Delirium in Acute Stroke
A Systematic Review and Meta-Analysis

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Background and Purpose—Delirium is common in the early stage after hospitalization for an acute stroke. We conducted a systematic review and meta-analysis to evaluate the outcomes of acute stroke patients with delirium.

Methods—We searched MEDLINE, EMBASE, CINAHL, Cochrane Library databases, and PsychInfo for relevant articles published in English up to September 2011. We included observational studies for review. Two reviewers independently assessed studies to determine eligibility, validity, and quality. The primary outcome was inpatient mortality and secondary outcomes were mortality at 12 months, institutionalization, and length of hospital stay.

Results—Among 78 eligible studies, 10 studies (n = 2004 patients) met the inclusion criteria. Stroke patients with delirium had higher inpatient mortality (OR, 4.71; 95% CI, 1.85–11.96) and mortality at 12 months (OR, 4.91; 95% CI, 3.18–7.6) compared to nondelirious patients. Patients with delirium also tended to stay longer in hospital compared to those who did not have delirium (mean difference, 9.39 days; 95% CI, 6.67–12.11) and were more likely to be discharged to a nursing homes or other institutions (OR, 3.39; 95% CI, 2.21–5.21).

Conclusions—Stroke patients with development of delirium have unfavorable outcomes, particularly higher mortality, longer hospitalizations, and a greater degree of dependence after discharge. Early recognition and prevention of delirium may improve outcomes in stroke patients. (Stroke. 2012;43:00-00.)

Key Words: delirium ■ length of stay ■ meta-analysis ■ stroke ■ mortality ■ systematic review

Delirium is characterized by an acute onset of altered level of consciousness with fluctuating course in orientation, memory, thought, or behavior. Although delirium is usually a transient phenomenon, it aggravates the familiar distress after an acute stroke. Previous studies suggest a higher incidence of delirium in stroke patients (13%–48%) compared to 10% to 25% in patients admitted to general internal medicine wards. Patients admitted to general hospitals with delirium have increased rates of mortality and institutionalization, and longer hospitalization for delirium. Advanced age, an underlying urinary or respiratory infection, and preexisting cognitive impairment are usual predisposing conditions.

However, little is known about outcomes in acute stroke patients presenting with delirium. Hence, we completed a systematic review and meta-analysis of the incidence risk of delirium in patients with acute stroke, associated factors, and clinical outcomes.

Materials and Methods

Searching Strategy
We conducted a literature search of MEDLINE, EMBASE, CINAHL, Cochrane Library databases, and PsychInfo last updated in September 2011. We used the MOOSE guidelines for reviews of observational studies. We also completed computer searches based on key words and manually searched for references from previously retrieved articles. Research articles examining the outcome of delirium in poststroke patients were included for review if they met the following inclusion criteria: (1) the study was designed as an observational study or case series; (2) stroke is defined as ischemic, hemorrhagic, transient ischemic attack, or subarachnoid hemorrhage; (3) delirium was either the presenting symptom or developed within 10 days of admission (acute phase of stroke); (4) reported the number of affected patients in each group; (5) reported at least 1 outcome of interest; and (6) the study was written in English. Research articles were excluded from review if they only discussed the incidence of delirium in poststroke patient or if raw data were not available for the assessment of outcomes in both patients with and without delirium.
Study Identification and Validity Assessment

Two reviewers (Q.S., R.P.) assessed titles and abstracts to determine eligibility. Disagreements between raters were solved by a third reviewer (G.S.). Two reviewers (Q.S., R.P.) independently extracted data using standardized data collection forms. Information was collected on study design, recruitment period, participant characteristics, and outcome measures.

The main outcomes of interest include inpatient mortality, mortality at 12 months, institutionalization, and length of hospital stay. We used the Newcastle-Ottawa Scale to assess quality of the studies. Previous studies use a classification for Newcastle-Ottawa Scale as follows: 7 to 9 points considered as high quality; 5 to 6 points considered as moderate quality; and 0 to 4 points considered as low quality.10

Data Synthesis and Analysis

We used Revman version 5.0.14 to conduct statistical analysis. For dichotomous outcomes, we used the number of events in each group and the total number of participants to calculate the odds ratio. For continuous variables, the mean and standard deviations from each study were used to calculate the mean difference. A fixed-effects model was initially used in this systematic review because we found substantial heterogeneity using the Cochran Q test and by calculating $I^2$ values ($I^2 > 50\%$ considered substantial heterogeneity).12

Results

Overall, there were 78 studies retrieved for detailed evaluations. Ten studies,13–22 including 2004 patients met the inclusion criteria (Figure 1). Study characteristics are summarized in the Table. The incidence of delirium in poststroke patients varied from 10%14 to 48%.16 Another study17 did not specify the timing of delirium assessment, however, but we decided to include it as the authors explicitly indicated the study population was selected from a stroke unit in which the median duration of hospitalization was 12 days.

Data Quality

There were no disagreements in quality assessment between reviewers that effected the categorization of studies as high or low quality. All studies were designed as prospective cohort studies comparing the outcomes of patients with delirium or without delirium. The majority of patients enrolled in studies had either ischemic or hemorrhagic stroke and were admitted to stroke units in teaching hospitals with the development of delirium within 7 days. Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV) and confusion assessment methods23 were commonly used to detect the existence of delirium, whereas the Delirium Rating Scale24 was used to rate the severity of the delirium.

The overall methodological quality of each study is presented in the Table. Most studies were high-quality, with only 1 study ranked as moderate.

Outcomes

The incidence of delirium ranged from 10% to 48%. We noticed that this range is largely driven by the study of Gustafan.16 If we exclude this single study, then the incidence upper limit decreased to 28%. The variance can be explained by methodological differences and measurement tools used in previous studies. Six studies15–18,21,22 (n=1345 patients) reported the outcomes of inpatient mortality (Figure 2). The risk of inpatient mortality was significantly higher among patients with delirium than those without delirium (OR, 4.71; 95% CI, 1.85–11.96). Three studies (n=765 patients)19,21,22 compared delirium with nondelirium groups regarding mortality at 12 months (Figure 3). Patients presenting with delirium after stroke were 4.91-times more likely to die within 12 months (OR, 4.91; 95% CI, 3.18–7.6). Four studies (n=585 patients)16,17,19,22 reported the discharge destination after hospitalization (Figure 4). Stroke patients with delirium were more likely to be discharged to long-term care institutions or to a nursing home (OR, 3.39; 95% CI, 2.21–5.21). Six studies (n=1290 patients) compared length of hospital-
ization in both groups (Figure 5). Although all of the studies showed patients with delirium stayed longer compared to those without delirium, we were only able to compute the results from 2 studies. Patients with delirium stayed on average 9 days longer than those without delirium (mean difference [days], 9.39; 95% CI, 6.67–12.11).

Initially, we planned to conduct a subgroup analysis to compare outcomes in patients with ischemic and hemorrhagic stroke. The characteristics of the studies included in the systematic review are summarized in the table below.

### Table. Characteristics of Studies Included in Systematic Review

<table>
<thead>
<tr>
<th>Author and Year</th>
<th>Place of Study</th>
<th>Population</th>
<th>Mean Age (y)</th>
<th>Type of Stroke</th>
<th>Delirium Assessment</th>
<th>Incidence of Delirium (%)</th>
<th>Study Quality</th>
<th>Outcomes Assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caeiro 200413</td>
<td>Portugal</td>
<td>Patient admitted to stroke unit</td>
<td>57.3</td>
<td>Cerebral infarction, hemorrhage, or subarachnoid hemorrhage</td>
<td>DSM-IV and DRS within 4 d of admission</td>
<td>13</td>
<td>7/High</td>
<td>Disability</td>
</tr>
<tr>
<td>Dahl 201014</td>
<td>Norway</td>
<td>Patient admitted to stroke unit</td>
<td>73</td>
<td>Cerebral infarction and hemorrhage</td>
<td>CAM within 7 d of admission</td>
<td>10</td>
<td>8/High</td>
<td>Length of stay, dysfunction, severity of stroke, complication, and others;</td>
</tr>
<tr>
<td>Dostovic 200815</td>
<td>Bosnia and Herzegovina</td>
<td>Hospitalized patients with first-ever stroke</td>
<td>70</td>
<td>Cerebral infarction, hemorrhage, or subarachnoid hemorrhage</td>
<td>DSM-IV and DRS within 4 d of admission</td>
<td>25.3</td>
<td>5/Moderate</td>
<td>Inpatient mortality</td>
</tr>
<tr>
<td>Gustafson 199116</td>
<td>Sweden</td>
<td>Patient admitted to stroke unit</td>
<td>73</td>
<td>Cerebral infarction and hemorrhage (including transient ischemic attack)</td>
<td>DSM-III within 7 d of admission</td>
<td>48.3</td>
<td>9/High</td>
<td>Length of stay, institutionalization, mortality</td>
</tr>
<tr>
<td>Henon 199917</td>
<td>France</td>
<td>Patient admitted to stroke unit</td>
<td>75</td>
<td>Cerebral infarction and hemorrhage</td>
<td>DSM-IV and DRS after admission in stroke unit</td>
<td>24.3</td>
<td>9/High</td>
<td>Length of stay, institutionalization, disability, mortality, complication, poststroke dementia</td>
</tr>
<tr>
<td>Mc Manus 201118</td>
<td>United Kingdom</td>
<td>Patient admitted to stroke unit</td>
<td>66.4</td>
<td>Cerebral infarction and hemorrhage</td>
<td>DRS or CAM within 4 d of admission</td>
<td>28</td>
<td>9/High</td>
<td>Inpatient mortality, mortality after discharge up to 2 y</td>
</tr>
<tr>
<td>Mc Manus 200919</td>
<td>United Kingdom</td>
<td>Patient admitted to stroke unit</td>
<td>66.4</td>
<td>Cerebral infarction and hemorrhage</td>
<td>CAM within 4 d of admission</td>
<td>28</td>
<td>7/High</td>
<td>Inpatient mortality, length of stay, institutionalization</td>
</tr>
<tr>
<td>Melkas 201120</td>
<td>Finland</td>
<td>Stroke patients from the Helsinki Stroke Aging Memory Cohort</td>
<td>70.8</td>
<td>Cerebral infarction, hemorrhage, or subarachnoid hemorrhage</td>
<td>DSM-IV at days 1 and 7 of admission</td>
<td>19</td>
<td>7/High</td>
<td>Long-term mortality and poststroke dementia</td>
</tr>
<tr>
<td>Oldenbeuving 201121</td>
<td>The Netherlands</td>
<td>Patient admitted to stroke unit</td>
<td>72</td>
<td>Cerebral infarction and hemorrhage</td>
<td>Screened with CAM between days 2 and 4, days 5–7 of admission, and assessed by DRS</td>
<td>11.8</td>
<td>7/High</td>
<td>Length of stay, disability, in-hospital mortality, complication</td>
</tr>
<tr>
<td>Sheng 200622</td>
<td>Australia</td>
<td>Elderly stroke patient admitted to stroke unit</td>
<td>80</td>
<td>Cerebral infarction and hemorrhage</td>
<td>DSM-IV within 3 d of admission</td>
<td>25</td>
<td>9/High</td>
<td>Length of stay, institutionalization, disability, mortality, complication</td>
</tr>
</tbody>
</table>

CAM indicates confusion assessment methods; DRS, Delirium Rating Scale; DSM-IV, *Diagnostic and statistical manual of mental disorders*, fourth edition.

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**Figure 2.** Inpatient mortality in patients with and without delirium.
stroke. However, the analysis was not possible because of the lack of relevant information available in individual study.

Heterogeneity and Publication Bias

We observed homogeneity in all findings of pooled estimates except for inpatient mortality ($I^2 = 71\%$). It was largely driven by a single study.\textsuperscript{17} This could be explained by the variance in the timing of delirium assessment. Assessments of publication bias in outcomes of delirium patients are shown in the supplemental Figures (online-only, http://stroke.ahajournals.org). The funnel plots are symmetrical, suggesting no major publication biases.

Discussion

Delirium is a common neurological manifestation in elderly patients hospitalized because of a general medical condition.\textsuperscript{7} The presence of delirium early after admission for an acute stroke represents a diagnostic dilemma and aggravates the family distress.

In the present systematic review and meta-analysis, we found delirium affects 10\% to 30\% of patients in the acute phase of stroke. Patients with poststroke delirium had less favorable clinical outcomes. Specifically, they were 4.7-times more likely to die in the hospital and within 12 months after discharge. Moreover, patients with delirium after stroke tend to have poorer functional outcomes and are more likely to be discharged to long-term care facilities. Because stroke patients with delirium usually require further medical investigations, it is not surprising they had a longer length of hospital stay.

These findings have practical implications for the management of stroke patients who have development of delirium within 10 days after admission. Clinicians are encouraged to use validated tools to identify early signs of delirium and to recognize modifiable risk factors related to delirium. Early screening for delirium and the identification of a metabolic or infectious condition should prompt the appropriate treatment and consequently improve clinical outcomes.

Early intervention might increase the chance of being discharged to home after stroke, maintaining independence, and a good quality of life.

Overall, the methodological quality of the included studies was considered good. All studies were designed as prospective cohort studies with an adequate sample size. Clinicians assessed delirium with validated diagnostic tools. Despite the diversity of the tools used across the studies, the results were consistent.

Our study has limitations and strengths that deserve comment. First, similar to other meta-analyses, the results were not adjusted for confounders (eg, severity of stroke, comorbid conditions) known to influence stroke outcomes. Second, the heterogeneity in inpatient mortality could be explained by the different timeframes of delirium onset and improved intensive care and management of stroke patients. Third, it is important to bear in mind that most participants were selected from stroke units at teaching or academic hospitals. It is possible that these patients had a more complex case-mix than stroke patients admitted to community hospitals. Fourth, although the pooled estimates can reflect the true effect size in the general population, patients treated in stroke units have better outcomes than those in general wards.\textsuperscript{25} As a result, our study may underestimate the severity of outcome in stroke patients with delirium. However, frequent use of stroke units might have increased the awareness and diagnosis of delirium and, consequently, influence short-term and long-term outcomes.

Despite these limitations, our study provides useful and novel information for understanding the prevalence and clinical outcomes in stroke patients with and without delirium. After a comprehensive search, we identified 10 studies including \text{}\textsuperscript{2004} patients. We included the most commonly investigated clinical outcomes influencing care and discharge planning. Finally, this information may help clinicians when counseling families and policymakers to adequately plan resources after acute stroke.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Delirium Events</th>
<th>Control Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gustafsson 1991</td>
<td>29</td>
<td>69</td>
<td>14</td>
<td>76</td>
<td>33.1%</td>
</tr>
<tr>
<td>Horner 1999</td>
<td>58</td>
<td>50</td>
<td>86</td>
<td>152</td>
<td>43.8%</td>
</tr>
<tr>
<td>Mc Manus 2009</td>
<td>7</td>
<td>21</td>
<td>5</td>
<td>57</td>
<td>4.6%</td>
</tr>
<tr>
<td>Sheng 2006</td>
<td>15</td>
<td>39</td>
<td>14</td>
<td>117</td>
<td>18.5%</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>179</td>
<td>402</td>
<td>100.0%</td>
<td>3.39</td>
<td>[2.21, 5.21]</td>
</tr>
<tr>
<td>Total events</td>
<td>89</td>
<td>117</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
A large prospective cohort study adjusting for potential confounders is needed to determine predisposing and precipitating factors. Further research is warranted to better-understand potential interventions that aimed at improving outcomes in stroke patients with delirium.

In conclusion, delirium is observed in up to one-third of patients admitted with an acute stroke. It is usually associated with higher mortality, longer hospitalization, and dependency after discharge. Early recognition and prevention of delirium in stroke patients may improve clinical outcomes and facilitate discharge planning.

Disclosures

None.

References

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SUPPLEMENTAL MATERIAL
1. Supplemental figure 1: Funnel plot: delirium and inpatient mortality

2. Supplemental figure 2: Funnel plot: delirium and institutionalization
3. Supplemental figure 3: Funnel plot: delirium and length of hospital stay

4. Supplemental figure 4: Funnel plot: delirium and mortality at 12 months