Risk Factors for Delirium at Discharge

Development and Validation of a Predictive Model

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Background: Persistent delirium at the time of hospital discharge is associated with poor outcomes. The objectives of this study were to develop and validate a predictive model for persistent delirium at hospital discharge.

Methods: This study followed a prospective validation design. For the development cohort, 491 consecutive patients age 70 years or older admitted to the hospital without delirium and surviving to discharge were enrolled from the general medical units of an academic teaching hospital. For the validation cohort, 461 comparable subjects were enrolled. Twenty-two candidate risk factors were examined, including 12 baseline factors (present on admission) and 10 precipitating factors (hospital related). The primary outcome was delirium at hospital discharge, measured by the Confusion Assessment Method.

Results: Delirium at discharge was present in 58 patients (11.8%) in the development cohort. Five independent risk factors for delirium at discharge were identified: dementia (odds ratio [OR], 2.3; 95% confidence interval [CI], 1.4-3.7); vision impairment (OR, 2.1; 95% CI, 1.3-3.2); functional impairment (OR, 1.7; 95% CI, 1.2-3.0); high comorbidity (OR, 1.7; 95% CI, 1.1-2.6); and use of physical restraints during delirium (OR, 3.2; 95% CI, 1.9-5.2). A risk stratification system was created by adding 1 point for each factor present. Rates of delirium for the low-risk (0-1 factors), intermediate-risk (2-3 factors), and high-risk (4-5 factors) groups were 4%, 18%, and 63%, respectively (P < .001). The corresponding rates in the validation cohort, where 28 patients (6.1%) had delirium at discharge, were 3%, 14%, and 27% (P < .001).

Conclusions: A predictive model based on 5 risk factors has been successfully validated for prediction of delirium at discharge in hospitalized older patients. At least 4 of these risk factors are amenable to intervention strategies.

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Delirium is a common, serious, and potentially preventable problem for older persons.

Delirium represents a particularly high-risk group. Hospital discharge has been recognized as a high-risk transition period. In previous studies, 49% of older patients experienced at least 1 medical error during transitions from the hospital, and 13% to 25% had serious complications. Delirium is reported in only 3% to 16% of documented cases at discharge, and unrecognized delirium is associated with high mortality. Patients with delirium at discharge from the emergency department had a 7-fold increased mortality risk, with the highest risk in the unrecognized delirium group. Delirium at discharge was also associated with a 2.6-fold increased risk of death or nursing home placement. Finally, delirium that persisted beyond discharge from acute care was associated with worse long-term cognitive sequelae.
associated with rehospitalization, prolonged institutionalization, and death.24

Our research group has previously examined predisposing factors (at admission)25 and precipitating factors (during hospitalization)26 for delirium. Our goal in the present study is to extend this work to examine persistence factors leading to delirium that persists until discharge. This work appears justified given that hospital discharge represents a transition to a less supervised environment, that delirium at discharge is associated with high morbidity and mortality, and that new interventions may be necessary to improve the transition period.

Specific objectives of the present study were to (1) identify risk factors for delirium at discharge, including baseline vulnerability factors and hospital-related factors; (2) develop a predictive model for delirium at discharge in an initial cohort; and (3) validate the model in an independent cohort. Our hypotheses were that baseline factors (eg, comorbidity) and precipitating factors (eg, iatrogenic events) would be associated with a higher risk of delirium at discharge. We further hypothesized that risk factors would differ between those contributing to delirium that resolves vs those contributing to persistent delirium. Our goals were to develop a predictive model that would help to identify patients at high risk for delirium at discharge for enrollment in intervention programs and to target appropriate interventions toward the identified risk factors for delirium at discharge.

**METHODS**

The study followed a prospective validation design. The predictive model was first developed in an initial cohort, then externally validated in a separate validation cohort.27,28

**MODEL DEVELOPMENT**

**Study Sample**

Potential participants were patients aged 70 years or older who were consecutively admitted to 6 general medicine units (non-intensive care) at Yale New Haven Hospital with no evidence of delirium. The sample of 525 patients has been described in detail previously.29,30 Of the 525 patients, 34 died during hospitalization and were excluded, yielding a final sample of 491 participants.

**Study Procedures**

Experienced clinical interviewers, who were blinded to the study hypotheses, conducted structured interviews with the patients and their nurses from admission until discharge. The baseline evaluation completed within 48 hours of admission included demographic information and the Mini-Mental State Examination31; Digit Span Test32; Confusion Assessment Method (CAM) rating33; activities of daily living (ADL)34 and instrumental ADL35 screening referent to the 2 weeks prior to hospitalization; the Jaeger36 test for vision and whisper test for hearing37; and the Geriatric Depression Scale (GDS).38 Trained abstractors reviewed hospital records for diagnoses, laboratory results, medications, length of stay, and discharge destination; they also determined the APACHE II score (Acute Physiology and Chronic Health Evaluation II)39,40 and Charlson Comorbidity Index.41 A family member was interviewed to rate the modified Blessed Dementia Rating Scale.42,43 Subsequently, patients were evaluated every other day with the Mini-Mental State Examination, Digit Span Test, and CAM, and directly observed for the use of physical restraints and bladder catheters.

Informed consent for study participation was obtained from the patients or, for those with substantial cognitive impairment, from a proxy (closest relative or legal guardian), according to procedures approved by the institutional review board of Yale University School of Medicine.

**Outcomes**

The primary outcome was delirium at hospital discharge. This was defined as meeting the full validated CAM criteria for delirium33 during hospitalization, then continuing to meet full or partial CAM criteria at discharge. The full CAM criteria for delirium required the presence of acute onset and fluctuating course, inattention, and either disorganized thinking or altered level of consciousness. These criteria have a sensitivity of 94% to 100% and specificity of 90% to 95% compared with geropsychiatrists’ ratings and high interrater reliability.41 Partial CAM criteria were defined as the presence of any 1 of the full CAM criteria, a definition used previously.7,23,24,44,45 Resolved delirium was defined as delirium that developed during hospitalization but resolved before discharge. The CAM has been used to measure changes or resolution in delirium symptoms.8,46-49

**Definition of Variables**

We chose cut points based on previous studies, data distributions, and clinical sensibility. Advanced age was defined as 85 years or older, representing the highest quartile in the sample. Male sex has been identified as a risk factor previously.25,50 The cut point of greater than 1 ADL impairment was chosen as the highest quartile in the sample. Vision impairment was defined as corrected near vision worse than 20/70 OU.25 A Mini-Mental State Examination score lower than 24 was used as our cut point.31 Dementia was defined by either a medical record diagnosis or modified Blessed Dementia Rating Scale score of 4 or higher.42,43 An APACHE II score higher than 16 or nurse rating of “severe” was used to identify high severity of illness.25 A Charlson score of 4 or higher was chosen as the highest quartile in the sample.41 A ratio greater than 18 of serum urea nitrogen to creatinine and albumin levels of 3.5 g/dL or lower were our cut points, as used previously.25,40-43-53 The number of iatrogenic events was defined by standard criteria26,54,55 and analyzed as a continuous variable, and the cut point of more than 4 events was used, representing the highest quartile. The cut points of more than 3 medications newly added in 1 day and more than 3 psychoactive medications received in 1 day were used, as previously.26 Delirium-related variables (eg, severity and/or duration) were not included because they could be determined only in delirious patients.

**MODEL VALIDATION**

**Study Sample**

This prospective cohort comprised the control arm of the Delirium Prevention Trial, described previously.21,22 Potential participants were patients 70 years or older who were consecutively admitted to the general medicine service (nonintensive...
null sample of 461 participants. Included 8 patients who died during hospitalization, yielding a matched and 43 unmatched patients. We excluded 8 patients who died during hospitalization, yielding a final sample of 461 participants.

**Study Procedures**

The clinical evaluations, outcomes, and definitions of variables were identical to those used in the development study. The only difference was that delirium assessments were conducted daily. The same research staff conducted the study using the same data-collection instruments, blinded to the study hypotheses.

**STATISTICAL ANALYSES**

Baseline characteristics of the development and validation cohorts were compared using t test statistics for continuous variables or χ² statistics for categorical variables. For bivariable and multivariable analyses, delirium at discharge represented the highest level of a 3-level outcome, which is ordinal and progressive: (1) no delirium; (2) resolved delirium; and (3) delirium at discharge. The ordinal nature is reflected by the increasing disease severity across categories; the progressive nature is demonstrated by the need to pass through each level to arrive at the next. All analyses were conducted using the continuation ratio model, a log-binomial regression model suited to progressive ordinal outcomes.

Baseline characteristics of the development cohort were summarized in Table 1. Of the 491 patients, 106 (21.6%) developed delirium during hospitalization, and median length of stay was 9 days (range, 3–67 days). Of the 58 patients with delirium at discharge (11.8%), median time from admission to delirium onset was 3 days (range, 2–20 days); median duration of delirium in the hospital was 7 days (range, 1–61 days); and median length of stay was 10 days (range, 3–67 days). Of the 48 patients with resolved delirium, median time from admission to delirium onset was 4 days (range, 1–21 days); median duration of delirium in the hospital was 5 days (range, 1–64 days); and median length of stay was 15 days (range, 3–67 days).
Distribution of Risk Factor Distribution of Risk Factor

<table>
<thead>
<tr>
<th>Potential Risk Factor</th>
<th>Delirium at Discharge</th>
<th>Resolved Delirium</th>
<th>No Delirium</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Axis 1 Baseline Risk Factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≥ 85 y</td>
<td>22 (37.9)</td>
<td>15 (31.3)</td>
<td>60 (15.6)</td>
</tr>
<tr>
<td>Male sex</td>
<td>22 (37.9)</td>
<td>19 (39.6)</td>
<td>170 (44.2)</td>
</tr>
<tr>
<td>Education, y</td>
<td>10.5 ± 3.3</td>
<td>10.2 ± 3.9</td>
<td>11.6 ± 3.4</td>
</tr>
<tr>
<td>Physical functioning</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADL impairment &gt; 1</td>
<td>26 (44.8)</td>
<td>15 (31.3)</td>
<td>56 (14.5)</td>
</tr>
<tr>
<td>Vision impairment</td>
<td>43 (74.1)</td>
<td>26 (54.2)</td>
<td>120 (31.2)</td>
</tr>
<tr>
<td>Cognitive functioning</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE score &lt; 24</td>
<td>41 (74.5)</td>
<td>30 (63.8)</td>
<td>116 (30.3)</td>
</tr>
<tr>
<td>Dementia, by diagnosis or mBDRS score ≥ 4</td>
<td>34 (58.6)</td>
<td>14 (29.2)</td>
<td>48 (12.5)</td>
</tr>
<tr>
<td><strong>Biomedical</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APACHE II score &gt; 15 or nurse rating of severe</td>
<td>23 (39.7)</td>
<td>16 (33.3)</td>
<td>96 (24.9)</td>
</tr>
<tr>
<td>Charlson score41 ≥ 4</td>
<td>25 (43.1)</td>
<td>16 (33.3)</td>
<td>99 (25.7)</td>
</tr>
<tr>
<td>SUN-Cr ratio ≥ 16</td>
<td>39 (67.2)</td>
<td>23 (48.9)</td>
<td>182 (47.3)</td>
</tr>
<tr>
<td>Albumin ≤ 3.5 g/dL</td>
<td>19 (32.8)</td>
<td>17 (35.4)</td>
<td>69 (17.9)</td>
</tr>
<tr>
<td><strong>Axis 2 Hospital-Related Factors</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Immobilization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Restraint use</td>
<td>30 (51.7)</td>
<td>12 (25.0)</td>
<td>33 (8.6)</td>
</tr>
<tr>
<td>Catheter use</td>
<td>30 (51.7)</td>
<td>24 (50.0)</td>
<td>110 (28.6)</td>
</tr>
<tr>
<td>Latrogenic events (range, 0-24)</td>
<td>2.6 ± 2.9</td>
<td>3 ± 2.8</td>
<td>1.2 ± 1.6</td>
</tr>
<tr>
<td>Any</td>
<td>46 (79.3)</td>
<td>41 (85.4)</td>
<td>218 (56.6)</td>
</tr>
<tr>
<td>≥ 4</td>
<td>14 (24.1)</td>
<td>17 (35.4)</td>
<td>33 (8.6)</td>
</tr>
<tr>
<td>Intercurrent illness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New diagnoses</td>
<td>2.7 ± 1.7</td>
<td>3.0 ± 1.8</td>
<td>2.1 ± 1.5</td>
</tr>
<tr>
<td>Any new diagnosis</td>
<td>52 (89.7)</td>
<td>46 (95.6)</td>
<td>339 (88.1)</td>
</tr>
<tr>
<td>Hospital medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 3 Added in 1 day</td>
<td>35 (60.3)</td>
<td>35 (72.9)</td>
<td>203 (52.7)</td>
</tr>
<tr>
<td>Total new medications</td>
<td>2.8 ± 2.9</td>
<td>4.0 ± 3.6</td>
<td>2.8 ± 2.3</td>
</tr>
</tbody>
</table>

**Odds Ratio (95% Confidence Interval)**

<table>
<thead>
<tr>
<th>Overall Model</th>
<th>Any Delirium vs No Delirium</th>
<th>Delirium at Discharge vs Resolved Delirium</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 491)</td>
<td>(n = 491)</td>
<td>(n = 106)</td>
</tr>
<tr>
<td>Age ≥ 85 y</td>
<td>2.4 (1.6-3.6)</td>
<td>2.9 (1.8-4.7)</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.8 (0.6-1.2)</td>
<td>0.8 (0.5-1.2)</td>
</tr>
<tr>
<td>Education, y</td>
<td>0.9 (0.9-1.0)</td>
<td>0.9 (0.9-1.0)</td>
</tr>
<tr>
<td>Physical functioning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADL impairment &gt; 1</td>
<td>3.1 (2.0-4.7)</td>
<td>3.7 (2.3-6.0)</td>
</tr>
<tr>
<td>Vision impairment</td>
<td>3.6 (2.5-5.4)</td>
<td>4.1 (2.6-6.5)</td>
</tr>
<tr>
<td>Cognitive functioning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE score &lt; 24</td>
<td>4.1 (2.7-6.1)</td>
<td>5.3 (3.3-8.5)</td>
</tr>
<tr>
<td>Dementia, by diagnosis or mBDRS score ≥ 4</td>
<td>5.1 (3.3-7.7)</td>
<td>5.8 (3.6-9.5)</td>
</tr>
<tr>
<td>Biomedical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APACHE II score &gt; 15 or nurse rating of severe</td>
<td>1.6 (1.1-2.4)</td>
<td>1.8 (1.1-2.8)</td>
</tr>
<tr>
<td>Charlson score41 ≥ 4</td>
<td>1.7 (1.2-2.6)</td>
<td>1.8 (1.2-2.9)</td>
</tr>
<tr>
<td>SUN-Cr ratio ≥ 16</td>
<td>1.7 (1.2-2.5)</td>
<td>1.6 (1.0-2.5)</td>
</tr>
<tr>
<td>Albumin ≤ 3.5 g/dL</td>
<td>1.8 (1.2-2.8)</td>
<td>2.4 (1.9-3.8)</td>
</tr>
</tbody>
</table>

**Abbreviations:** ADL, activities of daily living;44-46 APACHE II, Acute Physiology and Chronic Health Evaluation II;39-40 CAM, Confusion Assessment Method;42 mBDRS, modified Blessed Dementia Rating Scale;42 MMSE, Mini-Mental State Examination;31 SUN-Cr, serum urea nitrogen–creatinine.

Data were reported as mean ± SD values or number (percentage) of subjects.

For these analyses, an interaction term indicated a significant difference between the 2 comparisons (any delirium vs no delirium and delirium at discharge vs resolved delirium). None of these variables was included in the final model.

For the overall model, the at-risk period for defining risk factors was considered the delirium interval (ie, the inclusive days of delirium from the first day of CAM-positive rating until discharge) for the delirium at discharge group, the period from delirium onset to resolution in the resolved delirium group, and the entire hospitalization for the no delirium group.

**DEVELOPMENT OF THE PREDICTIVE MODEL**

The 22 candidate risk factor variables considered for the predictive model are listed in Table 2, including 12 baseline (admission) and 10 precipitating (hospital-related) factors. Using the a priori selection criteria, these variables were narrowed along the 2 axes. Five independent factors were selected for inclusion in the final predictive model (Table 3): dementia, vision impairment, ADL impairment, high comorbidity, and restraint use during delirium. These factors were entered into a single model to provide an overall estimate of the independent contribution of each variable to the persistence of delirium until discharge. The nested case-control analyses of medications and restraints did not yield any additional variables for the model.

**PERFORMANCE OF THE PREDICTIVE MODEL**

**Development Cohort**

In the development cohort, the final predictive model generated a C statistic of 0.80, indicating good prediction above chance.61 A risk stratification system was created by assigning 1 point to each of the final risk factors. Three risk groups were created: a low-risk group (0–1 factors), intermediate-risk group (2–3 factors), and high-risk group (4–5 factors). Rates of delirium at discharge increased from 4% to 18% to 63% in the low-, intermediate-, and high-risk groups, respectively (χ²=87.64 for trend, P<.001).
Clinical Outcomes Related to Delirium at Discharge

The predictive validity of the risk stratification system was evaluated for prediction of death or nursing home placement during 1-year follow-up (Table 5). The hierarchical outcome of either death or nursing home placement was chosen since the combination avoids inferential errors that arise because patients who die can no longer be institutionalized. In addition, a previous study demonstrated that delirium at discharge was associated with increased rates of this hierarchical outcome. In the development cohort, the rate of death or nursing home placement increased from 23% to 57% to 77% in the low-, intermediate-, and high-risk groups, respectively, for a 3.4-fold increase overall ($\chi^2=62.1$ for trend, $P<.001$). In the validation cohort, the corresponding rates increased from 15% to 39% to 64%, for a 4.4-fold increase overall ($\chi^2=42.1$ for trend, $P<.001$).

We developed and successfully validated, in a separate, clinically distinct sample, a predictive model for delirium persisting to hospital discharge based on 5 independent risk factors: dementia, vision impairment, functional impairment, high comorbidity, and use of physical restraints during delirium. Four of these factors were baseline factors, a finding that highlights the predominance of vulnerability or impaired cognitive reserve contributing to delirium at discharge and reinforces the importance of preventive approaches. Physical restraint use during delirium was the only hospital-related factor to emerge as a significant predictor. The association of physical restraint use with persistent delirium is not surprising, given the documented association of restraint use with incident delirium and its numerous adverse effects, including increased agitation, immobility, functional decline, incontinence, pressure ulcers, asphyxiation, and cardiac arrest. The present findings—that physical restraints may prolong delirium and worsen clinical outcomes—strongly indicate that physical restraints should not be used for older persons with delirium. While the prevalence of restraint use decreased over time between the 2 study cohorts—from 15% in the development cohort to 2% in the validation cohort—the association of restraint use with persistent delirium remained strong in both. Recent reports indicate an average rate of restraint use with persistent delirium of 7% in patients aged 75 years or older.
use of approximately 5% across 40 geographically diverse acute care hospitals and no change in restraint rates between 1998 and 2005. Moreover, currently, there are concerns about a potential resurgence of restraint use in acute care facilities attributable to nursing shortages, budgetary cutbacks, and decreased availability of alternatives such as sitters.

Previous studies have focused on outcomes related to persistent delirium. Only 1 study to our knowledge has examined risk factors for delirium persistence in patients with delirium entering a post–acute care setting. Thus, our study is unique, to our knowledge, in evaluating risk factors for persistence in patients with incident delirium and for separately examining risk factors for delirium onset and persistence.

In contrast to our a priori hypothesis, we did not discover different risk factors contributing to delirium that resolves vs persistent delirium. Baseline risk factors were qualitatively similar but differed in their magnitudes of association. Somewhat stronger relative risks were demonstrated for delirium that resolves than for persistent delirium. For hospital-related factors other than physical restraints, many factors were predictive of delirium that resolves but did not predict persistent delirium.

The analyses of the hospital-related factors presented many challenges, including differing exposure periods between delirium and nondelirium groups, multiple potential factors (eg, diagnoses or medications) that were too varied to examine individually, and limited power. Thus, important associations may have been overlooked. Moreover, the protective ORs demonstrated for some factors such as iatrogenic events raises the possibility that these factors, while precipitating delirium, might also heighten the recognition of delirium and thus lead to its treatment and diminished persistence. Future studies will be needed to confirm this possibility.

Strengths of this study include the frequent, systematic assessment for delirium using a validated instrument and the prospective collection of detailed risk-factor information. The validation of the predictive model in an independent cohort is another important strength. The 2 cohorts demonstrated significant differences in baseline characteristics and delirium rates; therefore, the finding that the predictive model works well in both cohorts lends support for its robustness and generalizability. Finally, the demonstration of the predictive validity of the model for the clinically relevant outcome of death or nursing home placement is another noteworthy strength.

Several caveats deserve comment. The numbers of patients with delirium at discharge were relatively low, limiting our power to examine a large number of potential factors in our model. While the axis approach we chose is well accepted, we recognize that alternative approaches may have been used for variable reduction. In addition, methodologic constraints and small sample sizes limited our ability to examine many hospital-related factors. The differing at-risk periods across the study groups, which included the entire hospitalization period for the no delirium group, may have tended to bias the results against finding a significant association in hospital-related factors. The shift in the magnitude of the ORs between any delirium and persistent delirium is most likely due to measurement issues (such as the difficulty in matching the at-risk periods). Finally, despite the validation of our predictive model in 1 independent sample, future studies will be needed to verify its usefulness in other populations.

Identifying risk factors is the critical first step in developing effective preventive strategies. Four of the identified risk factors are amenable to intervention. Persistent delirium in patients with dementia may respond to orientation procedures and therapeutic activities. Vision impairment may be improved with adaptive devices, magnifying lenses, and improved lighting. Functional impairment may respond to exercise and mobility interventions. Avoidance of physical restraints in delirious patients may help to prevent persistence. Finally, the model identifies patients at intermediate to high risk for persistent delirium who would be appropriate candidates for intervention strategies. Given the high prevalence and poor outcomes of persistent delirium in the older population, this study paves the way for targeted intervention trials to address this important problem.

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Author Contributions: Drs Inouye and Zhang had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Inouye. Acquisition of data: Inouye. Analysis and interpretation of data:
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