Risk Factors and Prediction of Postoperative Delirium in Elderly Hip-Surgery Patients: Implementation and Validation of a Medical Risk Factor Model

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OBJECTIVES: To evaluate risk factors for postoperative delirium in a cohort of elderly hip-surgery patients and to validate a medical risk stratification model.

DESIGN: Prospective cohort study.

SETTING: Medical school–affiliated general hospital in Alkmaar, the Netherlands.

PARTICIPANTS: Six hundred three hip-surgery patients aged 70 and older screened for risk factors for postoperative delirium.

MEASUREMENTS: Predefined risk factors for delirium were assessed on admission. One point was assigned for each of four risk factors present, resulting in three groups: low, intermediate, and high risk. Baseline screening and assessment included the Mini-Mental State Examination, the standardized Snellen test for visual impairment, chart review to determine Acute Physiological and Chronic Health Evaluation II score, and blood urea nitrogen to creatinine ratio. The primary outcome was postoperative delirium, as defined using Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, and Confusion Assessment Method criteria. All patients were screened daily for delirium.

RESULTS: Incidence of delirium was 3.8% in the low-risk group (P < .001), 11.1% in the intermediate-risk group (P = .27, relative risk (RR) = 3.0), and 37.1% in the high-risk group (P < .001, RR = 9.8). Cognitive impairment at admission had the highest predictive value for postoperative delirium (coefficient of determination = 0.15). Contrary to previous findings, age was an independent predictive factor for delirium. Moreover, postoperative delirium was four times as frequent in acute patients as in elective hip-replacement patients.


Key words: delirium; risk-stratification; risk factors; validation; elderly; hip surgery

Delirium is a serious postoperative complication in elderly patients.1–3 It is associated with high morbidity and mortality, longer length of hospital stay, and a high rate of institutionalization after discharge.2,4–7 Incidence rates for delirium of 5% to 45% in acute and elective hip-surgery patients emphasize the need for primary and secondary prevention.2,3,8,9 Effective prevention requires identification of risk factors for delirium.

Risk factors for delirium include a range of predisposing patient factors, as well as precipitating events occurring during admission.10,11 These include cognitive impairment, sensory impairment, severity of illness and dehydration, malnutrition, metabolic disturbances, intoxication, use of bladder catheter, and use of physical restraints.11–13 The etiology of delirium is largely still unknown, and risk factors are likely to interact in a complex way.13 A predictive medical risk factor model for delirium was developed in a pivotal study.10 Patient characteristics present on admission were assessed and related to the incidence of delirium during hospital stay. Four independent risk factors for delirium were identified: visual impairment, severe illness, cognitive impairment, and dehydration. Patients were classified as low, intermediate, and high risk based on the number of risk factors present. Nine percent of the people in the low-risk sample developed delirium, compared with 23% and 83% in the intermediate-risk and high-risk samples. Subsequent validation of the model in an independent patient sample indicated similar results.10

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The medical risk factor model has some clear advantages over other predictive models; results have been replicated in a similar patient sample, and model variables are readily identifiable upon clinical examination and can be quantified and monitored by trained nurses. Also, the risk for delirium can be adjusted when changes occur in patient status over the course of hospitalization. However, some issues need further clarification. Results have not been replicated in other patient samples, and generalizability of the model remains uncertain. Second, some studies, but not all, found that age was a predictor of delirium. This counterintuitive finding requires further exploration. Furthermore, other significant risk factors may operate in different populations. Acute admission, depression, and worse functional status can be important predisposing or precipitating factors of delirium in elderly hip-surgery patients.

The focus of this study was to evaluate baseline vulnerability characteristics that could be helpful in identifying patients at risk for developing postoperative delirium. The primary aims were to estimate the incidence of delirium in a general hospital cohort of elderly hip-surgery patients and to validate the medical four-factor predictive model. The secondary aim was to investigate whether age, type of admission, depression, and functional status are associated with the risk of delirium in this hip-surgery population.

METHODS

Ethical Considerations

The study was undertaken in accordance with the Declaration of Helsinki and the guidelines on Good Clinical Practice. Approval of the regional research ethics committee was obtained. All patients or their relatives gave informed consent.

Study Design and Objectives

The relationship between baseline risk factors, a medical risk factor model, and postoperative delirium was prospectively studied as part of a randomized, double-blind, placebo-controlled clinical trial that compared elderly hip-surgery patients at intermediate or high risk for delirium treated with haloperidol or placebo before surgery. Details of the intervention study and randomization process are described elsewhere. In essence, patients receiving haloperidol or placebo were closely balanced with regard to baseline risk factors, and the study showed that the intervention had an effect on duration and severity of delirium but not on incidence.

In this study, baseline patient characteristics of incident and nonincident cases with postoperative delirium were compared, including those not randomized to study medication and those receiving haloperidol or placebo. Postoperative delirium was defined as delirium occurring within a period of 5 postoperative days. Patients undergoing acute and elective surgery were included in this study, because delirium incidence rates for acute and elective patients tend to overlap. The predictive value of type of admission was evaluated in post hoc analyses.

Risk classification was based on the presence of one or more predictive risk factors: visual impairment, defined as binocular near vision worse than 20/70 after correction; severe illness, measured using the Acute Physiology Age and Chronic Health Examination (APACHE II, range 0–70, scores >16 indicating severe illness); cognitive impairment, measured using the Mini-Mental State Examination (MMSE, range 0–30, score <24 indicating cognitive impairment); and dehydration (ratio of blood urea nitrogen (BUN) to creatinine ≥18).

Analogous to the medical risk factor model, low, intermediate, and high risk for postoperative delirium were defined as the presence of baseline no risk factors, one or two risk factors, or three or four risk factors, respectively. Risk classification was not based on other potentially significant risk factors (age, baseline functional status, mood status, and type of admission), although these factors were recorded at baseline and used in post hoc analyses of study outcomes.

Participants

The study was conducted with a series of patients consecutively admitted for hip surgery to a 915-bed teaching hospital in Alkmaar, the Netherlands.

During the study period, from August 2000 to August 2002, 603 hip-surgery patients (acute/fracture, n = 135; elective, n = 468) aged 70 and older fulfilled criteria for being at low, intermediate, or high risk for delirium at baseline. Patients were ineligible if they had delirium at admission, were unable to participate in interviews (profound dementia, language barrier, intubation, respiratory isolation, aphasia, coma, or terminal illness), or experienced a delay of surgery of more than 72 hours after admission.

Eligibility was checked against the patients’ clinical notes. Patients were enrolled in the study after the trial had been explained to them and they had provided written informed consent. According to procedures approved by the medical ethics committee, a proxy, usually a close relative, gave informed consent when patients lacked capacity.

Measurements and Procedures

Experienced geriatricians and trained research nurses not involved in the clinical care of the patients performed all assessments. Staff members assessing risk factors were the same as those screening for incident delirium. Experienced geriatricians independently diagnosed any screen-positive patients. All data were collected on standardized patient record forms and were checked thoroughly for errors and validity.

Assessment

Baseline assessments were completed before surgery and within 12 hours after admission and included the MMSE, the standardized Snellen test for visual impairment, chart reviews to determine APACHE II score, and BUN/creatinine ratio. Geriatric Depression Scale score, for assessment of mood disorders, and the Barthel Index, for the assessment of baseline activities of daily living (ADLs) were recorded.

Outcomes

The primary outcomes were postoperative delirium and predefined risk factors. Diagnosis of the syndrome was de-
fined using Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), and Confusion Assessment Method criteria. Daily patient assessments with the MMSE, Delirium Rating Scale, revised version (for delirium severity, range 0 (no severity) to 45 (high severity)), and the Digit Span Test (assessment of attention, range 0 (no attention) to 42 (good attention)) were used to diagnose and rate severity of DSM-IV delirium. Confusion Assessment Method and Delirium Rating Scale assessments were continued once a day for 5 days once delirium was diagnosed. After the 5-day trial period, these assessments were continued as part of the regular delirium protocol.

Statistical Analysis
Statistical calculations were performed using SPSS for Windows, version 11.5 (SPSS, Inc., Chicago, IL).

Proportions of patients were compared using the chi-square statistic. Two-tailed P-values < .05 were considered to indicate statistical significance. Parametric values were tested using the Student t test. The results are expressed as relative risks (RRs) with 95% confidence intervals (CI) for the delirium group relative to the nondelirium group and the acute versus the elective patient groups, with a RR less than 1.0 in the CI indicating a beneficial effect. Performance of the risk-stratification models was measured using receiver operating characteristic (ROC) analysis. Values for the area under the ROC curve range from 0 to 1, corresponding to maximum predictive value, 0.5 to random performance (equivalent to chance alone), and 0 to completely incorrect predictive value. Multivariate logistic regression models were used to calculate the predictive value of independent risk factors for delirium (Nagelkerke coefficient of determination $R^2$, percentage explained variance).

RESULTS
A description of the 603 study participants (demographics, medical status, and type of admission) is provided in Table 1. A total of 123 patients had no risk factors (low risk), 409 had one or two risk factors (intermediate risk), and 62 had three or four risk factors (high risk). Overall, 74 patients (12.3%, 95% CI = 9.6–14.9%) developed delirium within 5 days after admission, which is comparable with the medical risk model's validation cohort (16.7%, 95% CI = 11.0–22.1%).

Individuals in the delirium group had significantly worse cognitive disturbances, as measured using the MMSE, poorer visual acuity scores, and lower APACHE II scores. There was no difference for the BUN/creatinine ratio in the two groups ($P = .26$) (Table 1).

The estimated risk of delirium for the four medical risk factors and the comparison with the original validation cohort of the medical risk factor model is shown in Table 2. A MMSE score lower than 24 was found in 48 (64.9%) of the 74 patients with delirium, versus 103 (19.5%) of the 529 without ($P < .001$). An APACHE II score higher than 16 was found for 27 (36.5%) with delirium, versus 57 (10.8%) of those without ($P < .001$). Vision was impaired (score > 20/70) in 15 (20.3%) of the patients with delirium, versus 60 (11.3%) of the patients without ($P = .03$).

The combination of the four risk factors in the stratification model (low, intermediate, and high risk) and its estimated risk for delirium as an indicator of the performance of the predictive model is shown in Table 3. The incidence of delirium in the low-risk (0 points) group was five of 132 (3.8%) and was used as a reference; in the intermediate-risk (1–2 points) group, the risk was 46 of 409 (11.1%, RR = 3.0), and in the high-risk (3–4 points) group, 23 of 62 (37.1%, RR = 9.8), documenting a substantially higher incidence of delirium in high-risk than low-risk patients. The area under the ROC curve for the surgical population (combining the four factors) was 0.73 (95% CI = 0.65–0.78), versus 0.66 (95% CI = 0.55–0.77) for the medical risk factor model validation cohort. Varying the cutoff value of the significant independent predictors in this sample (MMSE < 25 and APACHE II > 15) did not improve the predictive value of the model.

Table 1. Baseline Characteristics of the Patients on Admission

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Delirium (n = 74)</th>
<th>No Delirium (n = 529)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD</td>
<td>81.8 ± 6.7</td>
<td>77.4 ± 5.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>53 (71.6)</td>
<td>412 (77.9)</td>
<td>.23</td>
</tr>
<tr>
<td>Mini-Mental State Examination score, mean ± SD*</td>
<td>21.7 ± 4.6</td>
<td>25.7 ± 3.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Visual acuity, mean ± SD†</td>
<td>0.34 ± 0.14</td>
<td>0.43 ± 0.16</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Acute Physiological and Chronic Health Evaluation II score, mean ± SD‡</td>
<td>14.8 ± 3.8</td>
<td>12.8 ± 2.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Blood urea nitrogen/creatinine ratio, mean ± SD§</td>
<td>19.5 ± 6.6</td>
<td>20.5 ± 6.1</td>
<td>.26</td>
</tr>
<tr>
<td>Geriatric Depression Scale-15 score, mean ± SD‖</td>
<td>1.5 ± 1.7</td>
<td>1.1 ± 1.6</td>
<td>.01</td>
</tr>
<tr>
<td>Barthel Index score, mean ± SD*</td>
<td>18.3 ± 3.1</td>
<td>18.8 ± 3.1</td>
<td>.20</td>
</tr>
<tr>
<td>Acute admission (fracture), n (%)</td>
<td>40 (54.1)</td>
<td>95 (18.0)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

* Range 0 (severe cognitive impairment) to 30 (no cognitive impairment).
† Range 0 (no visual impairment) to 20/800 (severe visual impairment).
‡ Range 0 (no acute health problems) to 70 (severe acute health problems).
§ Ratio ≥18 indicating dehydration.
‖ Range 0 (depression not likely) to 15 (depression very likely).
* Range 0 (severe disability) to 20 (no disability).
SD = standard deviation.
A multivariate stepwise logistic regression analysis using the four risk factors from the medical risk factor model that were significant in univariate analysis only shows that cognitive impairment and illness severity predicted delirium ($R^2 = 0.17$; MMSE, Wald statistic = 28.99, $P < .001$; APACHE II, Wald statistic = 8.72, $P = .41$).

Baseline Geriatric Depression Scale depression scores were higher in the patients with postoperative delirium than in those without ($P = .01$), although the mean scores ± standard deviation of 1.5 ± 1.7 and 1.0 ± 1.5, respectively, were all well within the normal range, and no cases with clinical depression were observed. There was no difference in Barthel Index score between the groups ($P = .20$). The incidence of delirium was higher in the acute surgery group (40/74, 54.1%) than in the elective surgery group (95/529, 18.0%) ($P < .001$, RR = 4.08, 95% CI = 2.69–6.18).

A multivariate stepwise logistic regression analysis, using the four predefined risk factors, other significant risk factors, and type of treatment (haloperidol/placebo), shows that adding age and type of admission increased the predictive power of the model ($R^2 = 0.20$; age, Wald statistic = 5.70, $P = .02$; type of admission (acute), Wald statistic = 4.20, $P = .04$). Study treatment did not add significantly to the prediction of outcomes.

### DISCUSSION

This study demonstrates the usefulness of a medical risk factor model for predicting postoperative delirium in elderly patients undergoing hip surgery. The significant baseline differences found between patients with and without postoperative delirium suggest high vulnerability in the at-risk group. This supports the concept of higher risk for delirium with higher baseline vulnerability when more predisposing factors are present.

The overall prevalence of postoperative delirium was 12.3%. This is comparable to the range of 5% to 45% in hip-surgery patients reported by others. One study found that the incidence of delirium in the development and validation cohorts of elderly general medical patients was 9% and 3% for the low-risk group, 23% and 16% for the intermediate-risk group, and 83% and 32% for the high-risk group, respectively. In the present study, the incidence of delirium in the low-, intermediate-, and high-risk patients was 3.8%, 11.1%, and 37.1%, respectively. It was found that the risk of postoperative delirium was higher in patients with cognitive impairment, severe illness, or visual impairments. In contrast with previous work, dehydration, according to the BUN/creatinine ratio, did not predict postoperative delirium in this surgical cohort. This may reflect the different population samples, the validity of the

### Table 3. Performance of the Predictive Model in an Elderly Hip-Surgery Cohort Compared with the Medical Risk Factor Model Validation Cohort

<table>
<thead>
<tr>
<th>Risk Group*</th>
<th>Points</th>
<th>Study Group (Surgical)</th>
<th>Medical Validation Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n/N (%) Relative Risk</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>0</td>
<td>5/132 (3.8) 1.0</td>
<td>1/30 (3.3) 1.0</td>
</tr>
<tr>
<td>Intermediate</td>
<td>1–2</td>
<td>46/409 (11.2) 3.0</td>
<td>16/103 (15.5) 4.7</td>
</tr>
<tr>
<td>High</td>
<td>3–4</td>
<td>23/62 (37.1) 9.8</td>
<td>12/38 (31.6) 9.5</td>
</tr>
</tbody>
</table>

* Each patient's risk group was determined by adding 1 point for each risk factor present: Mini-Mental State Examination score < 24, Vision score > 20/70, Acute Physiological and Chronic Health Evaluation II score > 16, blood urea nitrogen/creatinine ratio ≥ 18.
† Chi-square, $P < .05$, using low-risk group as reference group.
‡ Chi-square trend, $P < .002$. 

### Table 2. Estimated Risk for Delirium: Surgical Risk Factors on Admission in Comparison with Original Medical Risk Factors Model Validation Cohort

<table>
<thead>
<tr>
<th>Characteristic*</th>
<th>Patients with Delirium (n = 74)</th>
<th>Patients with No Delirium (n = 529)</th>
<th>RR (95% CI)</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mini-Mental State Examination score &lt; 24</td>
<td>48 (64.9)</td>
<td>103 (19.5)</td>
<td>.001</td>
<td>5.53 (3.56–8.58)</td>
</tr>
<tr>
<td>Acute Physiological And Chronic Health Evaluation II score &gt; 16</td>
<td>27 (36.5)</td>
<td>57 (10.8)</td>
<td>.001</td>
<td>3.55 (2.35–5.37)</td>
</tr>
<tr>
<td>Vision score &gt; 20/70</td>
<td>15 (20.3)</td>
<td>60 (11.3)</td>
<td>.03</td>
<td>1.79 (1.07–2.99)</td>
</tr>
<tr>
<td>Blood urea nitrogen/creatinine ratio ≥ 18</td>
<td>52 (70.3)</td>
<td>353 (66.7)</td>
<td>.54</td>
<td>1.16 (0.72–1.85)</td>
</tr>
</tbody>
</table>

* The cutoff points as used previously determined each patient's risk.
† In the medical risk factor model development cohort, the 95% confidence interval (CI) excludes 1.0 for these factors ($P < .05$).
measure, or both. The validity of the measure must be taken into account because of the high percentages of high BUN/creatinine ratios in the current study and in the validation cohort of the medical risk factor model, indicating low predictive and discriminating value of the factor. The other three risk factors of the model emerged as useful baseline predictors of postoperative delirium risk. In a multivariate analysis, the MMSE and APACHE II scores were identified as independent predictors of delirium.

These findings underline the generalizability of the model. Varying the cutoff value of the MMSE (≤25) and the APACHE II (>15), the only independent risk factors predicting delirium in this cohort, did not enhance the predictive value of the model. Varying the cutoff value of the BUN/creatinine values did not change the predictive value of the model either. The strengths of the risk-stratification model are its simplicity and feasibility in clinical practice—a physician or a trained nurse can easily assess all of the risk factors, as part of an assessment that is minimally intrusive to the patient.

In addition to the predefined risk factors, other baseline characteristics indicating a risk for delirium in hip-surgery patients were identified. Age and acute admission were independent predictors of delirium. Age predicted delirium in other studies too. Contrary to these findings, age was not a predictor of delirium in the medical risk factor model. This may reflect the greater rate of falls (and hip fractures) with advancing age. In this study, acute hospital admission because of fractures was associated with four times the risk of delirium (29.6% vs 7.3%). In general, acute admission due to fractures indicates greater vulnerability than elective admission for hip replacement, with a high incidence of falls, more comorbidity, more pain, and more stress factors that may be associated with postoperative delirium. The inclusion of age and type of admission may increase the predictive power of the model, but this needs further confirmation in an independent patient cohort. Moreover, studies of other baseline vulnerability and precipitating factors such as type of anesthesia and postoperative factors (e.g., anemia, narcotic use, hypoxia) may further add to the model's predictive power.

The strengths of this study include the prospective, controlled design, the sample size, the use of a predefined risk-stratification model, and the use of standardized, validated diagnostic instruments for delirium.

The study also has some limitations, including the use of a single site, the possibility that some incident delirium cases may have been missed, and the fact that risk factors were studied in the context of a delirium prevention clinical trial. This study included all eligible patients from several orthopedic and surgical wards in one general teaching hospital. The large number of patients included underscores the results are robust. Nevertheless, generalizability of the conclusions would have benefited had this been a multicenter trial.

The postoperative observation period was limited to 5 days. All of the patients who developed delirium did so within the first 3 days. Similarly, a previous study found that the median onset of delirium in a medical patient sample was between 4 and 6 days. No posttrial delirium cases were referred for geriatric consultation. So, although it is possible that some incident delirium cases were missed because of the observation time limits, it seems likely that the majority of delirium cases occurred within the 5-day study period.

These patients were participants in a delirium-prevention study. An intervention targeted at preventing postoperative delirium may influence the incidence rate of delirium, or it may act as a confounder of baseline risk factors. In this study, baseline risk factors were equally distributed in haloperidol- and placebo-treated patients. The effect of treatment status was not significant in a multivariate analysis of predictors and primary outcomes, and as such, it seems unlikely that treatment status was a confounder of results.

Similarly, data from acute and elective patients were pooled for analyses, which may have affected the findings. Lower rates of postsurgery delirium are typically found in elective patient cohorts than in emergency cohorts, but some studies have found overlapping rates. Type of admission was not a predefined risk factor used in the risk-stratification process in this study but was examined in post hoc multivariate analysis of predictors and primary outcomes. Delirium risk was four times as high in the emergency/acute group. In future studies, results from acute and elective patient samples should be analyzed separately. Furthermore, it is possible that other important risk factors were not measured in this study.

In conclusion, the medical risk factor model proved to be reliable in predicting delirium in this surgical population. The identification of models that can assist in identifying patients at risk of postoperative delirium is of great clinical importance, because it allows for a more-intense targeted approach to high-risk patients. Age and acute admission were identified as independent predictors of delirium in this population. Adding these factors to the existing model made the predictive value even better. Further work is needed to study the potential additional effect of other, independent, risk factors in combination with this model or in a new model for different populations.

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manuscript for intellectual content, statistical analysis. Willem A. van Gool: responsibility for content, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for intellectual content, supervision, statistical analysis. Piet Eikelenboom: responsibility for content, conception and design, acquisition of data, analysis and interpretation of data, critical revision of the manuscript for intellectual content, supervision.

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