The Course of Delirium in Older Medical Inpatients

A Prospective Study

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OBJECTIVES: **To describe the clinical course and outcomes of delirium up to 12 months after diagnosis, the relationship between the in-hospital clinical course and post-discharge outcomes, and the role of dementia in both the clinical course and outcomes of delirium.**

DESIGN: **Prospective cohort study.**

SETTING: **Medical wards of a 400-bed, university-affiliated, primary acute care hospital in Montreal.**

PATIENTS: **Cohort of 193 medical inpatients aged 65 and over with delirium diagnosed at admission or during the first week in hospital, who were discharged alive from hospital.**

MEASUREMENTS AND MAIN RESULTS: **Study outcomes included cognitive impairment and activities of daily living (standardized, face-to-face clinical instruments at 1-, 2-, 6-, and 12-month follow-up), and mortality. Dementia, severity of illness, comorbidity, and sociodemographic variables were measured at time of diagnosis. Several measures of the in-hospital course of delirium were constructed. The mean numbers of symptoms of delirium at diagnosis and 12-month follow-up, respectively, were 4.5 and 3.5 in the subgroup of patients with dementia and 3.4 and 2.2 among those without dementia. Inattention, disorientation, and impaired memory were the most persistent symptoms in both subgroups. In multivariate analyses, pre-morbid and admission level of function, nursing home residence, and slower recovery during the initial hospitalization were associated with worse cognitive and functional outcomes but not mortality.**

CONCLUSIONS: **Among patients with and without dementia, symptoms of delirium persist up to 12 months after diagnosis. Quicker in-hospital recovery is associated with better outcomes.**

KEY WORDS: **delirium; aged; prognosis; longitudinal; dementia.**
J GEN INTERN MED 2003;18:696–704.

Delirium has been described as a transient syndrome characterized by disordered attention, thinking, and perception, and other symptoms. However, recent research has documented the heterogeneity of the in-hospital clinical course of delirium and high rates of persistence of delirium symptoms until discharge.[1–3] The clinical course of delirium both during and after hospitalization was described in a cohort of 135 hospitalized patients aged 65 and over, admitted from community and long-term care settings with delirium that met *Diagnostic and Statistical Manual of Mental Disorders, Version III* (DSM-III) criteria: 34 with delirium at admission (prevalent cases) and 91 with new onset delirium during their stay (incident cases).[4] At the time of discharge, 42% of patients no longer met DSM-III criteria, 31% initially recovered but relapsed before discharge, and 27% of patients continued to meet DSM-III criteria throughout their hospitalization. Only 5 (4%) of these cases experienced complete resolution of their symptoms before discharge from the hospital. At follow-up 3 and 6 months after discharge, among patients available for assessment, 63% and 69%, respectively, no longer met DSM-III criteria for delirium; 21% and 18%, respectively, had complete resolution of their symptoms. Limitations of this important study included: absence of a systematic, standardized measure of dementia; the use of family or caregiver reports rather than direct observation at follow-up; and no follow-up beyond 6 months. Furthermore, the prognostic importance of the initial clinical course of delirium was not described.

We have conducted a prospective, observational study of 2 cohorts of medical inpatients aged 65 and over, with and without delirium, using standardized, face-to-face clinical instruments at follow-up, up to 12 months after diagnosis. Members of the delirium cohort experienced significantly higher mortality than those without delirium, and survivors had worse cognition and physical function at follow-up, even after adjustment for dementia, comorbidity, severity of illness, and other confounders.[5,6] Using data from members of the delirium cohort who were discharged alive from hospital, we now describe the clinical course and outcomes of delirium at 12 months after diagnosis, the relation between in-hospital clinical course and post-discharge outcomes; and the role of dementia in both the clinical course and outcomes of delirium.

METHODS

The study was conducted at a 400-bed, university-affiliated, primary acute care hospital in Montreal. The study was a prospective design with follow-up at 1, 2, 6, and 12 months in a delirium cohort, in whom prevalent or incident delirium was detected during the first week of

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hospitalization. A subgroup of the delirium cohort also participated in a randomized trial of the detection and management of delirium by a physician-nurse consultation team versus usual care, which found small and statistically nonsignificant benefits of the intervention.[7]

Enrollment of Subjects

Methods of recruitment and detection of delirium have been described.[5,6] Briefly, a study nurse screened patients aged 65 and over who were admitted from the emergency department to the general medical services. We excluded patients with a primary diagnosis of stroke and those who did not speak English or French. At admission and during the first week of hospitalization patients were screened using the Short Portable Mental Status Questionnaire (SPMSQ)[8] and review of the nursing notes. The nurse administered the Confusion Assessment Method (CAM)[9] to those who made 3 or more errors on the initial SPMSQ, indicating moderate to severe cognitive impairment, or whose SPMSQ score increased by at least 1 error from the first assessment, or whose nursing notes indicated possible symptoms of delirium (e.g., disorientation or agitation). Prevalent delirium was diagnosed if the patient met DSM-III-R criteria for probable or definite delirium at enrollment and incident delirium if the criteria were met after enrollment.[10]

Subjects assented to participation, and a relative provided written informed consent. The study was approved by the hospital's Research Ethics Committee.

Data Collection and Measures

Patients were assessed at enrollment by a research assistant (RA), blind to the study group, who also interviewed a family member. The RA re-assessed patients at least every 2 to 3 days during the first week and then weekly during their hospital stay for up to 8 weeks from enrollment, and at 6 and 12 months after enrollment. In addition, patients discharged before 8 weeks were assessed at 8 weeks after discharge in order to assess the effect of the intervention on outcomes in the home setting. Date of death was ascertained.

The Barthel Index (BI), measuring activities of daily living,[11] was rated by the RA at enrollment and at follow-up, usually at a home visit. We used the modified scoring suggested by Shah et al.,[12] in which the total, weighted score ranges from 0 (complete dependence) to 100 (complete independence). The Mini-Mental State Examination (MMSE),[13] a widely used instrument with established reliability and validity,[14] was rated by the RA. The MMSE score ranges from 0 to 30, a lower score indicating greater cognitive impairment. The Instrumental Activities of Daily Living (IADL) questionnaire from the Older American Resources and Services project,[15] administered to an informant, was used to assess pre-morbid function at baseline (prior to the current illness but not more than 1 month before hospital admission) and current function at follow-up; the scale score ranges from 0 (completely dependent) to 16 (completely independent).

Delirium symptoms were assessed with the Delirium Index (DI), based solely upon patient observation, without additional information from family members, nursing staff, or the patient's medical chart.[16] In this instrument, 7 of 9 symptom domains assessed on the CAM (including disorders of attention, thought, consciousness, orientation, memory, perception, and psychomotor activity, but excluding acute onset and sleep-wake disturbance) are rated on a 4-point scale. In this study, we used the DI as a measure of the number of symptoms, not of their severity, giving a possible range of 0 to 7 symptoms. Dementia was assessed using the 16-item Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE).[17–19] Family members reported the cognitive change during the previous 10 years, up to the premorbid period. Cut-off points between 3.38[17,18] and 3.6[20] have been used; we used an intermediate cut-off of 3.5.

Three measures of illness burden and severity were used. Clinical severity of illness was assessed by the research nurse at diagnosis.[21,22] The score ranges from 1 (minimal) to 9 (most severe). Comorbidity at admission was assessed by chart review using the Charlson Comorbidity Index, a weighted index that takes into account both the number and severity of comorbid conditions, a higher score indicating greater severity.[23] Acute physiologic severity of illness at diagnosis was assessed with the Acute Physiology Score, derived from the Acute Physiology and Chronic Health Evaluation II scale.[24] The scale ranges from 0 to 56, with a higher score indicating greater severity.

Finally, demographic variables (age, sex, marital status, education, and residence) were recorded in study baseline forms.

Measures of the Clinical Course of Delirium

Using the Delirium Index, we constructed 4 measures of the in-hospital course of delirium: duration of the initial delirium episode (in days), total number of days with delirium, proportion of days with delirium, and a 3-category measure of the in-hospital course (transient, recovery within 24 hours; recovered, recovery by discharge; and persistent, delirium present at discharge). The time to cognitive improvement was estimated as a 2-point improvement in the baseline MMSE score (see Appendix A for further details).

We also constructed measures of the prevalence and number of symptoms at each of the following time points: 1) baseline (the first DI after diagnosis of delirium); 2) 1 month (28 days after diagnosis or the last DI before this date); 3) 2 months (8 weeks post-discharge, or 8 weeks after enrollment for those still in hospital, or the last in-hospital DI after 28 days from enrollment); 4) 6 months after enrollment; and 5) 12 months after enrollment. The mean (and standard deviation) of the number of days from enrollment to each time point were: 1 month, 13.3

Table 1. Baseline Characteristics of Cohort and In-hospital Course of Delirium

Characteristics	Overall (*N* = 193)*	Dementia (*N* = 136)	No dementia (*N* = 45)	*P* Value†
Categorical variables, *n* (%)				
Sex				.32
Female	119 (61.7)	84 (61.8)	24 (53.3)	
Male	74 (38.3)	52 (38.2)	21 (46.7)	
Marital status				.05
Married	62 (32.1)	39 (28.7)	20 (44.4)	
Single/widowed/divorced	131 (67.9)	97 (71.3)	25 (55.6)	
Education				.87
Secondary or less	91 (49.5)	66 (48.5)	22 (50.0)	
More than high school	93 (50.5)	70 (51.5)	22 (50.0)	
(missing)	(9)	(0)	(1)	
Residence				.003
Home	142 (73.6)	93 (68.4)	41 (91.1)	
Other	51 (26.4)	43 (31.6)	4 (8.9)	
Delirium type				.004
Prevalent	165 (85.5)	123 (90.4)	33 (73.3)	
Incident	28 (14.5)	13 (9.6)	12 (26.7)	
Course of delirium				.0001
Transient	76 (39.4)	40 (29.4)	30 (66.7)	
Recovered‡	56 (29.0)	43 (31.6)	10 (22.2)	
Persistent‡	61 (31.6)	53 (39.0)	5 (11.1)	
Mean continuous variables (±SD)				
At enrollment				
Age	83.4 (7.3)	84.3 (6.8)	80.4 (7.6)	.001
Severity of illness	5.1 (1.3)	5.2 (1.3)	5.2 (1.1)	.98
Acute physiology score	4.4 (2.8)	4.6 (2.9)	4.2 (2.8)	.40
Charlson Comorbidity Index	2.5 (1.8)	2.5 (1.6)	2.4 (1.9)	.77
In-hospital course of delirium				
Time to cognitive improvement (days)	10.8 (10.1)	11.7 (10.4)	9.0 (9.4)	.12
Number of days with delirium	7.0 (9.1)	8.3 (9.6)	4.1 (7.5)	.009
Length of 1st delirium episode (days)	6.3 (9.4)	8.3 (9.6)	3.9 (8.1)	.03
Proportion of days with delirium	0.4 (0.4)	0.5 (0.4)	0.2 (0.3)	<.001
Length of stay (days, from admission)	18.3§ (17.3§)	18.9§ (18.6§)	17.5 (14.5)	.60

* *Presence of dementia was unknown in 12 patients.*
† P *value of* χ^2 *or Fisher's exact test for categorical variables.* P *value of F test from 1-way ANOVA for continuous variables.*
‡ *At discharge or at 8 weeks if patient still in hospital.*
§ *One missing value.*
SD, standard deviation.

(8.0); 2 months, 70.5 (11.5); 6 months, 184.7 (6.3); 12 months, 366.6 (6.9).

Statistical Methods

Among the total of 243 delirium patients in the original study, 42 were excluded because they died during the initial hospital admission, and 8 were excluded because they had only 1 DI assessment before discharge, leaving 193 cases for the analysis. One hundred ten of these patients also participated in a randomized trial: 55 in the intervention and 55 in the control group. To study the impact of excluding the 42 patients who died, we carried out a descriptive analysis among them to estimate the number with transient, recovered, or persistent delirium.

The percentage of subjects with each delirium symptom (on the DI scale) was estimated separately among patients with and without dementia at baseline, and at the 1-, 2-, 6-, and 12-month follow-up. Similarly, the mean number of delirium symptoms at baseline and each follow-up time was estimated separately among patients with and without dementia. These results were obtained separately for patients with complete information at baseline and follow-up and for patients with any information at baseline or follow-up. Both approaches yielded similar results; we present the bar plots based on the latter approach.

The effect of delirium on cognitive status, functional status, and 1-year mortality was evaluated separately for each of the 5 measures of clinical course of delirium defined earlier. General linear models for longitudinal data were used to compare the effects of the clinical course of delirium on each of MMSE, BI and IADL over time. The advantage of these models over standard linear regression models is that they take into account the dependence between multiple (i.e., 2 or more) observations made on the same subject over time. We used an autoregressive structure for the error variance to model the dependence between successive observations on the same subject. MMSE and BI scores were recorded at the 2-, 6-, and 12-month follow-up, while the IADL score was recorded at

6- and 12-month follow-up only. The models presented in the article are based on patients with information at any follow-up. Similar results were obtained when using only those patients with complete information at follow-up. The effect of the clinical course of delirium on 1-year mortality was modeled using the Cox proportional hazards model. Survival time was accrued following baseline, and subjects were censored when they were lost during follow-up or at 1 year after the baseline if they did not die during follow-up, whichever occurred earlier. The proportional hazards assumption was checked.[25]

All the above models were adjusted for age, sex, education, marital status, residence, dementia, clinical severity, comorbidity, physiological severity, and incident/prevalent delirium. The presence of multicolinearity between the independent variables was examined using the variance inflation factor.[26] The effect of the interaction between dementia and the measures of clinical course also was evaluated for each model. In addition, the models for MMSE and BI were adjusted for the baseline values of these variables. We evaluated the effect of IADL on all the outcomes, but did not include it as a covariate in the final models since it was highly correlated with dementia. The effect of the intervention group in the randomized trial was evaluated also for all the outcomes but was dropped from the final models as it was not a significant predictor. Statistical tests were deemed significant if the 2-sided *P* value was less than .05. All statistical analyses were carried out using SAS for Windows, version 8 (SAS, Inc., Cary, NC).

RESULTS

Some characteristics of the study sample are shown in Table 1. Notably 39.4%, 29%, and 31.6% of subjects had transient, recovered, and persistent courses, respectively. Non-demented were more likely than demented patients to have incident rather than prevalent delirium and to have transient symptoms (recovery within 24 hours). Demented patients also had significantly longer episodes based on 3 measures of duration of delirium. However, mean time to cognitive improvement and length of stay were similar in patients with and without dementia.

Figure 1 shows the mean number of delirium symptoms present at each assessment, stratified by dementia status. Patients with dementia had a consistently higher mean number of symptoms at each time. Both groups had, on average, about 1 symptom less at follow-up than at enrollment. The mean numbers of symptoms of delirium at diagnosis and 12-month follow-up, respectively, were 4.5 and 3.5 in the subgroup of patients with dementia and 3.4 and 2.2 among those without dementia. Delirium was present at 6 and 12 months in 38.5% and 48.9%, respectively, of patients with dementia and 8.8% and 14.8%, respectively, of patients without dementia.

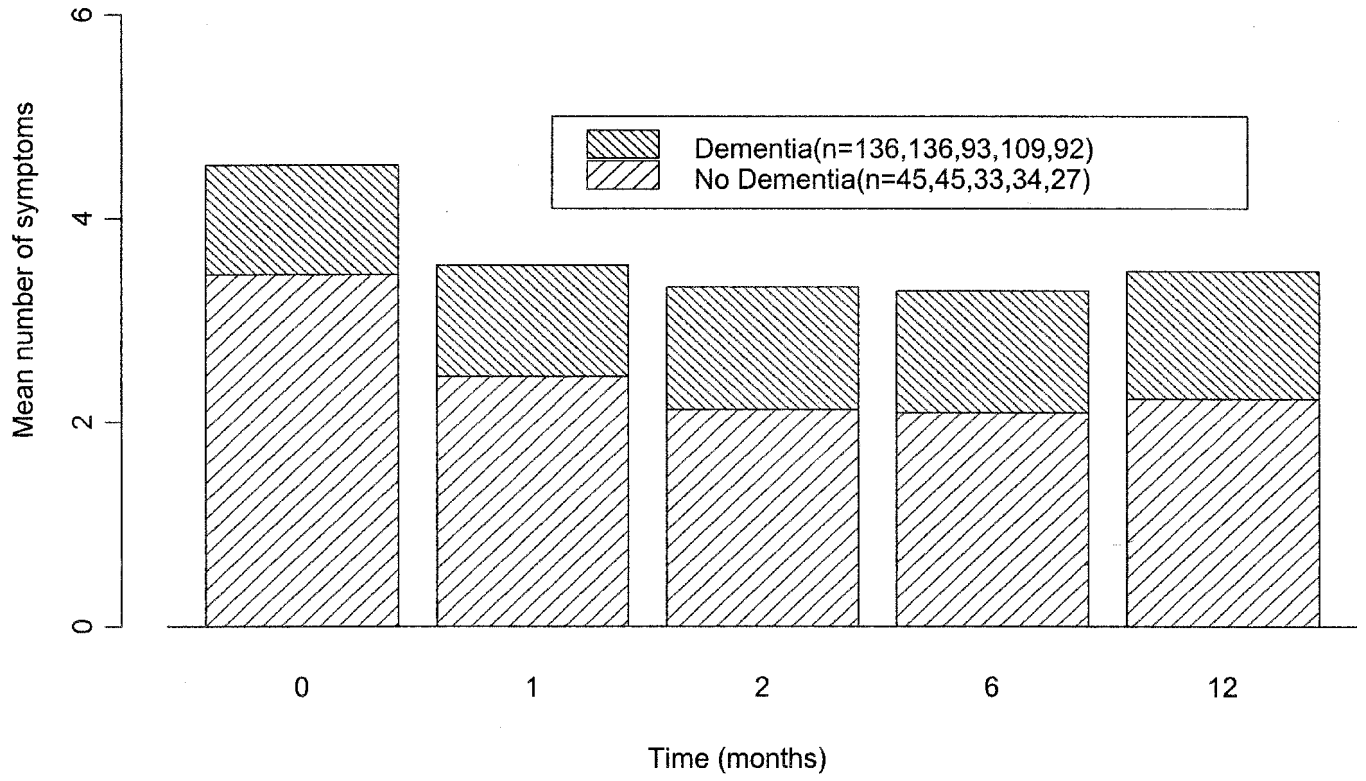

FIGURE 1. Mean number of delirium symptoms at baseline and follow-up in demented and non-demented patients.

Figure 2 shows the prevalence of each symptom at each time point, among patients with and without dementia, using all available data. Patients with dementia consistently had a higher prevalence of all symptoms at all time points. However, remarkably high proportions of non-demented patients also had many of these symptoms. The prevalence of all symptoms except memory impairment tended to be lower at follow-up than at diagnosis. The most persistent symptoms, in patients both with and without dementia, were inattention, disorientation, and impaired memory.

The MMSE and BI scores were somewhat improved at follow-up compared to those measures made at the time of diagnosis in the hospital (Table 2). However, in comparison with the premorbid IADL (prior to admission), the mean IADL score deteriorated at follow-up. Patients with dementia tended to have worse scores on all these measures than non-demented patients (Table 2).

The same data are shown in Table 3, stratified by the in-hospital course of delirium. In general, when considering the MMSE, BI, IADL, and delirium measures at follow-up, patients with transient delirium had the most favorable outcomes, the recovered group was intermediate, and those with persistent delirium had the worst outcomes. There was a small trend in the post-discharge mortality rates in the same direction. However, it should be noted that, among 36 patients of the 42 who died in hospital with at least 2 DI measures, 27 were classified as persistent, 4 as recovered, and 5 as transient delirium. The inclusion of these in-hospital deaths would yield a stronger relation between the course of delirium and mortality: transient delirium, 30.9% (25/81); recovered delirium, 35.0% (21/60); persistent delirium, 53.4% (47/88).

All 4 measures of the initial clinical course of delirium, when considered individually were significantly associated with the MMSE, BI, and IADL scores at follow-up, after adjusting for baseline covariates (Table 4). In comparison with patients with transient delirium, those with recovered delirium had significantly worse BI and IADL scores at follow-up, and those with persistent delirium had significantly worse MMSE, BI, and IADL scores at follow-up. Furthermore, in comparison to those with recovered delirium, patients with persistent delirium had significantly lower MMSE, BI, and IADL scores (adjusted

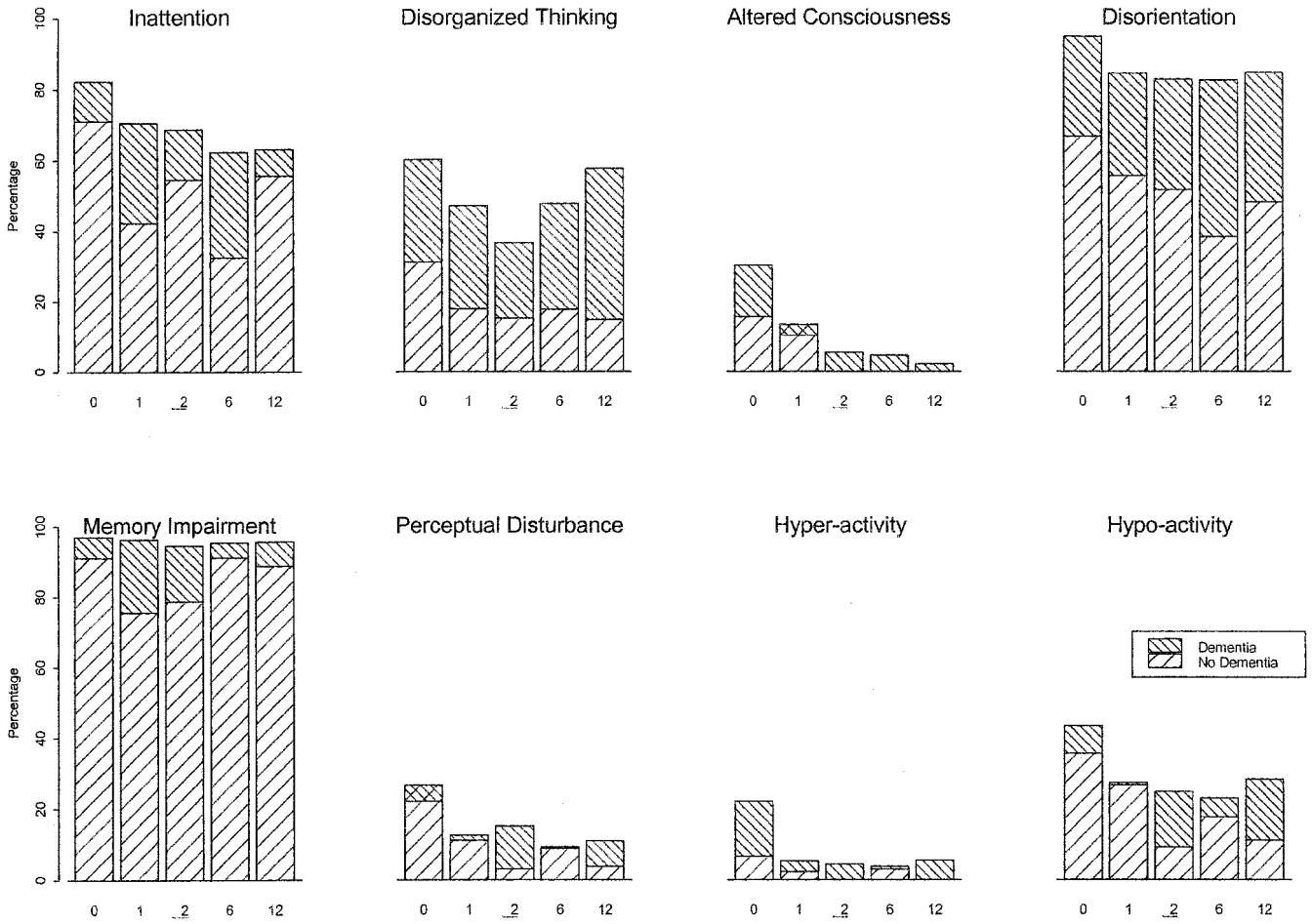

FIGURE 2. Percentage with specific delirium symptoms at baseline and follow-up. Note: Sample sizes at each time point are the same as those in Figure 1.

Table 2. Outcomes at Enrollment and Follow-up by Dementia Status

	Overall	Dementia	No Dementia
MMSE score, *n* (mean ± SD)			
Enrollment	193 (15.1 ± 7.2)	136 (13.7 ± 7.0)	45 (19.1 ± 5.7)
2 Mo	187 (18.0 ± 7.4)	136 (16.5 ± 7.4)	45 (22.1 ± 5.3)
6 Mo	145 (18.3 ± 7.6)	108 (16.9 ± 7.7)	34 (22.9 ± 5.2)
12 Mo	119 (17.8 ± 7.7)	91 (16.7 ± 8.0)	25 (21.7 ± 5.4)
BI score, *n* (mean ± SD)			
Enrollment	193 (42.4 ± 29.8)	136 (39.1 ± 28.5)	45 (53.9 ± 29.3)
2 Mo	181 (66.6 ± 30.7)	132 (63.1 ± 31.3)	44 (76.3 ± 27.7)
6 Mo	149 (67.6 ± 32.0)	110 (62.2 ± 32.6)	35 (81.7 ± 25.9)
12 Mo	124 (64.7 ± 33.0)	92 (59.1 ± 32.9)	28 (80.9 ± 27.7)
IADL score, *n* (mean ± SD)			
Enrollment*	193 (7.0 ± 3.7)	136 (5.8 ± 3.4)	45 (9.9 ± 3.0)
6 Mo	147 (5.4 ± 3.8)	109 (4.4 ± 3.3)	34 (8.3 ± 3.8)
12 Mo	123 (5.2 ± 4.0)	92 (4.2 ± 3.5)	27 (8.3 ± 3.7)
Post-discharge deaths (12 mo), *N*, *n* (%)	193, 57 (29.5)	136, 41 (30.2)	45, 15 (33.3)
Delirium, *N*, *n* (%)			
6 Mo	143, 45 (31.5)	109, 42 (38.5)	34, 3 (8.8)
12 Mo	119, 49 (41.2)	92, 45 (48.9)	27, 4 (14.8)

* *Premorbid status*

MMSE, Mini-Mental State Exam; BI, Barthel Index; IADL, Instrumental Activities of Daily Living; SD, Standard Deviation.

mean differences for the MMSE of −6.17 [95% confidence interval (95% CI),−8.10 to −4.25]; for the BI of −11.22 [95% CI, −20.31 to −2.13]; and for the IADL of −2.05 [95% CI, −3.40 to −0.70]). All measures of the initial course were associated with only small increases in risk of post-discharge death, and the 95% CIs of the hazard ratios included unity (Table 4). The proportional hazards assumption was found to be appropriate for all models. The variance inflation factor was close to 1 for all independent variables, indicating no linear dependence between them. The baseline covariates that were significant predictors of poor outcomes included: the presence of dementia, not living at home, and (for the MMSE and BI scores) the score on the respective outcome measure at the time of diagnosis. There was no significant interaction between the presence of dementia and any of the measures of initial clinical course; therefore, we did not add an interaction term to the final models presented in this article.

DISCUSSION

The overall study results on the duration of the initial episode of delirium and the number of symptoms are comparable to those of previous studies.[1,3,27] However, this study has 2 important new findings on the persistence of a delirium syndrome and individual symptoms up to

Table 3. Outcomes at Follow-up by In-hospital Course of Delirium

	Overall	Transient	Recovered	Persistent
MMSE score, *n* (mean ± SD)				
Enrollment	193 (15.10 ± 7.17)	76 (20.34 ± 3.65)	56 (14.00 ± 6.69)	61 (9.57 ± 6.30)
2 Mo	187 (17.96 ± 7.36)	75 (21.97 ± 4.05)	54 (19.52 ± 6.77)	58 (11.33 ± 6.67)
6 Mo	145 (18.34 ± 7.58)	60 (22.08 ± 5.14)	43 (19.58 ± 7.20)	42 (11.74 ± 6.63)
12 Mo	119 (17.84 ± 7.65)	48 (21.73 ± 4.83)	35 (20.43 ± 6.27)	36 (10.14 ± 6.28)
BI score, *n* (mean ± SD)				
Enrollment	193 (42.42 ± 29.82)	76 (54.42 ± 27.99)	56 (36.55 ± 27.38)	61 (32.85 ± 29.52)
2 Mo	181 (66.57 ± 30.66)	73 (80.25 ± 20.97)	52 (62.44 ± 33.48)	56 (52.57 ± 31.56)
6 Mo	149 (67.55 ± 32.01)	63 (81.35 ± 23.08)	43 (65.35 ± 35.34)	43 (49.53 ± 30.86)
12 Mo	124 (64.69 ± 33.02)	52 (78.56 ± 25.95)	36 (69.17 ± 32.01)	36 (40.17 ± 30.02)
IADL score, *n* (mean ± SD)				
Enrollment	186 (6.96 ± 3.77)	75 (8.64 ± 3.69)	53 (6.81 ± 3.63)	58 (4.93 ± 2.94)
6 Mo	147 (5.40 ± 3.80)	62 (7.03 ± 4.02)	43 (5.49 ± 3.28)	42 (2.90 ± 2.41)
12 Mo	123 (5.20 ± 4.02)	51 (7.10 ± 3.92)	36 (5.44 ± 3.83)	36 (2.25 ± 2.32)
Post-discharge deaths (12 mo), *N*, *n* (%)	193, 57 (29.5)	76, 20 (26.3)	56, 17 (30.4)	61, 20 (32.8)
Delirium, *N*, *n* (%)				
6 Mo	143, 45 (31.5)	57, 6 (10.5)	43, 9 (20.9)	43, 30 (69.8)
12 Mo	119, 49 (41.2)	47, 10 (21.3)	36, 8 (22.2)	36, 31 (86.1)

MMSE, Mini-Mental State Exam; BI, Barthel Index; IADL, Instrumental Activities of Daily Living; SD, Standard Deviation.

Table 4. Effects of Clinical Course of Delirium on Mini-Mental State Examination (MMSE), Barthel Index (BI), Instrumental Activities of Daily Living (IADL) and Post-discharge Mortality*

Measure of Clinical Course of Delirium	MMSE (*N* = 180), Adjusted Mean Difference† (95% CI)	BI (*N* = 176), Adjusted Mean Difference (95% CI)	IADL (*N* = 143), Adjusted Mean Difference (95% CI)	1-year Post-discharge Mortality (*N* = 180), Adjusted Hazard Ratio‡ (95% CI)
Days without cognitive improvement	−0.22 (−0.29 to −0.15)	−0.73 (−1.09 to −0.38)	−0.12 (−0.18 to −0.07)	1.02 (0.99 to 1.05)
Number of delirium days	−0.20 (−0.30 to −0.11)	−1.18 (−1.56 to −0.79)	−0.17 (−0.22 to −0.11)	1.02 (0.99 to 1.05)
Length of 1st delirium episode	−0.16 (−0.26 to −0.06)	−0.93 (−1.31 to −0.54)	−0.15 (−0.20 to −0.09)	1.01 (0.98 to 1.04)
Proportion of days with delirium	−6.72 (−9.29 to −4.15)	−26.55 (−36.35 to −16.75)	−3.75 (−5.21 to −2.28)	1.98 (0.89 to 4.39)
In-hospital course of delirium				
Transient§	0.00	0.00	0.00	1.00
Recovered	0.87 (−1.06 to 2.80)	−10.68 (−19.76 to −1.61)	−1.36 (−2.63 to −0.08)	1.62 (0.79 to 3.34)
Persistent	−5.31 (−7.54 to −3.07)	−21.90 (−31.11 to −12.70)	−3.40 (−4.71 to −2.09)	1.63 (0.77 to 3.44)

** All models were adjusted for age, gender, education, marital status, residence, dementia, clinical severity, comorbidity, physiological severity, and incident/prevalent delirium. Models for MMSE and BI were adjusted for the baseline value of the outcome.*

† Adjusted mean difference for a continuous variable represents the mean change in the outcome for a unit increase in the measure of clinical course of delirium across all follow-up times adjusted for the covariates listed above. For example, for every additional day without cognitive improvement, the MMSE score decreases by 0.2 after taking into account the effect of other covariates. For categorical variables, it represents the mean difference between each group and the reference group, after adjusting for covariates.

‡ Adjusted hazard ratio for a continuous variable represents the increase in the risk of death during the first year after baseline for a unit increase in the measure of clinical course of delirium adjusted for all covariates listed above. For example, for every additional day without cognitive improvement, the risk of dying increases by 1%. For categorical variables, it represents the risk ratio comparing each group with the reference group, after adjusting for covariates.

§ Reference category.

CI, confidence interval.

12 months after diagnosis (among patients with and without dementia) and on the prognostic importance of the initial in-hospital course of delirium.

Comparison of the course of delirium in patients with and without dementia indicates that patients with dementia had more symptoms at baseline and were more likely to meet criteria for delirium syndrome at follow-up. However, cognitive improvement during the hospitalization and longer term changes in the number of symptoms were remarkably similar in the 2 groups. Thus, we found that 39%, 38.5%, and 48.9% of patients with dementia met our criteria for delirium at discharge, 6-, and 12-month follow-ups, respectively. These proportions for patients without dementia were much lower (11.1, 8.8%, and 14.8%, respectively). In both groups, the symptoms of delirium persisted at follow-up, with a loss of about 1 symptom, on average, compared to baseline. The mean numbers of symptoms of delirium at diagnosis and 12-month follow-up, respectively, were 4.5 and 3.5 in the subgroup of patients with dementia and 3.4 and 2.2 among those without dementia. Inattention, disorientation, and impaired memory were the most persistent symptoms. By the 12-month follow-up, 30.9% of the cohort had died; the survivors were more dependent in IADL.

The duration of the initial delirium episode was longer for those with dementia. However, even after adjusting for baseline cognitive impairment, severity of illness, comorbidity, and other potentially confounding variables, the speed of resolution of the syndrome was associated with long-term functional and cognitive outcomes, but not with post-discharge mortality. It should be noted that patients who died in hospital were excluded from the current study; their inclusion would have strengthened the association between persistent delirium and mortality. We have previously reported that patients with delirium experienced higher rates of mortality than non-delirious controls, both in-hospital and post-discharge, even after adjustment for covariates.[5] Thus, the presence of delirium rather than its in-hospital clinical course appears to predict post-discharge mortality.

This study highlights some of the problems in distinguishing delirium from dementia and other types of cognitive impairment in an older medically ill population. The majority of the cohort had both prevalent delirium and dementia, according to our measures. The instrument we used to identify dementia, the IQCODE, may perform differently among patients with delirium. The IQCODE asks informants to rate the behavioral change that took place among patients from over 5 years previously until immediately before the illness that led to hospital admission; informants may have confused the acute behavioral changes of delirium with the longer term changes

associated with dementia. It also is possible that patients with delirium without dementia may have been experiencing symptoms of early dementia. Only longitudinal studies of community cohorts can address these issues.

Methodological strengths of this study include: use of a standardized, reliable, valid measure of symptoms based on direct patient observations and follow-up of patients for 12 months, with high rates of participation among those who were still alive. Because of our focus on post-discharge outcomes, we excluded patients who died in hospital. Limitations of our study, in addition to the methodological difficulties in distinguishing delirium and dementia described above, include: absence of a clinical assessment of premorbid symptoms; lack of daily patient observations during hospitalization, requiring us to approximate the duration of and number of days with delirium; variability in time to follow-up, particularly for the 2-month follow-up due to the different protocol for following patients discharged before 2 months; failure to include symptoms that could not be assessed based on direct observation (such as sleep disturbance), and failure to distinguish between persistence and recurrence of symptoms at follow-up. Further research is needed that includes prospective assessment of premorbid symptoms.

There are several clinical implications of these results for the care of patients with delirium. First, the assessment of symptoms may be a useful way to monitor the clinical progress of these patients. Second, the persistence of symptoms (particularly inattention, disorientation, and impaired memory) and a gradual deterioration in independence in IADL can be expected in patients with delirium, even among those who meet diagnostic criteria only transiently. Third, a more protracted initial episode of delirium carries a worse prognosis. The extent to which the in-hospital course of delirium is modifiable should be addressed in future studies, although evidence to date is disappointing, particularly in patients with dementia.[7] Fourth, although patients with dementia prior to the diagnosis of delirium have, on average, 1 more symptom of delirium (both at diagnosis and during the next 12 months) in comparison with those without dementia, the 2 groups are similar with respect to the rate of cognitive improvement in hospital (using the MMSE), or changes in functional or physical status at follow-up. Thus, the first 3 implications above apply equally to patients with or without dementia.

This research was supported by grants from the Medical Research Council of Canada (MA14709), the Fonds de la Recherche en Santé du Québec (980892), the National Health Research Development Program (6605-4686-403), and St. Mary's Hospital Center (96-27).

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Appendix A

Measures of the Clinical Course of Delirium

Using the Delirium Index, delirium was defined (based on DSM-III-R criteria) as the presence of disorders of attention and thought, and disorders of any 3 of the following: consciousness, orientation, memory, perception, and psychomotor activity. We constructed 5 measures of the in-hospital clinical course of delirium during the first 28 days from diagnosis.

1. The *duration of the initial delirium episode* was defined as the time from diagnosis to either the absence of delirium at 2 consecutive assessments or absence of delirium at one assessment and no further in-hospital assessments (due to discharge or withdrawal). In each case, the date of recovery was estimated at the mid-point between the last positive (with delirium) and the first negative (no delirium) assessment. Among patients who were discharged or withdrew before 28 days from enrollment with delirium at the last assessment before discharge or withdrawal, the duration of the episode was considered to be the time from enrollment to discharge. Among patients who were still in hospital at 28 days, the results of the first DI assessment after 28 days was considered in the definition of duration of the episode.
2. The *number of days with delirium* was estimated as follows. All the days between 2 consecutive positive assessments were considered to be positive, and all the days between 2 consecutive negative assessments were considered to be negative. Half of the days between 2 consecutive assessments, one of which was positive and one negative, were considered to be positive. Among patients who were discharged or withdrew before 28 days from enrollment with delirium at the last assessment before discharge or withdrawal, the patient was considered to have delirium on all the days between the last assessment and discharge or withdrawal, for a maximum of 28 days. Among patients who were still in hospital at 28 days, the results of the first DI assessment after 28 days were considered in the definition of delirium days.
3. The *proportion of days with delirium* was computed as the number of days with delirium (from 2 above) divided by the duration of observation, from enrollment up to the date of discharge or withdrawal or 28 days from enrollment, whichever was shorter.
4. The *time to cognitive improvement* was defined as the time to an increase in the MMSE score of 2 or more points compared to baseline, with no subsequent decrease below the baseline score plus 2 points. If the baseline MMSE score was 27 or more, patients whose MMSE score did not decline below 27 in subsequent assessments were considered to have improved in 0.5 days.
5. The *in-hospital course of delirium* was a 3-category measure: transient (recovery within 24 hours); recovered (recovery between 24 hours after diagnosis and discharge or at 8 weeks if patient was still in the hospital); and persistent (delirium present at discharge or at 8 weeks if patient was still in the hospital).

MMSE, Mini-Mental State Examination.