Impact of Delirium on Short-Term Mortality in Elderly Inpatients: A Prospective Cohort Study

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Background: *Delirium is an important problem especially in older medical inpatients.* **Objective:** *The authors asked whether delirium and its duration are associated with higher mortality in a 3-month follow-up period.* **Method:** *In this prospective cohort study, inpatients age 65 and older were assessed every 48 hours with the Confusion Assessment Method.* **Results:** *Of 542 patients enrolled, 192 (35.4%) developed delirium. After 3 months, mortality in the delirium cohort was 25.9%, and in the nondelirium cohort was 5.8%. Delirium was independently associated with mortality, and increased by 11% for every 48 hours of delirium.* **Conclusion:** *Delirium and increased delirium durations are significantly associated with higher mortality.*

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Delirium is a clinical manifestation of physical illness that is especially prevalent among older hospitalized patients. The impact of delirium on patients' health is often underestimated.[1] This condition results from one or more precipitating factors and is characterized by acute onset of fluctuating inattention, confusion, and global cognitive dysfunction.[1,2] The pathophysiology of delirium is poorly understood, although multiple mechanisms have been implicated in this condition. These include neurotransmission disturbances, overactivity of the hypothalamic-pituitary-adrenal axis, and overactive cytokine production.[1] MacLullich et al.[3] have recently constructed a basic classification for etiological factors and proposed that delirium can result from a direct brain insult or from a sustained or aberrant stress response.

The prevalence of delirium in the general inpatient population ranges from 11% to 42%.[4] In other settings, such as intensive care units, the prevalence may increase up to 80%.[5] Previous studies examining outcomes of delirium are influenced by elements of study design, delirium assessment, extent of follow-up, and confounder adjustment.[4] Main prospective studies have associated delirium with poor outcomes, including longer hospital stays, higher institutionalization, increased costs, cognitive decline, and functional decline.[6–8] The percentage of inpatient mortalities associated with delirium has been reported to range from 9% to 34.5%.[6,9] However, the association between delirium and mortality has not been consistently demonstrated. Inouye et al.[6] found no significant association between in-hospital delirium and mortality in a 3-month follow-up study, nor did Adamis et al.[10]

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in a 6-month follow-up study. In contrast, other follow-up studies[11,12] found that delirium is a risk factor for death in long-term follow-up. In their 12-month follow-up studies, both McCusker et al.[9] and Leslie et al.[13] found that delirium was an independent predictor of mortality.

Similar to the effect of delirium on prognosis, the effect of delirium duration on outcomes is unclear. This is important, considering that a decreased duration of delirium has been one of the positive outcomes in delirium-prevention or treatment trials.[14,15] The aim of the present study was to clarify the association between delirium and mortality in elderly inpatients, with particular focus on delirium duration.

METHOD

Study Design

This prospective, observational, cohort study was conducted on elderly patients admitted to the general-medical ward of a 536-bed, university-affiliated hospital that covers an extended area of Santiago City, Chile. Study subjects were admitted between March and October of 2006. The study protocol was approved by the ethical committee of the Medical Faculty of the Catholic University of Chile, and informed consent was obtained from patients or their surrogates before their enrollment.

Subjects

Consecutive patients who were at least 65 years of age and were admitted to the medical ward in the previous 48 hours were enrolled if informed consent was obtained from patients or their legal representative. Exclusion criteria included evidence of severe aphasia, coma, and inability to participate in cognitive assessments.

Study Protocol

Patients were enrolled every 48 hours by a research team composed of three psycho-geriatricians trained in delirium detection. Demographic data (gender, age, ID number, contact information) were collected, and five assessments were performed: Patients were administered to the Acute Physiology and Chronic Health Evaluation II (APACHE II), which measures severity of acute illness by use of clinical data and laboratory measures obtained during the first 24 hours of admission.[16] Subjects were assessed with the Charlson Comorbidity Index, which is a weighted index that estimates burden of comorbidity.[17] The preadmission functionality of subjects was determined with the Barthel Index. This index measures the ability of the patient to perform 10 basic activities of daily living,[18] with scores ranging from 0 (minimal functionality) to 100 (optimum functionality).[4] The Pfeffer Functional assessment questionnaire (PFAQ) was performed to detect previous dementia. This questionnaire estimates baseline functionality, using information obtained from the caregiver.[19] Scores over 7 can be used as a proxy for past dementia.[20] Because dementia cannot be diagnosed during a delirium episode, we used this proxy functional parameter in our analysis.[5] Delirium was determined with the Confusion Assessment Method (CAM). The CAM is a validated instrument for establishing the presence of delirium and is based on the operational application of the DSM-III–R criteria. This method relies on clinically relevant information obtained from the caregiver and the patient. It provides a diagnostic algorithm for delirium based on the presence of the two cardinal features: 1) acute onset and fluctuating course; and 2) inattention, and at least one of the two secondary features: 1) disorganized thinking; and 2) altered level of consciousness.[21] The CAM has been adapted and validated for Spanish speakers.[22]

Procedures

The research team evaluated enrolled patients for the presence and duration of delirium with the CAM.[22] Assessments were performed every 48 hours between 9 A.M. and 2 P.M. until discharge or for a maximum of 12 days. Data collected from medical and nurse records were used to fill out information for APACHE II[16] and the Charlson Comorbidity Index.[17] Caregiver interviews were performed to assess functionality with the Barthel[18] and Pffeffer indices.[19] In these interviews, caregivers were questioned about the patients' capacity to perform daily living activities in the 2 weeks before admission.

If delirium was diagnosed, either at the initial assessment or at follow-up visits during the hospital stay, then the patient was included in the delirium cohort. If delirium was not identified, the patient was included in the nondelirium cohort. Mortality at 3 months after enrollment was determined by telephone/structured interviews and the National Demographic Register. The research team had no participation in the usual care of the subjects.

Statistical Analysis

The Student *t*-test for independent samples and the chi-square test were used to analyze differences between means and proportions, respectively. Association of baseline characteristics (i.e., age, sex, APACHE II score, Charlson Comorbidity Index, Pfeffer functional assessment, and Barthel Index) and delirium was determined with logistic-regression models.[23] To estimate delirium duration, we used 48 hours as the time unit for delirium duration, since the delirium assessments were performed at 48-hour intervals. Cox's proportional-risks model was used to generate coefficients describing the relationship between time until death and delirium duration. Risk of death was estimated as relative risk (RR). To assess variables related to mortality, we analyzed baseline characteristics and delirium diagnosis with a univariate Cox proportional-hazards model. Survival curves for delirium and nondelirium cohorts were constructed with the Kaplan-Meier product-limit estimate.[24] The difference between curves was determined by the log-rank test. The effect of multiple covariates in mortality was evaluated with the Cox multiple-regression model. Univariate and multivariate Cox models were used to estimate unadjusted and adjusted hazard ratios (HR).[25,26] The variables included in the Cox model were determined by adjusting all subset models, provided that the number of potential predictor variables was not too large.[27] The criteria for selecting the final model were maximum likelihood and Akaike's information criterion.[28] Values of $p \leq 0.05$ were considered significant. SPSS Version 15.0 was used for statistical analysis.

RESULTS

A total of 542 patients were enrolled in the study. These patients had a mean age of 78 years and a mean hospital stay of 6 days. More than half (62%) were female. Primary medical diagnoses were infectious diseases (31%), metabolic disorders (15%), gastrointestinal diseases (14%), cardiovascular diseases (10.5%), or other conditions (30%). Delirium was diagnosed during hospitalization in 192 patients (35.4%). The majority of diagnoses were made within the first 48 hours of admission (87% within 48 hours and 13% thereafter). Mean delirium duration was 4.9 days (standard deviation [SD]: 3.1). The delirium cohort was significantly older and had lower baseline functional status, as seen by a lower Barthel index and higher Pfeffer score (Table 1). Also, the hospital stay for the delirium cohort (7.3 [5.9] days) was longer than that for the nondelirium cohort (5.0 [3.9] days; Table 1). The development of delirium was associated with greater age ($p < 0.001$) and decreased functional status (lower Barthel Index and higher Pfeffer scores; $p < 0.001$ for both).

At the 3-month follow-up, the overall mortality was 12.9% (69 of 536 patients). Six patients were lost during follow-up (1.1%). The mortality rate was 25.9% in the delirium cohort and 5.8% in the nondelirium cohort (RR: 4.50; 95% CI: 2.76 – 7.33). Both in-hospital and post-discharge mortality were higher in the delirium cohort (RR: 4.90; 95% CI: 1.95 – 12.30) than in the nondelirium cohort (RR: 4.33; 95% CI: 2.38 – 7.88).

Patients who had survived at 3 months were significantly younger (77.4 [7.4] years for the surviving cohort versus 81 [8.1] years for the nonsurviving cohort; $p < 0.001$) and had better baseline functionality (mean Barthel Index was 87.8 [19.6] for the surviving cohort versus 73.9 [25.6] for the nonsurviving cohort; $p < 0.001$). The surviving group

TABLE 1. Characteristics of Delirium and Non-Delirium Cohorts

Variable	Total (N=542)	Non-Delirium Cohort (N=350)	Delirium Cohort (N=192)	p[a]
Age, years	77.9 (7.6)	75.8 (7.0)	81.5 (7.2)	< 0.001
Women, N (%)	334 (61.6)	215 (61.4)	119 (62.0)	0.900
Hospital stay, days	5.8 (4.8)	5.0 (3.9)	7.3 (5.9)	< 0.001
APACHE II score	10.1 (4.2)	9.7 (4.1)	10.7 (4.3)	0.006
Charlson Comorbidity Index	1.7 (1.6)	1.6 (1.6)	1.8 (1.6)	0.141
Pfeffer functional score	4.6 (7.8)	2.2 (5.1)	9.1 (9.7)	< 0.001
Barthel Index	86.0 (20.9)	92.7 (15.1)	73.8 (24.3)	< 0.001
Pfeffer functional score >7, N (%)[b]	108 (20.1)	28 (8.1)	80 (42.3)	< 0.001
In-hospital mortality, N (%)	22/536 (4.1)	6 (1.7)	16 (8.5)	< 0.001
Post-discharge mortality, N (%)	47/536 (8.7)	14 (4.0)	33 (17.5)	< 0.001
3-month mortality, N/total N (%)	69/536 (12.9)	20/350 (5.8)	49/192 (25.9)	< 0.001

Values are mean (standard deviation), unless otherwise indicated.

[a] Analysis of variance and Student *t*-tests were used to analyze scores of continuous variables. The chi-square test was used to compare distributions of categorical and dichotomous data.

[b] Proxy for previous cognitive impairment.[19]

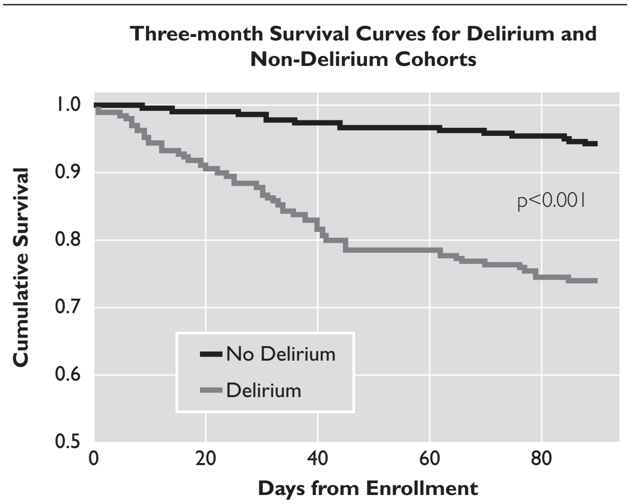
had fewer delirium diagnoses (30% versus 71%; $p < 0.001$) and shorter delirium durations (4.6 [2.8] days versus 6.0 [3.7] days; $p=0.02$). For the delirium cohort, the Kaplan-Meier survival curve declined rapidly over the first 30 days after enrollment and then continued to decline at a slower rate. Comparison of the survival curves using the log-rank test revealed a significant difference between survival times for the two cohorts ($p < 0.001$; Figure 1).

All baseline characteristics except gender and APACHE II score were significantly associated with mortality ($p < 0.005$). However, in the multivariate Cox model, the only remaining explanatory variables were delirium (adjusted HR: 4.04; 95% CI: 2.19 – 7.46) and Charlson Comorbidity Index (adjusted HR: 1.23; 95% CI: 1.06 – 1.43). Longer duration of delirium was also associated with a higher risk of death during the follow-up period. For every 48 hours of delirium, the probability of dying at 3 months increased by 11% (unadjusted HR: 1.11; 95% CI: 1.02 – 1.21). This probability was not affected after adjustment for age, sex, APACHE II score, Charlson Index, Pfeffer score, and Barthel score (HR: 1.116; 95% CI: 1.02 – 1.22).

DISCUSSION

This study confirms the high incidence and prevalence of delirium in elderly inpatients in medical wards. In accordance with previous studies, our work supports a significant association between delirium and mortality in elderly patients.[11,12] Similar to the work carried out by McCusker et al.[9] and Leslie et al.,[13] our work identifies delirium as an independent risk factor for mortality, even after adjustment for covariates such as age, functional dependency, comorbidity, and severity of acute illness.

FIGURE 1. Kaplan-Meier 3-Month Survival Curves for Delirium and Non-Delirium Cohorts



Our study confirms that delirium is associated with older age, higher severity of acute illness, worse baseline functionality, and cognitive impairment. In terms of outcomes, in accordance with previous studies, delirium patients had significantly longer hospitalizations,[4] and a four-times-higher in-hospital mortality rate. Remarkably, this remained unchanged in the post-discharge period, confirming a long-term effect of delirium on mortality, as noted by McCusker et al.[9] in a 1-year follow-up study. Failure of some studies to replicate these findings might be due to inadequate statistical power,[10] or samples with fewer delirium cases.[6]

To our knowledge, this is the first study to establish an association between delirium duration and prognosis. This study clearly demonstrated that mortality significantly increased 11% for every 48 hours of delirium. The clinical relevance of the association between delirium duration and mortality is highlighted by the finding that preventing or treating delirium significantly shortens the duration of delirium.[14,15] However, whether reducing the duration of delirium affects survival will require further investigation.

Although pathophysiology of delirium remains poorly understood, recently, two main mechanisms have been proposed: brain insult and aberrant stress responses mediated by inflammatory response and the activity of the limbic-hypothalamic-pituitary-adrenal axis. These aberrant stress responses are thought to be potentially deleterious when exaggerated or sustained.[3] Whether these mechanisms are responsible for the poor clinical outcomes associated with delirium is a question that remains unsolved; however it arises as an interesting hypothesis.

This study has some important strengths. First, delirium assessments were performed by a trained medical psychogeriatric team that was not involved in patient care. This could improve sensitivity, since nonmedical use of the CAM has been shown to lower the accuracy of this method.[29,30] Second, we analyzed a large sample size, and only 1% of patients were lost to follow-up. Therefore, the statistical power was adequate to detect an association between delirium and mortality. Finally, data analysis was carried out controlling for important confounding variables, such as comorbidity, severity of acute illness, previous functionality, and a proxy for dementia.

The present findings should be interpreted in the context of the study's limitations. Because this was a single-site cohort study of elderly medical inpatients, the findings might not necessarily apply to all elderly inpatient populations. On the other hand, despite the improvement in the frequency and duration of assessment in this study, as compared with previous studies,[6,9,12] 48-hour assessment-intervals might still be considered too long. Finally, this study did not include assessment of delirium severity, which could be associated with mortality, either alone or in combination with delirium duration. This remains an open and interesting avenue of research.

In summary, our results are in accordance with previous studies confirming that delirium is an independent risk factor for mortality in elderly medical inpatients. Moreover, this study demonstrates a strong relationship between delirium duration and mortality. Further studies will be necessary to determine whether management of delirium duration has an impact on clinical outcome.

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