Does Delirium Contribute to Poor Hospital Outcomes?

A Three-Site Epidemiologic Study

Sharon K. Inouye, MD, MPH, Julia T. Rushing, MStat, Marquis D. Foreman, PhD, RN,
Robert M. Palmer, MD, MPH, Peter Pompei, MD

OBJECTIVE: To determine the independent contribution of admission delirium to hospital outcomes including mortality, institutionalization, and functional decline.

DESIGN: Three prospective cohort studies.

SETTING: Three university-affiliated teaching hospitals.

PATIENTS: Consecutive samples of 727 patients, aged 65 years and older.

MEASUREMENTS AND MAIN RESULTS: Delirium was present at admission in 88 (12%) of 727 patients. The main outcome measures at hospital discharge and 3-month follow-up were death, new nursing home placement, death or new nursing home placement, and functional decline. At hospital discharge, new nursing home placement occurred in 60 (9%) of 692 patients, and the adjusted odds ratio (OR) for delirium, controlling for baseline covariates of age, gender, dementia, APACHE II score, and functional measures, was 3.0, (95% confidence interval [CI] 1.4, 6.2). Death or new nursing home placement occurred in 95 (13%) of 727 patients (adjusted OR for delirium 2.1, 95% CI 1.1, 4.0). The findings were replicated across all sites. The associations between delirium and death alone (in 35 [5%] of 727 patients) and between delirium and length of stay were not statistically significant. At 3-month follow-up, new nursing home placement occurred in 77 (13%) of 600 patients (adjusted OR for delirium 3.0; 95% CI 1.5, 6.0). Death or new nursing home placement occurred in 165 (25%) of 663 patients (adjusted OR for delirium 2.6; 95% CI 1.4, 4.5). The findings were replicated across all sites. For death alone (in 98 [14%] of 680 patients), the adjusted OR for delirium was 1.6 (95% CI 0.8, 3.2). Delirium was a significant predictor of functional decline at both hospital discharge (adjusted OR 3.0; 95% CI 1.6, 5.8) and follow-up (adjusted OR 2.7; 95% CI 1.4, 5.2).

CONCLUSIONS: Delirium is an important independent prognostic determinant of hospital outcomes including new nursing home placement, death or new nursing home placement, and functional decline—even after controlling for age, gender, dementia, illness severity, and functional status. Thus, delirium should be considered as a prognostic variable in case-mix adjustment systems and in studies examining hospital outcomes in older persons.

KEY WORDS: delirium; acute confusional state; risk adjustment; geriatrics; hospital outcomes.

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years) is the most rapidly growing sector of the U.S. population,¹ and is particularly vulnerable to developing delirium during acute illness and hospitalization.² Previous studies have estimated that delirium occurs in 14% to 56% of elderly hospitalized patients, with associated hospital mortality rates of 10% to 65%.²

Previous studies have documented that delirium is associated with poor outcomes, such as increased mortality rates, prolonged length of hospital stay, increased rates of institutional placement, and functional and cognitive decline.³⁻¹⁹ However, the unanswered question remains: Does delirium itself contribute to this poor prognosis, or does delirium simply serve as a marker identifying patients with poor prognostic features due to severe illness, dementia, functional impairment, advanced age, and the like? Unfortunately, many of the previous studies, which were not all designed to address this research question directly, were hindered by inadequate control for these potential confounders and by small numbers of relatively infrequent outcome events.

The objective of the present study was to examine the independent contribution of baseline delirium to hospital mortality, institutionalization, functional decline, and length of stay in three large prospective cohort studies of elderly hospitalized patients.²⁰ Uniform prospective data collection for this project facilitated collection of standardized information on delirium, study outcomes, and potential confounders. Our underlying hypothesis was that baseline delirium (present at admission) would be an important prognostic predictor even after controlling for underlying illness severity, age, dementia and functional status.

METHODS

Study Populations

The three study populations (University of Chicago Hospitals, University Hospitals of Cleveland, and Yale-New Haven Hospital) participated as part of the Hospital Outcomes Project for the Elderly (HOPE) examining func-

Received from the Department of Internal Medicine, Yale University School of Medicine, New Haven, Conn. (SKI); Department of Public Health Sciences, Bowman Gray School of Medicine of Wake Forest University, Winston-Salem, NC (JTR); Department of Nursing (MDF), Department of Medicine (PP), University of Chicago Hospitals, Ill.; and the Department of Medicine, University Hospitals of Cleveland, Ohio (RMP).

Address correspondence and reprint requests to Dr. Inouye: Yale University School of Medicine, Yale-New Haven Hospital; 20 York St., T-15, New Haven, CT 06504.

Delirium, defined as an acute disorder of attention and global cognitive functioning, has assumed increasing importance in the United States, with the burgeoning population of older citizens. In 1993, 35% of the population aged 65 years and older was hospitalized during the year, accounting for 36% of all hospital stays and 48% of all days of hospital care.¹ The oldest group (>75

tional decline in hospitalized older patients. The studies have been described in detail previously—including inclusion and exclusion criteria.²⁰ In brief, all of these acute care facilities are large urban teaching hospitals, serving extensive community as well as referral populations. All sites enrolled prospective cohorts of consecutive elderly subjects admitted to these acute care hospitals on non-intensive-care wards, but the entry age criteria differed (Chicago included age ≥ 65 years; Cleveland, age ≥ 75 years; and Yale, age ≥ 70 years). All sites included medical patients; Chicago and Yale included surgical patients as well. All sites excluded terminally ill patients. The enrollment periods varied from 5 to 8 months, from 1989 to 1990.

Assessments

Trained researchers carried out standardized interviews with the patients at admission and at hospital discharge. The same standardized questionnaires and interviewer training manuals were used across all sites with the exception of a shortened version of the Mini-Mental State Examination (MMSE) (first 21 items) being used at Cleveland. The admission patient interview, completed within 48 hours of hospital admission, included demographic information, activities of daily living (ADLs),²¹ instrumental activities of daily living (IADLs),²² MMSE,²³ and Confusion Assessment Method (CAM) rating.²⁴ The discharge interview included ADLs, MMSE, CAM rating, and determination of discharge location. For patients with substantial cognitive impairment, self-reported information was confirmed by surrogates. Medical records were reviewed for medical diagnoses, admission vital signs, and laboratory data. All subjects received a 3-month follow-up telephone interview to determine ADLs and new nursing home placement. Surrogate interviews were carried out for subjects who were deceased or unable to be interviewed.

The interviewers and medical record reviewers were blinded to the research question and study hypothesis. In addition, medical record reviewers and telephone interviewers were blinded to the delirium status of the subjects. Reliability checks of primary study variables, including CAM, ADLs, and IADLs, were carried out at each site.

Informed consent was obtained from each subject and from the closest relative for those with significant cognitive impairment. The study was approved by the Institutional Review Boards of University of Chicago Hospitals, University Hospitals of Cleveland, and Yale University School of Medicine/Yale-New Haven Hospital.

Identification of Delirium

Delirium was identified at admission and discharge interviews based on the diagnostic criteria of CAM,²⁴ which required the presence of acute onset and fluctuating course, inattention, and either disorganized thinking or altered level of consciousness. In a previous validation

study,²⁴ these criteria had sensitivity rates of 94% to 100% and specificity rates of 90% to 95%, when compared with the ratings of geropsychiatrists. A subsequent study demonstrated that the CAM instrument had comparable performance with other delirium measures when used by trained research assistants.²⁵

Definition of Variables

The complete 30-point MMSE was administered at the Chicago and Yale sites. A shortened version, consisting of the first 21 points of the MMSE, was administered at Cleveland. The score on the 21-point scale at Cleveland was adjusted to a denominator of 30 points for purposes of comparison across sites. For the present study, dementia was defined at the admission interview as an MMSE score below 20 (on the 30-point scale) and no evidence of acute onset or fluctuating course by the CAM rating at admission. The cutoff point of 20 on the MMSE was selected to account for the relatively low mean scores in these elderly populations and to increase specificity for clinically important dementia.²⁶

The ADL score was a simple additive sum of the number of activities of daily living as described by Katz et al.,²¹ on which the subject was independent (i.e., needed no assistance), including bathing, dressing, feeding, toileting, continence, and transferring; the total score ranged from 0 to 6. Similarly, the IADL score was a simple additive sum of the number of instrumental activities of daily living²² on which the subject was independent, including using the telephone, grocery shopping, using transportation, preparing meals, doing housework, taking medications, and handling money; the total score ranged from 0 to 7. To approximate the patient's prehospitalization status, both the ADLs and IADLs were referent to the patient's status 2 weeks prior to hospital admission. Predictive validity for these measures (i.e., ability to predict future mortality, rehospitalization, and institutionalization) has been documented in previous studies.²⁷⁻²⁹

The APACHE II score,³⁰ used as an index of illness severity at hospital admission, was scored based on admission vital signs, laboratory data, medical record data, and admission interview data. Primary medical problems were defined by the leading discharge diagnoses, based on groupings of related categories coded according to the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM).

Study Outcomes

The four major study outcomes were death, new nursing home placement, death or new nursing home placement, or ADL decline. Definitions of the four major study outcomes were either cumulative from the admission assessment until discharge or 3-month follow-up (e.g., death, new nursing home placement, death or new nursing home placement) or referent to the admission as-

assessment (e.g., ADL decline). At the time of hospital discharge, therefore, new nursing home placement was defined as a new placement of a patient who had not been institutionalized at the time of hospital admission (among survivors only). At the 3-month follow-up, new nursing home placement was defined as any new placement from the time of hospital admission until the 3-month follow-up (among survivors only). In addition to examining each outcome separately, we examined the combined outcome of death or new nursing home placement to avoid potential inferential errors that may arise because patients who die can no longer be placed in a nursing home.³¹

At hospital discharge, ADL decline was defined as a decline in ADL score from prehospitalization status (referent to 2 weeks prior to hospital admission) to discharge among survivors only. At 3-month follow-up, ADL decline was defined as a decline in ADL score from prehospitalization status until 3-month follow-up among survivors only. As a secondary analysis, we examined a combined outcome of death or ADL decline. This analysis allowed us to include all available subjects in the ADL analyses, incorporating death as a decline in functional status.

Statistical Analysis

For each baseline characteristic, the three cohorts were compared using Pearson's χ^2 test for categorical variables and the Student's *t* test for continuous variables.

Crude and adjusted odds ratios (ORs) used to measure the association between delirium and study outcomes were calculated by site. Baseline covariates used to obtain by-site adjusted ORs in multiple logistic regression models were age, gender, dementia, APACHE II score, ADL score, and IADL score. Pooled ORs (combined across sites) were calculated using two forms of adjustment. First, a site-stratified estimate of the OR was calculated using the Cochran-Mantel-Haenszel procedure.³² Second, an adjusted OR was obtained from estimated coefficient and standard errors calculated from logistic regression models that included indicator variables for site, as well as the baseline covariates mentioned above. All baseline covariates were included in models for outcomes of death, new nursing home placement, and death or new nursing home placement. For the outcome of ADL decline, all variables except ADL score were included. The Breslow-Day test for homogeneity³³ was used to determine whether site-stratified ORs were appropriate; *p* values $\geq .10$ for this test were considered acceptable, and a site-stratified estimate was presented. For logistic models, interaction terms between delirium and site were examined. Estimated ORs from these models were considered acceptable provided that *p* $\geq .10$ for the interaction term.

Cox proportional hazards analysis was used to assess the effect of delirium on hospital length of stay.³⁴ For these analyses, persons who were discharged were considered "events," while persons who died in the hospital were considered censored at date of death. Both unad-

justed and adjusted models were fitted by site and overall (stratified by site). The adjusted models included baseline covariates as described above. The adjusted median length of stay represents a modeled value derived from the proportional hazards analysis, which controls for the effects of the baseline covariates.

Characteristics of subjects who did and did not have data at a specific time point (either discharge or follow-up) were compared to assess for any potential association of missing data with important predictor variables.³⁵ For subjects with up to three missing items on the 7-item IADL score, an "estimated" IADL score was calculated, using standard methods to impute missing data (BMDP Statistical Software. Description and estimation of missing data: AM procedure. BMDP Statistical Software Manual. 1990;2:873–89). Missing items, rather than being left blank, most often reflected a response of "not applicable" and occurred most frequently for patients in assisted living situations for the activities of housework, shopping, and finances. To estimate a missing item, we first regressed that item on all other IADL items that were not missing for that subject, and a predicted value for that item was calculated. The IADL score for these subjects was created by summing the observed (nonmissing) and predicted (missing) items. This method allowed us to estimate a value for the IADL score, a baseline covariate, and avoid excluding 101 (14%) of 727 patients who were missing one or two IADL items from the analyses.

All analyses were carried out using SAS version 6.08 (SAS Institute, Cary, NC) or BMDP (BMDP Statistical Software, Los Angeles, Calif.) software.

RESULTS

Characteristics of the three study populations are shown in Table 1. Overall, the group was elderly (mean age 78.9 years), frail (42% with an ADL impairment at baseline), and predominantly female (60%); 32% were minority, 4% were admitted from a nursing home, and 19% met criteria for dementia at baseline. The baseline rates of delirium were similar in the three cohorts, ranging from 20 (10%) of 199 to 33 (16%) of 205, with an overall rate of 88 (12%) of 727 total. These rates are comparable with those from previous studies.^{9,36–40} However, these three cohorts have statistically significant differences in many baseline characteristics—indicating the distinct and diverse nature of these three cohorts.

Hospital Outcomes

New Nursing Home Placement and Death or New Nursing Home Placement. The outcomes of new nursing home placement and death or new nursing home placement at hospital discharge (Table 2) occurred with rates of 60 (9%) of 692 and 95 (13%) of 727, respectively. For both of these outcomes, the crude ORs associated with delirium are

Table 1. Baseline Characteristics of Study Population

Feature	Study Site			
	Chicago (n = 199)	Cleveland (n = 205)	Yale (n = 323)	Overall (n = 727)
Age, mean years $\pm$ SD	74.1 $\pm$ 6.6*	82.2 $\pm$ 6.0*	78.7 $\pm$ 6.0*	78.9 $\pm$ 6.9
Female, %	53*	74*	55*	60
White, %	39*	59*	90*	68
Living alone, %	35*	46*	41	41
Nursing home, %	0*	5*	6*	4
Admission MMSE, mean $\pm$ SD	23.7 $\pm$ 4.9	23.9 $\pm$ 5.6	23.1 $\pm$ 5.6	23.5 $\pm$ 5.4
Dementia, %	14*	22*	20*	19
ADL sum, mean $\pm$ SD	5.2 $\pm$ 1.4*	4.9 $\pm$ 1.6*	5.1 $\pm$ 1.3	5.1 $\pm$ 1.4
IADL sum, mean $\pm$ SD	5.2 $\pm$ 2.0	4.6 $\pm$ 2.1	4.8 $\pm$ 2.3	4.9 $\pm$ 2.2
APACHE II sum, mean $\pm$ SD	9.2 $\pm$ 4.1*	13.1 $\pm$ 4.6*	13.9 $\pm$ 3.8*	12.4 $\pm$ 4.5
Primary medical problem, %				
Cancer	13*	7	6*	8.3
Coronary artery disease	0*	9*	4*	4.6
Cardiac arrhythmias	0*	5*	6*	4.2
Congestive heart failure	4	7	7	6.2
Chronic lung disease	3	5	2	3.2
Pneumonia	5	4	8	6.3
Gastrointestinal	13	14	17	15.3
Cerebrovascular disease	11*	8*	2*	5.8
Diabetes	3	2	1	1.8
Renal disease	4	3	5	4.3
Other	45*	34*	41	40.0
Delirium at admission, %	10	16	11	12

* $p < .05$ for comparison.

substantial and statistically significant. Although the effects are somewhat diminished with multivariate adjustment, the adjusted ORs remain substantial and statistically significant for all sites combined for new nursing home placement (adjusted OR 3.0; 95% confidence interval [CI] 1.4, 6.2) and for death or new nursing home placement (adjusted OR 2.1; 95% CI 1.1, 4.0). Notably, the trends are similar and the findings are replicated across sites.

In-Hospital Deaths. The relatively small number of in-hospital deaths in the combined sample, 35 (5%) of 727, limits drawing any definitive conclusions about the effect of delirium on hospital mortality. Although the crude ORs for death associated with delirium were substantial (OR > 2.0; Table 2), these effects were diminished after multivariate adjustment for other potential confounders (i.e., age, gender, dementia, APACHE II score, ADL score, and IADL score). However, the adjusted values represent unstable estimates with wide CIs because of the small number of outcome events. Based on a sample size of 727 with the observed death rates of 9% in the delirious group and 4% in the nondelirious group (Table 2), our power to detect a statistically significant association (two-sided α level of 0.05) was only 32%.

Length of Stay. In unadjusted analyses, the median hospital length of stay for delirious patients was significantly longer than in nondelirious patients at Cleveland ($p =$

.02), and trended toward significance ($p = .07$) in overall site-stratified analyses. The unadjusted median lengths of stay for delirious and nondelirious patients, respectively, were as follows: Chicago, 8.5 vs 8.0 days; Cleveland, 10.0 vs 6.0 days; Yale, 10.0 vs 9.0 days; and overall, 8.5 vs 7.3 days. After incorporating the effects of baseline covariates (i.e., age, gender, dementia, APACHE II score, ADL score, and IADL score), the adjusted median lengths of stay for delirious and nondelirious patients, respectively, were: Chicago, 7.5 vs 7.0 days; Cleveland, 6.8 vs 5.8 days; Yale, 7.5 vs 8.0 days; and overall, 8.0 vs 7.5 days. Although the trend was for longer lengths of stay for delirious patients at two sites and overall, these differences did not achieve statistical significance.

Three-Month Follow-up Outcomes

As shown in Table 3, a total of 47 (6.5%) of 727 subjects were lost to follow-up at 3 months. These subjects could not be located for their 3-month follow-up interview. Overall, the missing group ($n = 47$) did not differ significantly from the group included in analyses ($n = 680$) in terms of delirium rates, age, gender, dementia, APACHE II score, ADL score, and IADL score.

New Nursing Home Placement and Death or New Nursing Home Placement. The findings for new nursing home placement and death or new nursing home placement by

Table 2. Hospital Outcomes by Delirium Status*

Delirium Status	Death (In-Hospital)				New Nursing Home Placement†				Death or New Nursing Home Placement			
	n/N (%)	OR	Adj OR‡	95% CI‡ (Adj OR)	n/N (%)	OR	Adj OR‡	95% CI‡ (Adj OR)	n/N (%)	OR	Adj OR‡	95% CI‡ (Adj OR)
Chicago												
Delirious	0/20 (0)	NA	NA	NA	2/20 (10)	NA	NA	NA	2/20 (10)	3.2	3.7	(0.6, 24.7)
Nondelirious	6/179 (3)				0/173 (0)				6/179 (3)			
Cleveland												
Delirious	3/33 (9)	2.8	0.9	(0.1, 7.0)	12/30 (40)	4.6§	2.7	(0.9, 7.9)	15/33 (45)	4.5§	2.5	(0.9, 6.6)
Nondelirious	6/172 (3)				21/166 (12)				27/172 (16)			
Yale												
Delirious	5/37 (14)	2.8	0.7	(0.1, 5.9)	6/32 (19)	3.1§	2.3	(0.7, 7.2)	11/37 (30)	3.1§	1.7	(0.6, 4.7)
Nondelirious	15/286 (5)				19/271 (7)				34/286 (12)			
All sites												
Delirious	8/90 (9)	2.2	0.7	(0.2, 2.5)	20/82 (24)	4.4§	3.0	(1.4, 6.2)	28/90 (31)	3.7§	2.1	(1.1, 4.0)
Nondelirious	27/637 (4)				40/610 (6)				67/637 (10)			
	Homog test $p = .41$				Homog test $p = .10$				Homog test $p = .81$			

*NA indicates not available (could not be calculated due to zero-cell); OR, odds ratio; adj OR, adjusted odds ratio; CI, confidence interval; Homog test, Breslow-Day test for homogeneity (see text for details).

†Deaths excluded.

‡Adjusted for age, gender, dementia, APACHE II score, ADL score, IADL score.

§ $p < .05$ (95% CI for crude OR excludes 1.0).

3 months, which occurred in 77 (13%) of 600 and 165 (25%) of 663 patients, respectively, achieved both clinical and statistical significance, even after controlling for all potential confounders (adjusted OR 3.0; 95% CI 1.5, 6.0, for new nursing home placement; adjusted OR 2.6; 95% CI 1.4, 4.5, for death or new nursing home placement).

Once again, the trends are similar and the findings are replicated across sites.

Death. By 3-month follow-up (Table 3), the number of deaths in the combined sample increased to 98 (14%) of 680. Although the crude OR of 2.9 for death associated

Table 3. Three-Month Outcomes by Delirium Status*

Delirium Status	Death				New Nursing Home Placement†				Death or New Nursing Home Placement			
	n/N (%)	OR	Adj OR‡	95% CI‡ (Adj OR)	n/N (%)	OR	Adj OR‡	95% CI‡ (Adj OR)	n/N (%)	OR	Adj OR‡	95% CI‡ (Adj OR)
Chicago												
Delirious	3/16 (19)	1.7	1.4	(0.2, 9.4)	4/12 (33)	12.9§	8.6	(1.3, 56.2)	6/14 (43)	4.0§	3.8	(0.8, 16.4)
Nondelirious	19/160 (12)				5/134 (4)				24/153 (16)			
Cleveland												
Delirious	11/30 (37)	3.8§	1.6	(0.5, 5.2)	13/23 (56)	6.7§	3.9	(1.1, 13.3)	21/30 (70)	6.6§	2.9	(1.0, 8.4)
Nondelirious	21/160 (13)				24/147 (16)				42/161 (26)			
Yale												
Delirious	10/35 (28)	2.9§	1.5	(0.5, 4.6)	7/29 (24)	2.6§	2.0	(0.6, 6.0)	16/34 (47)	3.4§	2.0	(0.8, 5.0)
Nondelirious	34/279 (12)				28/255 (11)				56/271 (21)			
All sites												
Delirious	24/81 (30)	2.9§	1.6	(0.8, 3.2)	20/64 (38)	4.8§	3.0	(1.5, 6.0)	43/78 (55)	4.5§	2.6	(1.4, 4.5)
Nondelirious	74/599 (12)				57/536 (11)				122/585 (21)			
	Homog test $p = .61$				Homog test $p = .14$				Homog test $p = .51$			

*All outcomes from baseline to 3-month follow-up. OR indicates odds ratio; adj OR, adjusted odds ratio; CI, confidence interval; Homog test, Breslow-Day test for homogeneity (see text for details). A total of 47 subjects were lost to follow-up at 3 months: 23 from Chicago, 15 from Cleveland, and 9 from Yale.

†Excludes all deaths.

‡Adjusted for age, gender, dementia, APACHE II score, ADL score, IADL score.

§ $p < .05$ (95% CI for crude OR excludes 1.0).

with delirium is statistically significant, the adjusted OR of 1.6 achieves clinical but not statistical significance.

Functional Decline at Discharge and Follow-up

As shown in Table 4, a total of 215 (30%) of 727 subjects were missing ADL information at hospital discharge. These subjects were discharged before a discharge interview could be completed, or had incomplete information needed to rate the ADL score at discharge. The group with missing ADL information ($n = 215$) did not differ from the included group ($n = 512$) in terms of delirium rate, age, gender, dementia, APACHE II score, ADL score, or IADL score at baseline. At 3-month follow-up, 146 (21%) of 680 subjects with some follow-up information had incomplete information needed to rate the ADL score. At the Chicago site, the group with missing ADL information ($n = 45$) was more likely to be delirious, demented, and with more ADL and IADL dependency at baseline, than the group included in analyses ($n = 131$). However, for the other sites, the group with missing ADL information ($n = 101$) did not differ from the included group ($n = 403$) in terms of delirium rate, age, gender, dementia, APACHE II score, ADL score, or IADL score at baseline. Although results from Chicago must be interpreted with caution for these analyses, the missing data from Cleveland and Yale were not related to our prognostic predictors and were equally distributed between delirious and nondelirious groups.

Delirium is a significant predictor of ADL decline at both hospital discharge and 3-month follow-up at Cleveland, Yale, and all sites combined. ADL decline occurred

in 194 (38%) of 512 patients at discharge and 150 (28%) of 534 at follow-up. Even after controlling for relevant confounding factors (e.g., age, gender, dementia, APACHE II score, and IADL score), the effect remains clinically and statistically significant (adjusted OR 3.0; 95% CI 1.6, 5.8, at hospital discharge; adjusted OR 2.7; 95% CI 1.4, 2.5, at 3-month follow-up). Excluding Chicago from the overall results because of the large amount of missing data would yield an adjusted OR of 3.3 (95% CI 1.7, 6.7) at hospital discharge and adjusted OR of 3.3 (95% CI 1.6, 7.0) at 3-month follow-up.

The average magnitude of ADL decline overall was significantly greater in delirious than in nondelirious patients. At hospital discharge, delirious patients declined by a mean of 1.9 ($\pm$ SE 2.2) ADLs, while nondelirious patients declined by a mean of 0.5 ($\pm$ 1.6) ADLs ($p < .05$). At follow-up, delirious patients declined by a mean of 1.3 ($\pm$ 2.1) ADLs, while nondelirious patients declined by a mean of 0.2 ($\pm$ 1.4) ADLs ($p < .05$).

For the secondary analysis of the combined outcome of death or ADL decline (Table 5), the results are quite similar. Delirium remains a significant predictor at both hospital discharge and 3-month follow-up at Cleveland, Yale, and all sites combined. Death or ADL decline occurred in 229 (42%) of 547 patients at discharge and 248 (39%) of 632 patients at follow-up. Even after controlling for relevant confounding factors (e.g., age, gender, dementia, APACHE II score, and IADL score), the overall effect remains clinically and statistically significant with adjusted OR of 2.9 (95% CI 1.5, 5.5) at hospital discharge and adjusted OR of 2.8 (95% CI 1.5, 5.0) at 3-month follow-up.

Table 4. Decline in Activities of Daily Living*

Delirium Status	Baseline to Hospital Discharge				Baseline to 3 Months			
	Declines n/N (%)	OR	Adj OR [†]	95% CI [†]	Declines n/N (%)	OR	Adj OR [†]	95% CI [†]
Chicago								
Delirious	2/4 (50)	2.0	1.0	(0.9, 1.1)	2/7 (28)	1.2	0.9	(0.2, 5.6)
Nondelirious	24/71 (34)				31/124 (25)			
Cleveland								
Delirious	17/24 (71)	5.2 [‡]	3.3	(1.2, 9.7)	12/18 (67)	4.8 [‡]	4.4	(1.3, 14.9)
Nondelirious	45/142 (32)				39/133 (29)			
Yale								
Delirious	17/26 (65)	3.3 [‡]	3.4	(1.3, 8.8)	11/22 (50)	3.2 [‡]	3.5	(1.2, 9.7)
Nondelirious	89/245 (36)				55/230 (24)			
All sites								
Delirious	36/54 (67)	3.8 [‡]	3.0	(1.6, 5.8)	25/47 (53)	3.2 [‡]	2.7	(1.4, 5.2)
Nondelirious	158/458 (34)				125/487 (26)			
	Homog test <i>p</i> = .62				Homog test <i>p</i> = .37			

*OR indicates odds ratio; adj OR, adjusted odds ratio; CI, confidence interval; Homog test, Breslow-Day test for homogeneity (see text for details). A total of 215 (of 727 available) subjects were missing from these analyses at hospital discharge: 124 from Chicago, 39 from Cleveland, and 52 from Yale. A total of 146 (of 680 available) subjects were missing at 3-month follow-up: 45 from Chicago, 39 from Cleveland, and 62 from Yale.

[†]Adjusted for age, gender, dementia, APACHE II score, baseline IADL score.

[‡] $p < .05$ (95% CI for crude OR excludes 1.0).

Table 5. Death or Decline in Activities of Daily Living*

Delirium Status	Baseline to Hospital Discharge				Baseline to 3 Months			
	Events n/N (%)	OR	Adj OR [†]	95% CI	Events n/N (%)	OR	Adj OR [†]	95% CI
Chicago								
Delirious	2/4 (50)	1.6	0.8	(0.1, 8.0)	5/10 (50)	1.9	1.7	(0.4, 6.8)
Nondelirious	30/77 (39)				50/143 (35)			
Cleveland								
Delirious	20/27 (74)	5.4 [‡]	3.2	(1.1, 9.0)	23/29 (79)	6.0 [‡]	4.6	(1.5, 13.7)
Nondelirious	51/148 (34)				60/154 (39)			
Yale								
Delirious	22/31 (71)	3.7 [‡]	3.3	(1.3, 8.5)	21/32 (66)	3.8 [‡]	2.9	(2.2, 3.8)
Nondelirious	104/260 (40)				89/264 (34)			
All sites								
Delirious	44/62 (71)	4.0 [‡]	2.9	(1.5, 5.5)	49/71 (69)	4.0 [‡]	2.8	(1.5, 5.0)
Nondelirious	185/485 (38)				199/561 (35)			
	Homog test <i>p</i> = .616				Homog test <i>p</i> = .372			

*OR indicates odds ratio; adj OR, adjusted odds ratio; CI, confidence interval; Homog test, Breslow-Day test for homogeneity (see text for details). A total of 180 (of 727 available) subjects were missing from these analyses at hospital discharge: 118 from Chicago, 30 from Cleveland, and 32 from Yale. A total of 48 (of 680 available) subjects were missing at 3-month follow-up: 23 from Chicago, 7 from Cleveland, and 18 from Yale.

[†]Adjusted for age, gender, dementia, APACHE II score, baseline IADL score.

[‡]*p* < .05 (95% CI for crude OR excludes 1.0).

DISCUSSION

Delirium at admission was significantly associated with poor hospital outcomes in overall (combined three-site) analyses at discharge and 3-month follow-up, including new nursing home placement, death or new nursing home placement, and decline in ADLs. The contribution of delirium to these poor outcomes remained statistically significant even after controlling for age, gender, dementia, APACHE II score, ADL score, and IADL score in all of these analyses. The relationship of delirium at admission to death alone (35 events at discharge and 98 at 3-month follow-up) and to length of hospital stay were not statistically significant. The relatively small number of in-hospital deaths in the combined sample, with a limited power of 32% to detect a significant association, precluded drawing any definitive conclusions about the effect of delirium on hospital mortality. By 3-month follow-up, the number of deaths in the combined sample increased, yielding a statistically significant association of delirium and mortality in the crude analysis. However, after multivariate adjustment, the effect was diminished (adjusted OR 1.6; 95% CI 0.8, 3.2) and no longer achieved statistical significance. Future studies with increased sample sizes are needed to further examine the relationship of delirium to hospital and longer-term mortality.

The advantages of the current study include its multisite nature, which allowed us to maximize the number of our relatively infrequent study outcomes. This is one of the largest prospective studies of delirium to date. In addition, the replication of findings across sites with diverse study populations provides substantial evidence

of the robustness of the overall conclusions. Finally, the standardized, prospective nature of the data collection enhanced the uniformity and validity of our measurements of delirium, control variables, and study outcomes.

Our findings of the long-term effect of delirium on poor outcomes corroborate recent studies on the long persistence and duration of delirium symptoms.^{7,11,41} These studies indicate that delirium and its effects may be much more enduring than previously believed, and that persistent partial forms of the syndrome are quite common—contributing further to the long-term deleterious effects of delirium.

Several important caveats and limitations of this study should be highlighted. First, the three study populations examined were disparate in many baseline characteristics (Table 1). Thus, homogeneity needed to be carefully assessed before combining site-specific results. Before pooling any data for combined analyses, we verified that the Breslow-Day test for homogeneity resulted in *p* ≥ .10. The fact that the trends were similar across all sites, despite the diverse nature of the populations, supports the external validity of the findings.

Second, incident delirium (developing during hospitalization) was not examined as an additional prognostic variable because it was not assessed at all sites. In this study, only prevalent delirium (present at hospital admission) was examined, and those with incident delirium were classified as not delirious at admission. Because patients with incident delirium are more likely to behave like patients who had prevalent delirium rather than patients who never developed delirium, a potential misclassification bias was present, which most likely reduced the overall power of the

study and diminished the magnitude of the associations found. The inclusion of incident delirium would most likely have increased the predictive power of our models. However, the fact that associations with the outcomes of interest were still found, despite the potential bias against them, supports the robustness of the findings.

Third, only one of many available measures of illness severity or comorbidity was included in these analyses. The APACHE II score was selected by the core group of investigators involved in the HOPE project,²⁰ because of its well-accepted and widely used nature, its inclusion of both acute and chronic disease components, and the availability of comparative data from other samples of acutely ill elderly patients. Individual diagnoses were not examined as predictors of mortality because previous studies in older populations have shown that functional measures are stronger predictors of hospital outcomes than medical diagnoses or diagnosis-related groups.^{42,43} The inclusion of functional and cognitive measures in our models provided additional control for important prognostic variables, which have been widely recognized to reflect the overall "burden of illness" and to exert substantial prognostic impact on outcomes of hospitalization.^{26,42-44} Taken together, the APACHE II, functional, and cognitive measures provide a potent and plausible indicator of illness severity and comorbidity for older hospitalized patients.

Fourth, the large amount of missing data for our functional decline outcome may have limited our ability to draw definitive conclusions about the effect of delirium. In many cases, these missing interviews were unavoidable owing to unanticipated discharges, refusals of patients to be interviewed when discharge was imminent, and lack of availability of sufficient interview staff. In particular, the Chicago site had a large amount of missing data, and the group with missing data were considerably more likely to have poor prognostic predictors. Thus, it was not surprising that the delirious group did not have significantly more functional decline, because much of the data were missing from this group. However, the missing data from Yale and Cleveland were not related to our prognostic predictors and were equally distributed between delirious and nondelirious groups. Thus, the findings from these two sites should still be valid.³⁵

Our findings suggest that delirium itself is an important prognostic determinant of hospital outcomes, rather than merely a marker of poor prognostic characteristics. Even after controlling for age, gender, dementia, APACHE II score, and functional measures (ADL and IADL scores), delirium emerged as an important independent predictor of new nursing home placement, death or new nursing home placement (combined outcome), and functional decline. Although the exact mechanisms by which delirium leads to these poor hospital outcomes need further investigation, the effect is plausible because delirium has been hypothesized to contribute to aspiration pneumonia; daytime somnolence with immobilization, pressure ulcers, and pulmonary emboli; use of psychoactive medications

to control agitation and insomnia (with their attendant complications); injury; and related problems.⁴⁵⁻⁴⁸

Thus, delirium serves as an important prognostic variable for hospitalized older patients, and should potentially be considered in case-mix adjustment or risk stratification systems in hospitalized older populations. At a minimum, delirium should be included as a control variable in studies examining hospital outcomes in acutely ill older persons. Furthermore, we hope that the results of this study motivate clinicians to more closely monitor high-risk patients, avoid use of psychoactive medications in these patients, and aggressively monitor mental status for incipient delirium.

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