliric version 2 model, the cut-off score was 22% (with a score above 39% indicating high-risk delirium; AUROC=1). In this study, we found both versions of the model to be valid and reliable in the detection of delirium in the ICU.

In the pre-deliric model's international calibration study[19], the studied patients' mean APACHE-II score was 19 (±9), their mean age was 60 (±17) years, and 57% of them were males. The demographic and clinical characteristics of our study's patients were similar. The similarities in age, gender and disease severity – the most important risk factors for the development of delirium – suggest that our study and that of van den Boogaard et al[19] may be compared with confidence.

Wassenaar et al[20] developed the E-pre-deliric model in 2015. This model also predicts delirium with a score of 0-100 points, using data collected upon a patient's ICU admission. This model's cut-off score is 24.5% (sensitivity=71%; specificity=69%; AUROC=0.75). In our study using ICDSC for the diagnosis of delirium, the cut-off score was 28% (AUROC=1, with a score above 41% indicating high-risk delirium).

Studies[1,5,30,31] conducted using ICDSC diagnostic criteria reflect delirium incidence rates of 15-85%. In a meta-analysis of 42 studies, Salluh et al[32] reported that delirium had been detected in 5,280 (31.8%) of 16,595 ICU patients. This proportion is similar to that found in our cohort (27.29%). Differences among studies using the ICDSC in terms of reported incidence of delirium may be due to population characteristics and variations in patients' delirium types and severities.

The most common factors associated with delirium's development are ICU admission category (elective or emergent), chronic disease history, drugs and toxins, metabolic disorders, infections and central nervous system diseases[33]. Mehta et al[30], in a study involving 430 patients, discovered that patients with histories of surgery or trauma demonstrated an elevated likelihood of developing delirium in the ICU. In a study of 55 patients, Yasayacak and Eker[34] reported no significant difference in the development of delirium based on admission category, surgical intervention or chronic disease status (p=.05). In contrast, in our cohort, emergency admission and trauma history were risk factors for delirium. We hypothesize that differences among studies in terms of patient classification have produced these disparities in risk factors.

Van Rompaey et al[35] demonstrated that the use of psychoactive drugs disrupts neurotransmission in the brain and thus may cause delirium. In our study, the use of sedative drugs was a main risk factor contributing to delirium (p<0.001). Although sedation minimization is recommended to reduce the risk of delirium, no published studies have confirmed this association of delirium with sedation, and we suggest that care should be taken to identify ICU patients at risk of developing delirium who may receive sedative drugs.

The relationship between delirium and ICU stay length has been evaluated[32] in 28 studies, revealing longer ICU stay lengths in patients with delirium (p<0.001). In our study, the ICU stay lengths were significantly longer among patients who developed delirium. This result may be interpreted in various ways; delirium may extend ICU stay durations, prolonged exposure to the ICU environment may increase delirium risk, or the likelihood of being diagnosed may have increased because delirium was screened more times in patients who stayed in the ICU for extended periods. It is not possible to identify which of these possible causes, if any, contributed to this result.

Relatively few studies have examined the relationship between delirium and mortality. In their meta-analysis, Salluh et al[32] determined that the adjusted mortality risk was higher in patients

with delirium after adjusting for age, gender and APACHE-II scores. Although some studies[5,10,32] have indicated increased mortality in patients with delirium, others[36,37] have not indicated such a relationship. In our study, mortality was higher in patients with delirium than in those without it. We think that these discordant results are related to the types of patients enrolled in various studies (medical vs. surgical patients), varying disease severity, variable timing of mortality follow-up and varying analytical approaches.

Limitations

Our study had some limitations. No definite and clear guidance exists regarding the timing and frequency with which delirium assessment should be conducted. In our study, we performed delirium screening twice a day. In some studies, evaluation has occurred three times a day[1,5,38,39], twice a day[29,40] or once a day[30]. Another limitation is unmeasurable variables, such as the total dose of sedative medication and differences in the medical management of ICU patients. In our study, we evaluated only sedative drugs and alcohol use history (such as yes-no). We did not evaluate all drugs that patients used, which may contribute to the development of delirium. We obtained patients' neurological histories by evaluating each patients' clinical picture and by obtaining information from family members. Only patients with ICDSC scores of 4 or higher were consulted by psychiatrists. Patients with scores of 1, 2 or 3 on the ICDSC and thus remained in the subsyndromal group were excluded from our study and thus did not undergo psychiatric consultations. Excluding these patients may have changed the prediction models' cut-off values. We excluded patients with dementia partially because there is no validated differential screening tool to distinguish delirium from dementia in the ICU. Finally, we excluded patients with ICDSC rating scale compliance rates below 80%. Moreover, our study included no data on patients' long-term outcomes because our patients were followed during their hospital stays only. Finally, because our unit is a tertiary reference hospital ICU, it may not accurately represent Turkey's ICU patient population; however, this does not affect the prediction models' reliability and validity.

Conclusions

This study reveals statistical associations between delirium and extended ICU stays, extended hospital stays and mortality. For the first time, the pre-deliric and E-pre-deliric prediction models have been calibrated against the ICDSC. Additionally, we have compared the two models to each other for the first time. Thus, we have investigated these prediction models' validity and reliability, supported their reliability and determined their cut-off values for our study population. Through their calibration against the ICDSC, these models' sensitivity and specificity have increased. We have found these models to be useful, effective, and easy tools. To provide holistic patient care in the ICU, prediction scores should be calculated for each patient admitted to the ICU during routine follow-up. We suggest that calculating these prediction scores should become standard practice in the evaluation and follow-up of delirium in the ICU. The use of these tools will facilitate comparison among populations both within and between countries. Accurate prediction of delirium risk in the ICU promotes early intervention, allowing for expensive or labor-intensive treatments to be targeted toward high-risk patients.

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Conflict of Interest

The authors declare that they have no competing interests.

Funding

The Ethical Committee of the Trakya University Medical Faculty in Edirne, Turkey (Chairperson Prof. Ülfet Vatansever Özbek) provided ethical approval for this study (TÜTF-BAEK 2017/263) on 25 October 2017. All procedures followed were in accordance with the (institutional and national) ethical standards of the committee and the 1975 Declaration of Helsinki (revised in 2008).

Informed Consent

All participants (conscious patients and their first-degree relatives, as well as the first-degree relatives of unconscious patients) provided informed consent.

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