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Original Study

Assessing the Risk of Developing Delirium on Admission to Inpatient Rehabilitation: A Clinical Prediction Model

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A B S T R A C T

Objectives: To develop a clinical model to predict the risk of an individual patient developing delirium during inpatient rehabilitation, based on patient characteristics and clinical data available on admission.
Design: Retrospective observational study based on electronic health record data.
Setting and Participants: We studied a previously validated data set of inpatients including incident delirium episodes during rehabilitation. These patients were admitted to ZURZACH Care, Rehaklinik Bad Zurzach, a Swiss inpatient rehabilitation clinic, between January 1, 2015, and December 31, 2018.
Methods: We performed logistic regression analysis using backward and forward selection with alpha = 0.01 to remove any noninformative potential predictor. We subsequentially used the Akaike information criterion (AIC) to select the final model among the resulting "intermediate" models. Discrimination of the final prediction model was evaluated using the C-statistic.
Results: Of the 20 candidate predictor variables, 6 were included in the final prediction model: a linear spline of age with 1 knot at 60 years and a linear spline of the functional independence measure (FIM), a measure of the functional degree of patients independency, with 1 knot at 64 points, diagnosis of disorders of fluid, electrolyte, and acid-base balance (E87), use of other analgesic and antipyretics (N02B), use of anti-parkinson drugs (N04B), and an anticholinergic burden score (ACB) of $\geq$3 points.
Conclusions and Implications: Our clinical prediction model could, upon validation, identify patients at risk of incident delirium at admission to inpatient rehabilitation, and thus enable targeted prevention strategies.

Delirium is defined as an etiologically unspecified organic brain syndrome in which consciousness, attention, perception, thought, memory, psychomotor behaviors, emotions, and the sleep-wake cycle are simultaneously impaired. Delirium is reversible, and its duration and severity can range from hours to days.[1,2] Delirium has been associated with a longer duration of stay and higher mortality in both acute hospital and inpatient rehabilitation settings.[3-8] Because of the inability of delirious patients to follow the challenging interdisciplinary therapeutic rehabilitation schedule, delirium has also been associated with poor functional rehabilitation outcomes.[9,10]

Because of the highly fluctuating nature of delirium and the wide spectrum of potential risk factors, identifying patients at risk of delirium is challenging.[11,12] Being able to identify patients at risk of delirium on admission to inpatient rehabilitation would allow a targeted observation of these patients and subsequent implementation of nonpharmacologic prevention measures for delirium, which have been demonstrated to be more effective than treatment measures.[13] Such targeted interventions would allow more efficient use of available resources.

Clinical prediction models (CPM) are research-based tools that quantify the contributions of relevant patient characteristics to

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calculate a numeric probability of the presence or development of a specific disorder; thus, they assist clinicians in making predictions.[14]

In a previous case-control study based on electronic health records (EHR) of ZURZACH Care, an inpatient rehabilitation clinic in Switzerland, we evaluated a broad spectrum of risk factors for incident delirium during inpatient rehabilitation, including patient characteristics, specific conditions, and administered drugs.[15]

Based on the results of the previous case-control study, this study aimed to develop a CPM to predict the risk of an individual patient of developing incident delirium during an inpatient rehabilitation stay, based on patient characteristics, functional scores, diagnosed conditions, and administered drugs on admission to rehabilitation.

Methods

Source of Data

We used data from the EHR of ZURZACH Care, Rehaklinik Bad Zurzach, an inpatient rehabilitation clinic in Switzerland. EHRs comprise medical notes (including terms that are suggestive of incident delirium, as validated in a previous study),[16] patient- and rehabilitation-specific characteristics such as age, sex, and rehabilitation discipline, as well as clinical data such as diagnoses [recorded as International Classification of Diseases, 10th Revision (ICD-10) codes],[2] administered drugs [recorded as Anatomical Therapeutic Chemical (ATC) codes],[17] the functional independence measure (FIM),[18] a rating scale assessing the patients functional degree of independency in several cognitive and motoric activity of daily life (total score 18–126), and the Cumulative Illness Rating Scale (CIRS),[19] a rating scale assessing the impairment degree due to comorbidities based on 13 independent organ areas (total score 0–52).

Participants

We included all rehabilitation stays of patients who were admitted for inpatient rehabilitation between January 1, 2015, and December 31, 2018. Single patients may have contributed to more than 1 rehabilitation stay, if they were referred for rehabilitation several times during the study period. We excluded all stays of patients with missing information on age, sex, and rehabilitation discipline. This study was approved by the Ethics Committee Northwest/Central Switzerland (Project-ID 2018-01351).

Outcome

The outcome was defined as an incident delirium at some point during the rehabilitation stay, excluding the first day of the stay. The definition and validation of the outcome delirium in this dataset has been described in detail previously.[16] Briefly, we defined 15 key words commonly used to describe delirious patients in medical notes. Profiles of patients with at least 2 recorded key words during rehabilitation but at the earliest 24 hours after admission and no recorded diagnosis of delirium on admission were reviewed by at least 2 independent physicians, based on predefined evaluation criteria to confirm or refute the diagnosis of delirium. Patients with only 1 delirium predictive key word in their EHR, patients whose potential delirium diagnosis was refuted in medical review, and patients with prevalent delirium (record of a delirium diagnosis on admission) were excluded from the study population.

Predictor Variables

Based on the results of our previous case-control study,[15] evidence in the literature,[20-22] and clinical expertise of a senior neurologist (P.S.S.), we selected the following variables as potential predictors for the development of our model[23]: sex; age on admission; rehabilitation discipline (neurology/non-neurology); FIM[18] and CIRS[19] assessed on admission; records of any of the following conditions (ICD-10) and/or at least 1 administration of any of the following drug classes (*ATC codes*) recorded on admission: infections (A00-B99 or *J01*), disorders of fluid, electrolyte, and acid-base balance (E87), epilepsy (G40-G41), ischemic heart disease (I20-I25), cerebrovascular hemorrhage (I60-I62), cerebral infarction (I63), antidiabetic drugs (*A10A* and *A10B*), drugs for urinary frequency and incontinence (*G04BD*), corticosteroids systemic (*H02*), thyroid therapy (*H03*), opioid drugs (*N02A*), other analgesic and antipyretics (*N02B*), anti-Parkinson drugs (*N04B*), antidepressants (*N06A*), and anticholinergic burden score (ACB)[24] assessed on admission. Newly assessed conditions or medications prescribed during the rehabilitation stay were not considered predictor variables.

Statistical Analysis

We described baseline characteristics of patients with or without incident delirium during rehabilitation using mean and SD for continuous variables and absolute numbers and frequencies for categorical variables.

ACB was categorized into high ($\geq$3) and low ($<$3) anticholinergic burden, for all other continuous variables (age, FIM, and CIRS), the linearity of their relationships with the logit of the outcome probability was assessed using linear splines with an initial number of 19 knots placed at the 5th, 10th,… and 95th percentiles. The respective spline terms were defined as $(x-x_{k\times 0.05}) \times (x > x_{k\times 0.05})$ for $k = 0, 5,\ldots 19$. The term with $k = 0$ denotes the respective variable itself. We performed logistic regression analysis using both backward and forward selection with alpha = 0.01 to remove any noninformative binary variables and spline terms. Because we aimed to obtain a parsimonious prediction model, we deliberately set a low alpha value as selection criterion. As the models obtained by forward and backward selection differed slightly in the selected spline terms for age, we assessed different "intermediate" models and used the Akaike information criterion (AIC) to select the final model among them. Discrimination of the final prediction model was evaluated using the C-statistic [area under the receiver operating characteristic (ROC) curve]. All statistical analyses were conducted using SAS 9.4 (SAS Institute).

Results

Study Population and Outcome

Of 9406 patients who underwent a total of 10,515 rehabilitation stays during the study period, we included 8774 stays for the analysis (Figure 1). Among these, we identified 125 validated incident delirium episodes (outcome). Table 1 provides baseline characteristics at rehabilitation admission of patients with or without incident delirium. Patients with incident delirium during rehabilitation were more often male (56.0% vs 42.9%), older (mean, 77.2 vs 65.3 years), had a lower FIM (mean, 45.6 vs 79.4), a higher CIRS (mean, 18.8 vs 14.1), and were more often exposed to a high ACB ($\geq$3) (22.4% vs 9.1%) than patients without incident delirium.

Development of the Prediction Model

Of the 20 candidate predictor variables, 6 were included in the prediction model after backward selection: a linear spline of age with 1 knot at 55 years and a linear spline of FIM with 1 knot at 64, diagnosis of disorders of fluid, electrolyte and acid-base balance (E87), use of other analgesic and antipyretics (N02B), use of anti-Parkinson drugs (N04B), and ACB $\geq$3. Initially, age and FIM were

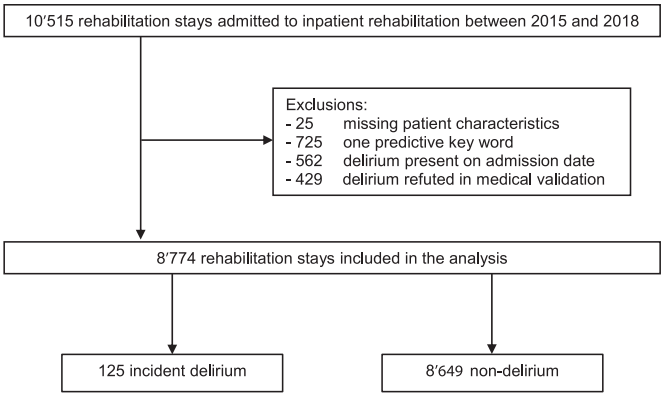

Fig. 1. Flowchart of study population selection. Patients with incident delirium had at least 2 recorded delirium predictive key words (commonly used terms to describe delirious patients) who were classified as incident delirium episodes by 2 to 3 independent physicians as defined in a previous validation study.[16] Patients with non-delirium did not have any record of delirium predictive key words in their medical notes or a diagnosis of prevalent delirium on admission.

included as linear splines with 19 knots (5th to 95th percentiles). Almost the same variables were included after forward selection, except that age >63 years was selected in the forward selection, and age >55 years was selected in the backward selection. We thus ran a model including 2 knots of age, at 55 and 63 years. Here, the first knot turned out to be statistically highly insignificant so that we kept the knot at 63 years only. However, we then also tested models with knots between 55 and 63 years. Here the model with the knot at 60 years showed the lowest AIC with a value of 959.48 (as compared with 959.53 for the model with the knot at 63 years). We thus considered the model with age >60 years as final. The area under the ROC curve of this model yielded 0.9167 (value of c) (Figure 2). The resulting prediction function for the logit of the probability of developing delirium (DP) thus equaled:

Table 1
Baseline Characteristics of the Incident Delirium Group and the Non-Delirium Group at Rehabilitation Admission

Characteristics	Non-Delirium (n = 8649)	Incident Delirium (n = 125)
Sex, n (%)		
Female	4937 (57.08)	55 (44.00)
Male	3712 (42.92)	70 (56.00)
Age, mean (SD)	65.28 (15.86)	77.17 (9.88)
Age group, y, n (%)		
<65	3710 (42.90)	13 (10.40)
65–74	2026 (23.42)	23 (18.40)
75–84	2190 (25.32)	62 (49.60)
≥85	723 (8.36)	27 (21.60)
Rehabilitation disciplines, n (%)		
Angiology	554 (6.41)	5 (4.00)
Cardiology	967 (11.18)	6 (4.80)
Headache program	430 (4.97)	0
Neurology	2429 (28.08)	89 (71.20)
Orthopedics	2578 (29.81)	19 (15.20)
Pain program	467 (5.40)	1 (0.80)
Rheumatology	1008 (11.65)	2 (1.60)
Others	216 (2.50)	3 (2.40)
FIM at admission, mean (SD)	79.38 (19.43)	45.64 (18.40)
CIRS at admission, mean (SD)	14.14 (8.63)	18.77 (8.19)
ACB at admission, n (%)		
High anticholinergic last (≥3)	790 (9.13)	28 (22.40)
Low anticholinergic last (<3)	7859 (90.87)	97 (77.60)

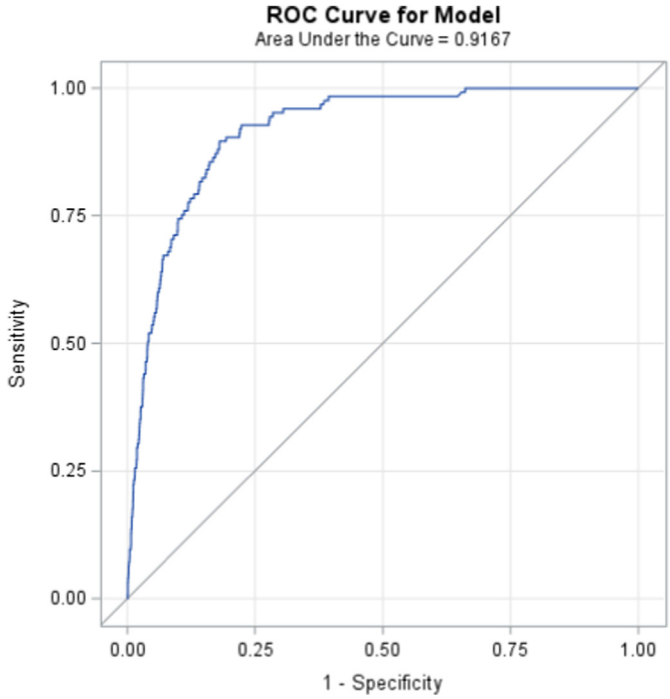

Fig. 2. ROC curve of the final model.

$$\text{logit}\,(\text{DP}) = -1.5984 - 0.5913 \times (\text{N02B} = \text{yes}) + 0.8469 \times (\text{N04B} = \text{yes}) + 0.7440 \times (\text{ACB} > 2) + 1.0297 \times (\text{E87} = \text{yes}) + 0.0476 \times (\text{age} - 60) \times (\text{age} > 60) - 0.0466 \times \text{FIM} - 0.0788 \times (\text{FIM} - 64) \times (\text{FIM} > 64)$$

where the variables (x = yes) evaluate to 1, if x = yes and to 0 if x = no, and where the variables (x > a) evaluate to 1, if x > a and to 0 if x ≤ a.
The estimated probability of developing delirium is then given by the following equation:

$$\text{DP} = \exp\,(\text{logit}\,(\text{DP}))\,/\,(1 + \exp\,(\text{logit}\,(\text{DP})))$$

We subsequently implemented the prediction function of delirium within an Excel file, in order to render it user-friendly (supplementary material).

Discussion

In this observational study based on EHRs, we developed a clinical prediction model to predict the risk of an individual patient developing incident delirium during inpatient rehabilitation. Age; FIM; diagnoses of disorders of fluid, electrolyte, and acid-base balance (E87); use of other analgesic and antipyretics (N02B) or anti-Parkinson drugs (N04B) on admission; and an ACB ≥3 were selected as predictor parameters. The measured area under the ROC curve of the final model was 0.916 (value of c), which indicates a very good level of discrimination between positive and negative predictions.

Age and FIM showed proportional respectively inversely proportional associations with the risk of delirium, but only above 60 years for age. Advanced age (>60 to >70 years, depending on the study) has repeatedly been reported as a risk factor for delirium within the rehabilitation setting.[20-22,25] A previous study also suggested that a

low FIM, which indicates an impaired degree of patients' independency in daily life activities, is associated with an increased risk of delirium. Patients who developed incident delirium during inpatient rehabilitation had a significantly lower FIM on admission compared with patients who did not develop delirium.[20] Interestingly, we observed that use of analgesics and antipyretics (N02 B) was associated with a lower risk of delirium. This may suggest that an effective pain management may reduce the risk of delirium not only within postoperative settings,[26] but also in rehabilitation. However, this is only a hypothesis that would have to be proven. Several previous studies reported a clinical prediction model for the risk of incident delirium in non-rehabilitation settings.[27-34] Six of them were performed in an acute hospital,[27-31] one in intensive care,[33] and the last one among patients after a stroke.[34] Excluding age, which was included in 6[27,29,31,33,34] of the 8 models, the included predictive parameters were highly heterogeneous across studies. Of the models developed in acute hospital settings, the first one (among trauma patients >18 years of age) included the Glasgow Coma Scale, the body mass index, the Clinical Frailty Score, and 2 laboratory parameters (fibrinogen degradation products and lactate).[28] The second model (among patients >60 years of age) included age, the C-reactive protein (CRP), the blood urea level, the number of prescribed drugs, and use of 1 of the following drug classes (ATC-Code): anxiolytics (N05B), antidementia drugs (N06D), antidepressants (N06A), anti-Parkinson drugs (N04), drugs used in diabetes (A10), antipsychotics (N05A), opioids (N02A), and hypnotics and sedatives (N05C) as predictive parameters for the risk of delirium.[27] The third model (among internal medicine patients >18 years of age) included age (≥85 years old), dependence in activities of daily life, and taking psychotropic drugs.[29] The fourth one (among older patients of internal medicine) included infections, cognitive impairment, and low functional status at admission.[30] The fifth model (among patients of internal medicine, cardiology, or neurology ≥50 years of age) included age (≥80 years old), inability to spell "World" backward, disorientation to place, and moderate or severe illness severity.[31] The last model, developed on a very large database of internal medicine and surgery patients aged ≥50 years, included approximately 20 predictor variables. among them age, a range of prevalent conditions such as psychiatric disorders, dementia and history of delirium, laboratory parameters such as creatinine, white blood cells (WBC) count, and sodium, and some administered drugs, such as opioid analgesics and opioid antagonists.[32] The model developed in the intensive care unit included the medical discipline (internal medicine, surgery, traumatology, or neurology), the diagnoses of infection or metabolic acidosis, the use of morphine or sedatives, and the urea blood level.[33] Finally, the model based on patients after a stroke included age, the presence of cerebral hemorrhage, or a brain lesion volume of >40 cm^3 and 2 laboratory parameters (gamma-glutamyl transferase and bilirubin).[34] Despite the fact that all models were developed based on high mathematical accuracy, it seems that the subjectivity in the preselection of potential predictive parameters due to different settings and parameters available had a great influence on the final prediction parameters included in the models. However, some of these parameters are common for conditions that are associated with delirium, as the "dependence in activities of daily life" or the "low functional status at admission" for the FIM, the CRP value or the WBC count for infections, lactate or urea values for metabolic acidosis or acid-base regulation imbalance, or the "number of prescribed drugs" for the dopaminergic system or the anticholinergic burden on the central nervous system. Our model also includes parameters related to some of these conditions [FIM, electrolyte and acid-base balance (E87), use of anti-Parkinson drugs (N04B), and ACB ≥3], with the exception of infections. This may be due to the different settings, with a lower incidence of infections in the rehabilitation setting than in acute hospital or intensive care.

Strengths and Limitations

The following limitations of our study must be considered. First, our analyses were based on routine clinical data, which were not primarily collected for research purposes. However, the cases of delirium were validated in a previous study,[16] and the same database was also used for a case-control study, in which results showed consistency with published literature.[15] Second, although we consider the charts-based method supplemented by experts review appropriate to validate delirium episodes, in some cases (eg, by use of non-considered key words or insufficient recording of medical notes) some delirium episodes could have been missed. Third, although we used a systematic method to preselect predictive parameters, based on literature and expert opinion, we were restricted to available data in the database; thus it is possible that some parameters selected in prediction models of other studies were not considered, although they are associated with the risk of incident delirium. Fourth, because we aimed to develop an accurate and reliable clinical prediction model, we excluded any uncertain episode of delirium that was not clearly classifiable as either incident delirium or non-delirium. This conservative approach may have led to the exclusion of some delirium episodes, resulting in a lower delirium incidence in our study population compared with the literature.[35] Last, although the statistical parameters indicate very good robustness of our model, the model has not yet been externally validated. An external validation would confirm the sensitivity and specificity of our model and should be performed before implementing the model in clinical practice.

An important strength of our model is the suitability to be used directly on admission to inpatient rehabilitation, as the parameters necessary for prediction are part of routine clinical data and already available at that time. Furthermore, our model is the first one developed in rehabilitation settings, considering specific parameters in this field such as the FIM.

Conclusions and Implications

In our study, we developed a clinical prediction model to predict the risk of an individual patient of developing delirium during inpatient rehabilitation, based on patient characteristics, functional scores, diagnosed conditions, and administered drugs recorded in the EHR of the patient on admission to the rehabilitation facility. Considering the previously mentioned limitations, and after performing external validation as a further step, our model could provide an innovative method to screen patients for the risk of developing delirium during rehabilitation, based on factors present at admission, and thus allow a targeted implementation of well-established delirium prevention strategies.[13]

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Supplementary Data

Supplementary data related to this article can be found online at 10.1016/j.jamda.2023.07.003.

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