ORIGINAL INVESTIGATION

Delirium Predicts 12-Month Mortality

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Background: Delirium has not been found to be a significant predictor of postdischarge mortality, but previous research has methodologic limitations including small sample sizes and inadequate control of confounding. This study aimed to determine the independent effects of presence of delirium, type of delirium (incident vs prevalent), and severity of delirium symptoms on 12-month mortality among older medical inpatients.

Methods: A prospective, observational study of 2 cohorts of medical inpatients was conducted with patients 65 years or older: 243 patients had prevalent or incident delirium, and 118 controls had no delirium. Baseline measures included presence of delirium and/or dementia, severity of delirium symptoms, physical function, comorbidity, and physiological and clinical severity of illness. Mortality during the 12 months after enrollment was analyzed with the Cox proportional hazards model with adjustment for covariates.

Results: The unadjusted hazard ratio of delirium with mortality was 3.44 (95% confidence interval, 2.05-5.75); the adjusted hazard ratio was 2.11 (95% confidence interval, 1.18-3.77). The effect of delirium was sustained over the entire 12-month period after adjustment for covariates and was stronger among patients without dementia. Among patients with dementia, there was a weak, nonsignificant effect of delirium on survival. After adjustment for covariates, mortality did not differ between patients with incident and prevalent delirium, but among patients with delirium without dementia, greater severity of delirium symptoms was associated with higher mortality.

Conclusions: Delirium is an independent marker for increased mortality among older medical inpatients during the 12 months after hospital admission. It is a particularly important prognostic marker among patients without dementia.

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DELIRIUM is a frequent phenomenon among older hospitalized patients and has been found to be related to several adverse outcomes, including a longer mean length of hospital stay, poor functional status and need for institutional care, and mortality.[1] With respect to mortality, the evidence is not consistent[2]; controlled studies have reported that delirium is associated with increased in-hospital mortality.[2,3] However, Inouye et al[4] controlled for age, sex, dementia, illness severity, and functional status and found no significant elevation in in-hospital or 3-month mortality. Several studies with up to 2 years of follow-up reported no significant increase in postdischarge mortality.[3,5-7] A recent study with a median follow-up of 32.5 months reported a hazard ratio (HR) of 1.71 (95% confidence interval [CI], 1.02-2.87) after adjustment for comorbidity, dementia, frailty, age, sex, marital status, and institutional residence.[8] Nevertheless, these studies have a number of methodologic limitations, including small sample sizes, often-limited follow-up, and inadequate control of confounding factors such as dementia, comorbidity, and severity of illness. Furthermore, it is not known whether survival depends on the severity of the delirium, or on whether the delirium is diagnosed at admission (prevalent delirium) or after admission (incident delirium). The former is related to factors preceding hospital admission, whereas the latter may be due to aspects of the care received in the hospital. Also, little is known about whether the adverse consequences of delirium are similar among demented and nondemented patients.

We undertook this study to determine the prognostic effect of delirium on the outcome of older hospital medical inpatients during the 12 months after admission. In this article, we report the independent effect of delirium, adjusted for important confounding variables, on 12-month mortality and examine the effects on mortality of type of delirium (incident vs prevalent), severity of delirium symptoms, and presence of dementia.

METHODS

This prospective, observational, cohort study was conducted at a 400-bed, university-affiliated, primary acute care hospital in Montreal, Quebec. We compared 6- and 12-month outcomes in 2 cohorts: a delirium cohort with prevalent or incident delirium detected during the first week of hospitalization, and a control cohort without delirium. The study was conducted simultaneously with a randomized controlled trial of the detection and treatment of delirium, and a subgroup of the delirium cohort also participated in the trial.

ENROLLMENT OF SUBJECTS

A study nurse was responsible for patient screening and enrollment in the 2 studies. Only patients 65 years or older who were admitted from the emergency department to the medical services were included in the studies. We excluded patients with a primary diagnosis of stroke, those admitted to the oncology unit, those who spoke neither English nor French, and those admitted to the intensive care unit or cardiac monitoring unit unless they were transferred to a medical ward within 48 hours of admission. At enrollment and during the first week of hospitalization, the nurse screened eligible patients for delirium using the Short Portable Mental Status Questionnaire (SPMSQ), a 10-item questionnaire that evaluates orientation, memory, and concentration,[9] and review of the nursing notes. The nurse conducted the Confusion Assessment Method (CAM)[10] interview with subjects who made 3 or more errors on the initial SPMSQ (indicating moderate to severe cognitive impairment), subjects whose SPMSQ scores increased by at least 1 error from the first assessment, and subjects whose nursing notes indicated possible symptoms of delirium. (The CAM is a structured interview that assesses 9 symptom domains of delirium specified in the *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*.[10])

Prevalent delirium was diagnosed if the criteria for probable or definite delirium[11] were met at enrollment; incident delirium was diagnosed if the criteria were not met until after enrollment. Controls were selected from patients who were screened for delirium and found not to have it. To balance the distributions of age and prior cognitive impairment among patients with delirium and controls, the sampling method took into account each patient's age and initial SPMSQ score. Thus, controls were selected from patients 70 years and older, and patients with SPMSQ scores of 3 or more were oversampled.

Subjects with fewer than 5 errors on the SPMSQ gave informed consent to participate in the study; those with 5 or more errors assented to participation, and a relative provided written consent. The studies were approved by the hospital's research ethics committee.

DATA COLLECTION AND MEASURES

Patients were assessed at enrollment by a research assistant, blind to study group, who also interviewed a family member. Date of death during follow-up was ascertained by the research assistant, who observed patients at least weekly during their hospital stay, at 8 weeks after discharge, and at 6 and 12 months after enrollment. Other baseline data were collected by chart review by a nurse abstracter, blind to study group.

Dementia was assessed from the 16-item Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE),[12] which has high internal consistency and test-retest reliability[12-14] in both its original 32-item form and in its 16-item short-form. Cutoff points of 3.38,[12,13] and 3.6 or higher[15] have been used; we used an intermediate cutoff of higher than 3.5 to define dementia.

We assessed the severity of delirium symptoms with the Delirium Index (DI)[16] based solely on patient observation, without additional information from family members, nursing staff, or the patient's medical chart. Only 7 of 9 symptom domains assessed on the CAM (disorders of attention, thought, consciousness, orientation, memory, perception, and psychomotor activity; acute onset and sleep-wake disturbance were excluded) were rated on a 4-point scale (0, absent; 1, mild; 2, moderate; 3, severe); the minimum and maximum possible scores, therefore, were 0 (no symptoms) and 21 (maximum severity), respectively. The DI has satisfactory interrater reliability and concurrent criterion validity.[17]

We administered the Instrumental Activities of Daily Living (IADL) questionnaire from the Older American Resources and Services (OARS) project[17] to an informant and used it to assess premorbid function (prior to the current illness but not more than 1 month before hospital admission). The scale score range is 0 (completely dependent) to 16 (completely independent).

Three measures of illness burden and severity were used. Comorbidity at admission was assessed by chart review using the Charlson Comorbidity Index, a weighted index that takes into account the number and severity of comorbid conditions.[18] Acute physiologic severity of illness was assessed with the Acute Physiology Score, derived from the APACHE II scale.[19] The index was coded by chart review based on laboratory and clinical measures

RESULTS

During the study enrollment period, there were 4085 medical admissions, of which 1552 (38.0%) were screened for delirium. The reasons for exclusion were admission to oncology (n=452), admission to intensive care or coronary care units (n=377), transfer to long-term care before screening (n=332), language barrier (n=301), stroke (n=289), missed or not sampled (n=181), refused screening (n=164), previously enrolled in study (n=127), transferred or discharged (n=113), communication problem (n=105), residence outside geographic area (n=69), died before screening (n=20), and other (n=3). Of the 1552 patients screened, 243 with a diagnosis of delirium and 118 controls were enrolled in the study.

At enrollment, there were significant differences between the cohorts with respect to demographic, clinical, and functional status measures (Table 1). Members of the delirium cohort were more likely than controls to be male, more likely to have been admitted to nongeriatric units, and, as expected, more severely impaired in all clinical and functional status measures. They were also

made on or before the date of enrollment. Clinical severity of illness was assessed by the research nurse at enrollment.[20,21] The scores ranged from 1 (minimal) to 9 (most severe).

The *International Classification of Diseases, Ninth Revision*, codes for primary discharge diagnoses were obtained from the hospital administrative database. Demographic variables (age, sex, marital status, and residence) were recorded in study baseline forms.

STATISTICAL METHODS

Analyses of mortality focused on 2 main questions: (1) the role of delirium as an independent prognostic factor for death; and (2) identification of prognostic factors for mortality in the delirium cohort. First, the 2 cohorts were compared with respect to the baseline distribution of various prognostic risk factors, using the independent groups *t* test and χ^2 test for quantitative and categorical variables, respectively. To assess the impact of delirium on mortality, survival analytical techniques were used to compare survival rates in delirium and control cohorts. Time 0 was defined as the study enrollment, and subjects were censored at the time of loss to follow-up or at the end of the 12-month follow-up period, whichever occurred earlier. We used the exponential model for the survival time distribution to estimate the yearly mortality rates separately for each of the 2 cohorts. Unadjusted analysis relied on the comparison of the Kaplan-Meier survival curves and on the score test in the univariate Cox proportional hazards model, which is equivalent to the log-rank test.[22]

To adjust the estimated effect of delirium on mortality for the possible differences in the distribution of other risk factors in the 2 cohorts, we used the multivariable Cox proportional hazards model with the following covariates selected a priori: dementia, comorbidity, clinical severity, Acute Physiology Score, admitting service (medicine vs geriatrics), and demographic variables.

In our primary analysis we did not adjust for premorbid IADL because this measure is affected by the presence of dementia, a variable of interest in this study. In our secondary analysis (not reported here) adjusting also for IADL, we found that, as expected, the effect of delirium was essentially unchanged, whereas the effect of dementia was slightly smaller. We also conducted a secondary analysis (not reported here) in which we evaluated the effect of considering primary discharge diagnosis as an additional covariate, grouped into the 13 categories shown in **Table 1**. The inclusion of diagnosis had no effect on the magnitude of the effect of delirium on survival.

The proportional hazards assumption was verified using the regression spline model–based likelihood ratio test.[23] This allowed us to formally test whether the prognostic value of an initial diagnosis of delirium changed during the 12-month follow-up. The importance of such potential changes was then assessed based on a graph representing the variation of the logarithm of the HR for the delirium vs control group as a function of the follow-up duration. In addition, to further assess whether the association between delirium diagnosis at baseline and mortality changed with increasing follow-up duration, separate analyses were carried out for 3 time intervals: from inception to the end of the first month; from the second month through the sixth month; and from the seventh month through the 12th month. In each case, the analysis was restricted to subjects alive at the beginning of the respective interval; and subjects who did not die until the end of the interval were censored at that time. Using a similar approach, separate analyses were also carried out for within-hospital and postdischarge mortality.

To assess whether the impact of delirium on mortality depended on some other patient characteristic(s), we evaluated first-order interactions between delirium and each of the covariates by forcing all the covariates into the multivariable Cox model and then selecting statistically significant interactions through forward selection. Cutoff for entry into the model was $P<.10$.

Finally, to explore more fully the separate and joint effects of delirium and dementia on mortality, subjects were classified into 4 categories of delirium/dementia: (1) delirium alone; (2) delirium superimposed on dementia; (3) dementia alone; and (4) no delirium or dementia. Using the group with no delirium or dementia as the reference category, we estimated the relative risks associated with each of the 3 other categories by including the corresponding dummy variables in the Cox model.

Similar methods were used to identify prognostic factors for mortality in the delirium cohort. The main focus of the analysis was on the assessment of the role of delirium type and severity. Specifically, the following 3 delirium-related variables were considered: (1) the mean of the first 2 DI scores (if obtained during the first week of follow-up); (2) the binary indicator of definite vs probable delirium (from the CAM); and (3) the binary indicator of prevalent vs incident cases. Because these 3 variables were conceptually and statistically related, we examined their effects in separate models, each time adjusting for the covariates listed above, study group (inclusion in the intervention or control group of the randomized trial), and for premorbid IADL.

more likely to be demented. These differences in the distribution of important prognostic factors made it essential to adjust the comparison of mortality in the 2 cohorts for these factors.

The cohorts did not differ with respect to age (owing in part to the study design, which restricted age of controls to 70 years and older) and several other characteristics not shown in Table 1 (marital status, level of education, type and length of relationship to informant, visual or hearing impairment, and history of drug or alcohol abuse). Dementia status was missing for 19 delirium cases and 20 controls because of failure to interview an informant.

IMPACT OF DELIRIUM ON MORTALITY

During the 12-month follow-up, 41.6% of the patients in the delirium cohort and 14.4% of the controls died; 4.9% of the delirium cohort and 7.6% of the controls withdrew from the study. Most withdrawals took place before hospital discharge and were at the request of family members who did not want the patients to be dis-

Table 1. Selected Characteristics of Cohorts at Enrollment*

Characteristic	Cohort		*P* Value†
	Delirium	Control	
Total	243 (100)	118 (100)	. . .
Age, y	. . .	. . .	.65
65-74	29 (11.9)	11 (9.3)	. . .
75-84	99 (40.7)	53 (44.9)	. . .
≥85	115 (47.3)	54 (45.8)	. . .
Sex	. . .	. . .	.02
Female	147 (60.5)	86 (72.9)	. . .
Male	96 (39.5)	32 (27.1)	. . .
Marital status	. . .	. . .	.13
Single	30 (12.4)	19 (16.2)	. . .
Married	78 (32.2)	26 (22.2)	. . .
Widowed/divorced/separated	134 (55.4)	72 (61.5)	. . .
(Missing)	(1)	(1)	. . .
Living arrangement	. . .	. . .	.01
Home alone	76 (31.4)	46 (39.0)	. . .
Home with others	102 (42.1)	34 (28.8)	. . .
Senior residence/foster home	36 (14.9)	30 (25.4)	. . .
Nursing home	28 (11.6)	8 (6.8)	. . .
(Missing)	(1)	(0)	. . .
Admission service	. . .	. . .	.02
Medicine	170 (70.0)	68 (57.6)	. . .
Geriatrics	73 (30.0)	50 (42.4)	. . .
Clinical severity	. . .	. . .	.001
1-2	5 (2.1)	18 (15.3)	. . .
3-4	66 (27.2)	72 (61.0)	. . .
5	58 (23.9)	15 (12.7)	. . .
6-7	99 (40.7)	12 (10.2)	. . .
8-9	15 (6.2)	1 (0.8)	. . .
Mean (SD) MMSE score	14.8 (7.3)	21.7 (5.2)	<.001
Mean (SD) DI score	8.7 (3.9)	4.3 (2.8)	<.001
(Missing)	(0)	(0)	. . .
Mean (SD) IADL score before admission	6.8 (3.8)	7.8 (3.5)	.02
(Missing)	(14)	(7)	. . .
Dementia present per IQCODE score	. . .	. . .	.002
No	58 (25.9)	42 (42.9)	. . .
Yes	166 (74.1)	56 (57.1)	. . .
(Missing)	(19)	(20)	. . .
Mean (SD) Charlson Comorbidity Index	2.7 (2.0)	2.1 (1.8)	.01
Mean (SD) Acute Physiology Score	5.0 (3.6)	2.9 (2.7)	<.001
Primary discharge diagnosis (*ICD-9* codes)	. . .	. . .	NC
Infectious disease (0-139)	4 (1.6)	2 (1.7)	. . .
Neoplasms (140-239)	10 (4.1)	3 (2.5)	. . .
Endocrine, metabolic (240-289)	13 (5.3)	8 (6.8)	. . .
Mental/neurological (290-359)	43 (17.7)	7 (5.9)	. . .
Cardiovascular (390-429)	47 (19.3)	17 (14.4)	. . .
Cerebrovascular (430-459)	9 (3.7)	5 (4.2)	. . .
Respiratory (460-519)	46 (18.9)	22 (18.6)	. . .
Digestive (530-579)	11 (4.5)	13 (11.0)	. . .
Urogenital (580-629)	8 (3.3)	3 (2.5)	. . .
Musculoskeletal (710-739)	12 (4.9)	10 (8.5)	. . .
Symptoms (782-789)	23 (9.5)	11 (9.3)	. . .
Injuries (790-799)	13 (5.3)	11 (9.3)	. . .
Ill-defined, skin, or missing (680-709)	4 (1.6)	6 (5.1)	. . .

*Unless otherwise indicated, data are number (percentage) of patients. Ellipses indicate not applicable; MMSE, Mini-Mental State Examination; DI, Delirium Index; IADL, Instrumental Activities of Daily Living; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; *ICD-9, International Classification of Diseases, Ninth Revision*; and NC, not computed because of small cell sizes.

†*P* value for χ^2 test in the case of categorical variables, and for a 2-tailed independent groups *t* test in the case of quantitative variables.

turbed because of their medical illness. The estimated yearly 12-month mortality rates were 63.3% for the delirium cohort and 17.4% for controls (**Figure 1**). In the delirium cohort, Kaplan-Meier survival decreased rapidly during the first month after enrollment and then continued to decline but more slowly; the survival curve declined more slowly in the control cohort (Figure 1).

Table 2 lists the univariate and multivariate proportional hazards models for 12-month mortality. The unadjusted association of delirium with mortality was very strong (HR, 3.44; 95% CI, 2.05-5.75). After adjustment for the differences between the distributions of other prognostic factors in the 2 cohorts, the estimated effect of delirium on mortality decreased but remained statistically significant ($P=.01$). Among patients with the same values for all other covariates, delirium was independently associated with a 2-fold increase in mortality during the 12-month follow-up (adjusted HR, 2.11; 95% CI, 1.18-3.77). Other baseline variables significantly independently associated with higher mortality in the final model included older age, not being currently married, and higher scores on the comorbidity, clinical severity, and acute physiology scales; male sex had a marginally nonsignificant effect ($P=.07$).

The presence of dementia, on the other hand, was associated with a significant protective effect, whereas patients whose dementia status was missing had a nonsignificantly increased risk. There was an interaction between delirium and dementia ($P=.08$), with a stronger effect of delirium on mortality among patients without dementia (data not shown). To further explore the effects of delirium and dementia on mortality, we compared mortality among the 4 delirium/dementia groups (delirium alone; delirium superimposed on dementia; dementia alone; and no delirium or dementia) while adjusting for covariates. Using as the reference category patients with no delirium or dementia, patients with delirium only are at a particularly high risk (HR, 3.77; 95% CI, 1.39-10.20). The HRs for patients with dementia and delirium (1.96; 95% CI, 0.76-5.05) or with dementia alone (1.57; 95% CI, 0.52-4.71), although elevated, did not differ significantly from the reference group.

Mortality was examined by time period using 2 different time groupings. First, we investigated separately in-hospital mortality and postdischarge mortality. Delirium was a significant predictor of postdischarge mortality (HR, 2.16; 95% CI, 1.06-4.42). In the analysis of in-hospital mortality, there were statistically significant interactions between delirium and comorbidity ($P=.01$) and the Acute Physiology Score ($P=.03$); the effect of delirium was stronger among patients with lower scores on these scales. Second, we investigated mortality in 3 time periods following enrollment: the first month, months 2 through 6, and months 7 through 12. Delirium was associated with higher mortality in all 3 periods (**Figure 2**).

The formal test of the changes over time in the effect of delirium on mortality yielded a definitely nonsignificant result ($P=.70$), indicating that this effect remained fairly constant over the 12 months of follow-up. Figure 2 provides additional support for this conclusion. The solid line in Figure 2 represents the estimated adjusted effect of delirium in terms of logarithm of HR delirium/controls as a function of follow-up time obtained using regression spline model.[23] The almost perfect flatness of this estimate in spite of its potential flexibility demonstrates that the effect of delirium diagnosed at study enrollment does not show any tendency to decrease during the next 12 months.

Some other variables differed in their associations with in-hospital vs postdischarge mortality. The Charlson Co-

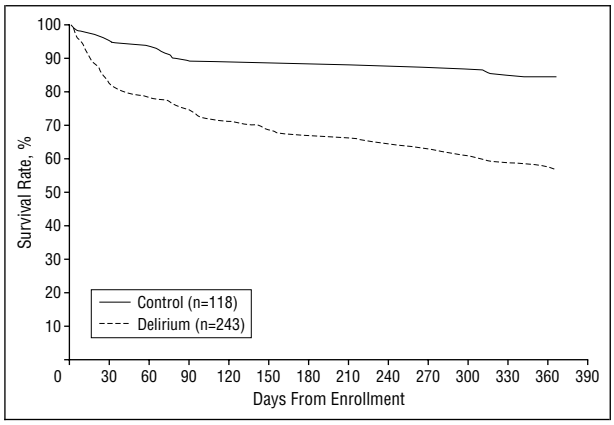

Figure 1. Unadjusted Kaplan-Meier survival curves of the 12-month mortality rate by study group.

Table 2. Results of Proportional Hazards Analyses of 1-Year Mortality*

Variable	Statistical Model	
	Univariate	Multivariable
Delirium/control	3.44† (2.05-5.75)	2.11‡ (1.18-3.77)
Age, y	1.01 (0.99-1.04)	1.04§ (1.01-1.07)
Male/female	1.80§ (1.25-2.58)	1.48 (0.98-2.24)
Married/single‖	1.10 (0.75-1.62)	0.61‡ (0.38-0.99)
Institution/home	1.33 (0.91-1.96)	1.14 (0.74-1.75)
Charlson Comorbidity Index	1.31† (1.23-1.40)	1.27† (1.18-1.38)
Acute Physiology Score	1.18† (1.13-1.24)	1.14† (1.08-1.20)
Clinical severity of illness	1.57† (1.38-1.79)	1.28§ (1.09-1.50)
Dementia (present)/absent	1.03 (0.69-1.55)	0.62‡ (0.40-0.97)
Dementia (missing)/absent	1.09 (0.52-2.28)	1.86 (0.85-4.09)
Medical/geriatric	2.33† (1.50-3.63)	1.13 (0.68-1.89)
Likelihood ratio statistic¶	. . .	123.38†

*Data are hazard ratio (95% confidence interval). Ellipses indicate not applicable. Of 361 patients, 118 died.
†$P<.001$.
‡$.01 \le P < .05$.
§$.001 \le P < .01$.
‖Single includes widowed, divorced, and separated.
¶Likelihood ratio statistics for testing the significance of the model.

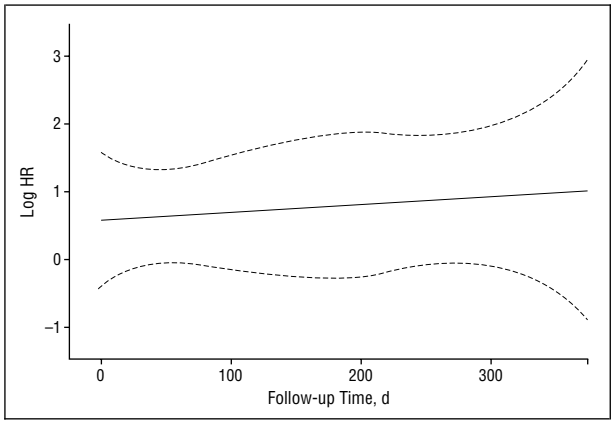

Figure 2. Assessing changes over time in the adjusted effect of delirium on mortality. The solid line shows the logarithm of the hazard ratio (log HR) expressing relative risks in the delirium cohort compared with controls adjusted for all covariates included in the multivariable model summarized in Table 2 as a function of follow-up time. The dotted curves represent pointwise 95% confidence intervals around the estimated log HR. The fact that the estimate is an almost constant function of time indicates that the prognostic ability of the baseline delirium remains stable over 12 months of follow-up.

Table 3. Results of Proportional Hazards Analysis of 1-Year Mortality in the Delirium Cohort*

Variable	Univariate Models	Multivariable Models	
		A	B
Definite/probable delirium	1.24 (0.78-2.00)	1.01 (0.60-1.69)	. . .
Mean delirium severity†	1.09‖ (1.03-1.15)	. . .	1.02 (0.95-1.09)
Prevalent/incident delirium	1.09 (0.74-1.62)	0.74 (0.39-1.39)	0.73 (0.39-1.38)
Age, y	1.01 (0.98-1.04)	1.03 (1.00-1.06)	1.03 (1.00-1.06)
Male/female	1.59¶ (1.08-2.36)	1.64¶ (1.01-2.65)	1.66¶ (1.03-2.69)
Married/single‡	0.96 (0.64-1.46)	0.50¶ (0.29-0.85)	0.50¶ (0.30-0.86)
Institution/home	1.33 (0.86-2.04)	0.89 (0.51-1.55)	0.87 (0.50-1.52)
Charlson Comorbidity Index	1.26# (1.18-1.36)	1.28# (1.17-1.40)	1.27# (1.17-1.39)
Acute Physiology Score	1.17# (1.11-1.23)	1.15# (1.09-1.22)	1.15# (1.08-1.22)
Clinical severity of illness	1.41# (1.21-1.64)	1.23¶ (1.03-1.47)	1.20 (1.00-1.45)
Dementia (present)/absent	0.79 (0.51-1.22)	0.44‖ (0.26-0.76)	0.43‖ (0.25-0.75)
Dementia (missing)/absent	1.55 (0.64-3.75)	2.11 (0.78-5.69)	2.10 (0.78-5.70)
Not in RCT/RCT-control	0.78 (0.49-1.24)	0.85 (0.40-1.79)	0.81 (0.38-1.73)
RCT intervention/RCT-control	0.91 (0.55-1.48)	0.90 (0.54-1.51)	0.91 (0.54-1.53)
IADL	0.95¶ (0.90-1.00)	0.93 (0.86-1.01)	0.93 (0.86-1.01)
Likelihood ratio statistics§	. . .	86.73#	87.08#

*Data are hazard ratio (95% confidence interval). RCT indicates randomized controlled trial of detection and treatment of delirium; IADL, Instrumental Activities of Daily Living; and ellipses, not applicable. Of 243 patients, 101 died.
†Mean of the first 2 Delirium Index scores.
‡Single includes widowed, divorced, and separated.
§Likelihood ratio statistics for testing the significance of the model.
‖$.001 \leq P < .01$.
¶$.01 \leq P < .05$.
#$P < .001$.

morbidity Index was a significant predictor of mortality in both time periods, while the Acute Physiology Score as well as admission to a medical rather than geriatric ward predicted only in-hospital mortality and not postdischarge mortality. On the other hand, demographic factors such as male sex and unmarried status were associated with higher risks of postdischarge mortality only. (The subgroup of patients with missing dementia status had an elevated HR only for in-hospital mortality, suggesting that this effect results from the failure to interview an informant among patients who were imminently terminal.)

SURVIVAL ANALYSIS WITHIN THE DELIRIUM COHORT

We examined the following prognostic factors for mortality within the delirium cohort: definite vs probable delirium (from the CAM findings), mean DI score based on the first 2 DI measures during the first week, and prevalent vs incident delirium. Because the first 2 measures were related to each other, they were examined in separate models, each time adjusted for prevalent vs incident delirium and for the dementia, comorbidity, clinical severity, Acute Physiology Score, admitting service, and demographic variables (**Table 3**). In models that did not consider interactions, none of these variables was significantly associated with mortality. However, there was a significant interaction between the mean DI score and dementia: a higher mean DI score was associated with higher mortality among patients without dementia only (data not shown). There were no statistically significant interactions of either definite/probable delirium or prevalent/incident delirium with dementia or any of the other predictors (data not shown).

COMMENT

The results of this study indicate a significantly higher 12-month mortality rate among medical inpatients diagnosed with delirium than for controls without delirium, even after adjustment for confounding by several measures of severity and comorbidity, prior dementia, and other relevant factors. Notably, delirium had a strong, sustained effect on mortality during the entire 12-month follow-up period after adjustment for covariates. The effect of delirium was particularly strong among patients without dementia. Among those with dementia, there was a weak, nonsignificant effect of delirium on mortality.

Our study provides new evidence of the importance of delirium as a prognostic indicator for mortality. Previous research has found an association only with in-hospital mortality,[2,24] and even then not in all studies[4]; postdischarge mortality has not previously been associated with delirium.[3,5-7] The ability of our study to demonstrate a longer-term effect of delirium on mortality may be related to our ability to recruit a large sample with excellent follow-up and to control for other important characteristics, particularly the presence of dementia, comorbidity, and severity of illness.

Of interest is the observation that all 3 measures of disease burden and severity used in this study were significant independent predictors of mortality. All these measures are known to predict mortality,[17,18,20,22] but seldom have all 3 been controlled simultaneously. This emphasizes the importance of multiple measures of these constructs to avoid confounding. In particular, the Charlson Comorbidity Index was a significant independent predictor of mortality both during and after hospitalization, while the Acute Physiology Score predicted only in-hospital and not postdischarge mortality. Interestingly, primary discharge

diagnosis did not confound the effect of delirium on mortality and did not contribute further to our ability to predict mortality in the presence of these other covariates.

Delirium during hospitalization seems to be a strong, independent marker of high risk of mortality not just in the hospital, as indicated in previous research, but for at least 12 months after admission. Furthermore, among patients with delirium only, those with more severe delirium symptoms had the highest mortality risk. We were unable to directly assess the effect on mortality of the duration of delirium. Our results suggest that delirium has a particularly strong effect on mortality among patients without preexisting dementia; the HR in this group (compared with subjects with neither delirium nor dementia) was 3.77 (95% CI, 1.39-10.20). In contrast, among patients with preexisting dementia, there was a weaker, nonsignificant effect of delirium (and severity of delirium symptoms) on mortality.

Three reasons for this discrepancy can be considered. First, delirium among those with dementia may result from different pathological processes compared with patients without dementia. The delirium in the former may be primarily a manifestation of the underlying disease responsible for the dementia and, therefore, of little additional prognostic importance. Second, delirium may be harder to detect in those with dementia, leading to misclassification and bias toward the null. Third, our instrument to identify dementia, the IQCODE, may perform differently in patients with delirium. The IQCODE asks informants to rate the behavioral change that took place among subjects 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. Further research is needed in this complex area of measurement.

The results of this study have implications for the care of older medical inpatients and for research in this population. First, delirium should be considered a significant, serious problem in its own right and/or as a marker of serious risk of mortality. The detection of delirium should prompt efforts to identify and treat underlying medical problems. Previous research has demonstrated consistently that in most cases, delirium is not detected in hospital settings.[25] A randomized trial of the systematic detection and management of delirium by a physician-nurse team, conducted by members of our group in conjunction with the present study, found no overall significant benefit on mortality or other outcomes.[26] However, there was a potentially clinically important, although statistically nonsignificant, benefit of the intervention among patients without dementia. Further research is warranted in this high-risk population to identify potentially modifiable factors leading to death. It is also important to investigate postdischarge interventions because the increased mortality risk in these patients seems to be sustained well beyond hospital discharge.

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