ORIGINAL INVESTIGATION

One-Year Health Care Costs Associated With Delirium in the Elderly Population

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Background: While delirium has been increasingly recognized as a serious and potentially preventable condition, its long-term implications are not well understood. This study determined the total 1-year health care costs associated with delirium.

Methods: Hospitalized patients aged 70 years and older who participated in a previous controlled clinical trial of a delirium prevention intervention at an academic medical center between 1995 and 1998 were followed up for 1 year after discharge. Total inflation-adjusted health care costs, calculated as either reimbursed amounts or hospital charges converted to costs, were computed by means of data from Medicare administrative files, hospital billing records, and the Connecticut Long-term Care Registry. Regression models were used to determine costs associated with delirium after adjusting for patient sociodemographic and clinical characteristics.

Results: During the index hospitalization, 109 patients (13.0%) developed delirium while 732 did not. Patients with delirium had significantly higher unadjusted health care costs and survived fewer days. After adjusting for pertinent demographic and clinical characteristics, average costs per day survived among patients with delirium were more than 2½ times the costs among patients without delirium. Total cost estimates attributable to delirium ranged from $16 303 to $64 421 per patient, implying that the national burden of delirium on the health care system ranges from $38 billion to $152 billion each year.

Conclusions: The economic impact of delirium is substantial, rivaling the health care costs of falls and diabetes mellitus. These results highlight the need for increased efforts to mitigate this clinically significant and costly disorder.

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DELIRIUM, CHARACTERIZED as an acute decline in cognition and attention, represents a common and severe problem for hospitalized older patients, with occurrence rates from 14% to 56% and hospital mortality rates from 25% to 33%.[1,2] The development of delirium has been associated with increased morbidity, persistent functional decline, increased nursing time per patient, higher per-day hospital costs, increased length of hospital stay, higher rates of nursing home placement, and increased mortality.[3-6] Delirium often initiates a cascade of events that can include functional decline, caregiver burden, increased morbidity and mortality, and higher health care costs.[3-5,7-10] The problem of delirium in older hospitalized patients has assumed particular importance because patients 65 years and older currently account for more than 48% of all days of hospital care.[11]

Although the short-term implications of delirium have been well documented, recent evidence[2-6,8,10,12-17] suggests that delirium also has substantial long-term sequelae with significant implications for health care utilization and costs. However, previous studies of health care costs related to delirium have been limited to specific services (ie, hospital length of stay, intensive care unit stay, or nursing home care). To document the broader economic and health care burden of delirium, we determined the long-term direct health care costs associated with delirium. The present study provides a comprehensive cost estimate for all direct health care services from the index hospitalization through 1 year after discharge.

METHODS

SAMPLE

The study sample consisted of 841 individuals who participated in a controlled trial of a delirium prevention intervention at Yale–New Haven Hospital between 1995 and 1998. Details of the study are described elsewhere.[18] Briefly, patients meeting the following criteria were enrolled: consecutive admissions to

Table 1. Baseline Characteristics of Patients in the Sample[a]

Measure	Total Cohort (N=841)	Delirium Group (n=109)	Nondelirium Group (n=732)	*P* Value[b]
Age, mean (SD), y	80.2 (6.4)	81.7 (7.1)	80.0 (6.3)	.02
Male sex	329 (39.1)	41 (37.6)	288 (39.3)	.73
Nonwhite race	104 (12.4)	20 (18.3)	84 (11.5)	.04
Married	302 (35.9)	32 (29.4)	270 (36.9)	.13
Residence in nursing home before admission	53 (6.3)	12 (11.0)	41 (5.6)	.03
Education, mean (SD), y	11.1 (3.5)	10.2 (3.3)	11.2 (3.5)	.004
Charlson comorbidity score, mean (SD)	3.0 (2.3)	3.4 (2.4)	2.9 (2.3)	.03
APACHE II score for first 48 h of admission, mean (SD)	15.7 (4.1)	17.0 (4.3)	15.5 (4.0)	<.001
Dementia	110 (13.1)	30 (27.5)	80 (10.9)	<.001
No. of ADL disabilities before hospitalization, mean (SD)	1.0 (1.7)	2.0 (2.4)	0.9 (1.6)	<.001
MMSE score at hospital admission, mean (SD)	23.3 (4.9)	19.8 (5.1)	23.8 (4.6)	<.001
Principal diagnosis				
Pneumonia	92 (10.9)	10 (9.2)	82 (11.2)	.53
Chronic lung disease	90 (10.7)	6 (5.5)	84 (11.5)	.06
Congestive heart failure	96 (11.4)	17 (15.6)	79 (10.8)	.14
Ischemic heart attack	72 (8.6)	4 (3.7)	68 (9.3)	.05
Gastrointestinal tract disease	111 (13.2)	14 (12.8)	97 (13.3)	.91
Diabetes mellitus or metabolic disorder	37 (4.4)	6 (5.5)	31 (4.2)	.55
Cancer	22 (2.6	4 (3.7)	18 (2.5)	.46
Cerebrovascular disease	20 (2.4)	4 (3.7)	16 (2.2)	.34
Renal failure	17 (2.0)	2 (1.8)	15 (2.0)	.88
Anemia	12 (1.4)	0	12 (1.6)	.18
Other	272 (32.3)	42 (38.5)	230 (31.4)	.14
Received delirium prevention intervention	413 (49.1)	43 (39.4)	370 (50.5)	.03

Abbreviations: ADL, activities of daily living; APACHE, Acute Physiology and Chronic Health Evaluation; MMSE, Mini-Mental State Examination.
[a] Values reported are number (percentage) unless otherwise indicated.
[b] *P* values are for comparison of the delirium and nondelirium groups.

3 non–intensive care general medical units, aged 70 years or older, no evidence of delirium at admission, and intermediate or high risk for delirium based on a previously developed risk model.[19] Patients who could not participate in interviews (eg, profound dementia, language barrier, profound aphasia, intubation, coma, or respiratory isolation), who had a terminal illness, who had a hospital stay of 48 hours or less, or who had prior enrollment in the study were excluded. Informed consent for participation and permission to acquire subsequent follow-up data were obtained from the patients, or from a proxy for those with substantial cognitive impairment, according to procedures approved by the institutional review board of the Yale University School of Medicine.

Delirium was ascertained daily during hospitalization by the Confusion Assessment Method,[20,21] with delirium defined by the presence of acute onset and fluctuating course, inattention, and either disorganized thinking or altered level of consciousness. Patients who developed delirium while hospitalized were identified, and all patients were followed up for up to 1 year after discharge to determine health care service use and costs. Of the 919 subjects enrolled in the original trial,[18] 25 were excluded because they could not be linked to the Medicare files, 50 were excluded because they were enrolled in a Medicare managed care health maintenance organization and hence did not have detailed cost data, and 3 were excluded because they were missing cost data from the index hospitalization. Thus, the final study sample, which included both intervention and control subjects, consisted of 841 individuals.

SOURCES OF DATA

Information on patient demographic characteristics, comorbidities, and functional status were obtained from primary data collected during the controlled trial. Data on health care service use and costs, including inpatient, outpatient, nursing home, home health, rehabilitation, and other services, were obtained from Medicare Parts A and B administrative claims files for these patients. Additional service use and cost data were obtained from Yale Medical Information Systems for the index hospitalization and subsequent readmissions to Yale–New Haven Hospital. Because Medicare nursing home coverage is limited to 100 days of care and information on stays beyond this limit may be inaccurate or missing, the Connecticut Long-term Care Registry was used to supplement the Medicare files. The Long-term Care Registry is a longitudinal database containing demographic, health status, and nursing home length of stay information (including dates of all nursing home admissions and discharges) for all Connecticut nursing facility resident stays.

Patient deaths were identified by telephone follow-up contacts at 1-, 6-, and 12-month periods; by daily obituary review; and by the Social Security Death Index. All deaths and dates of death were confirmed by at least 2 sources: review of medical records, death certificates, systematic obituary review, Medicare Enrollment and Claims files, and/or National Death Index or Social Security databases.

MEASURES

Total health care costs for patients in the controlled trial were computed during the index hospitalization and through 1 year after discharge. For costs incurred during the index hospitalization, hospital charges were converted to costs by means of the hospital-specific cost to charge ratio. For all other services, costs were calculated with the use of Medicare reimbursed amounts rather than charges because reimbursed amounts are payments actually received by providers for their services and hence are a better measure of transaction prices than billed charges.[22-24] For patients with unqualified nursing home days (ie, days not reim-

Table 2. Unadjusted Survival and Cost Outcomes

Measure	Total Cohort (N=841)	Delirium Group (n=109)	Nondelirium Group (n=732)	*P* Value[a]
Died within 1 y, No. (%)	208 (24.7)	47 (43.1)	161 (22.0)	<.001
Days of follow-up				
Mean (SD)	313 (116)	256 (157)	322 (106)	.89
Median	369	369	369	
Total health care costs, $[b]				
Mean (SD)	50 745 (48 113)	69 498 (59 120)	47 958 (45 640)	<.001
Median	33 295	56 722	30 662	
Total costs per day survived, $[b]				
All patients				
Mean (SD)	256 (396)	563 (774)	211 (276)	<.001
Median	140	322	117	
Patients who died during study period				
Mean (SD)	461 (481)	732 (773)	382 (316)	.004
Median	332	471	287	
Patients who survived during entire study period				
Mean (SD)	104 (100)	186 (122)	95 (92)	<.001
Median	66	159	60	

[a] *P* values are for comparison of the delirium and nondelirium groups.
[b] Costs are adjusted for inflation and are reported in 2005 dollars.

bursed by Medicare because they exceed the 100-day limit), the number of additional days of care for these patients was determined from the Medicare records or Long-term Care Registry, and costs for these days were imputed by means of the average daily cost of care associated with the nursing home in which the patient was admitted. Costs were adjusted for inflation by means of the medical care component of the consumer price index and are reported in 2005 dollars.

STATISTICAL ANALYSES

We used SAS statistical software, version 9.1 (SAS Institute Inc, Cary, North Carolina) for all analyses. We first compared unadjusted mean total costs across the delirium and nondelirium groups by means of a Wilcoxon test. Next, we calculated adjusted mean total costs by linear regression models. Independent variables in the model included whether the patient had delirium during the index hospitalization, patient age, race, sex, whether the patient received the delirium prevention intervention, Charlson comorbidity score, whether the patient had dementia, the number of impairments in activities of daily living, whether the patient died during the study period, and an interaction term of the Charlson comorbidity score with whether the patient died during the study period. We explored other interaction terms as well, but the interaction of the Charlson score and whether the patient died was the only interaction term that significantly improved the fit of the model. Because traditional ordinary least-squares regression is not appropriate for skewed data, costs were log-transformed before running the regression model, and adjusted average total costs were retransformed to the nonlog scale by means of the smearing estimator,[25] after ascertaining that the log-scale residuals were homoscedastic.[26]

Because some patients died during the study period, costs may be right-censored. Moreover, if more patients with delirium than patients without delirium died before the end of the study period, the costs associated with delirium may be underestimated. To account for this potential bias, total direct health care costs were also modeled in 2 additional ways. First, total costs were divided by total days survived to derive an average cost per day survived. Adjusted costs per day survived were computed for patients with delirium and for those without delirium by the same regression model techniques described in the preceding paragraph, with average cost per day survived used as the dependent variable. These adjusted average costs per day survived were then multiplied by the average number of days survived in each group to derive a total cost for each group. Standard errors of these total cost estimates were calculated by bootstrapping methods,[27] and an unpaired, 2-tailed *t* test was used to compare costs across the delirium and nondelirium groups.

The second approach was to use a partitioned estimator to model total costs based on methods developed by Lin et al[28] and Bang and Tsiatis.[29] The study period was divided into 1-month intervals, and average total direct health care costs for patients with and without delirium were computed in each month among individuals who survived to the end of that month. A Cox proportional hazards regression model was used to estimate fitted Kaplan-Meier estimators for surviving to the end of each month, and costs were summed across months with the Kaplan-Meier estimators used as inverse weights. Bootstrapping methods[27] were again used to compute standard errors for the cost estimates, and an unpaired, 2-tailed *t* test was used to compare costs across the delirium and nondelirium groups.

RESULTS

Characteristics of the sample are presented in **Table 1**. Of the 841 individuals included in the study sample, 109 (13.0%) developed delirium during the index hospitalization. A higher proportion of patients with delirium were admitted from a nursing home, had comorbid dementia, or died during the study period (**Table 2**) compared with patients who did not develop delirium. Patients with delirium also had more impairments in activities of daily living, higher Charlson and Acute Physiology and Chronic Health Evaluation II scores, and lower Mini-Mental State Examination scores. A smaller proportion of patients who received the delirium prevention intervention developed delirium compared with patients who did not receive the intervention.

As shown in Table 2, patients with delirium survived an average of 256 days during the 1-year follow-up period, compared with 322 days for patients without delirium, although this difference was not statistically significant ($P = .89$). Despite the shorter survival time, total unadjusted health care costs were significantly higher for patients who developed delirium during the index hospitalization than for those without delirium (mean [SD], $69 498 [$59 120] vs $47 958 [$45 640], respectively; $P < .001$). Total costs per day survived were also higher for patients with delirium than for those without, both among patients who died during the study period and among those who survived.

Results from the regression models showed that patients with delirium had significantly higher costs than patients without delirium even after adjusting for relevant demographic and clinical characteristics. As expected, patients with higher Charlson scores, who had dementia, or who died during the follow-up period also had significantly higher total health care costs. Receipt of the delirium prevention intervention did not significantly affect costs (data not shown). Adjusted total health care costs by month for the delirium and nondelirium groups based on the regression models are illustrated in the **Figure**. Adjusted costs were higher for the delirium group in each month. The difference in adjusted total costs between the delirium and nondelirium groups was initially relatively large ($6613 in the first month), then declined over time until about month 5, and then generally increased again through month 9.

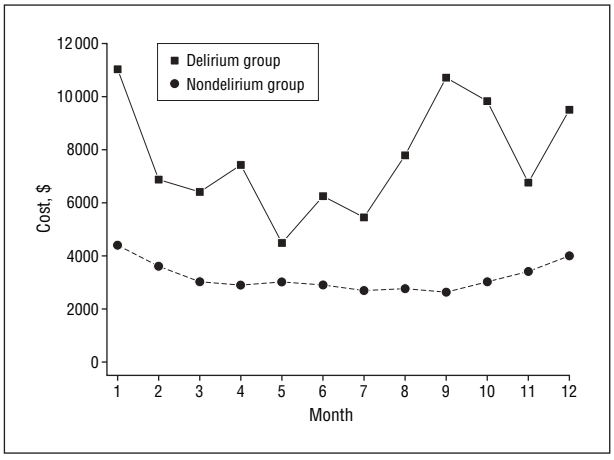

Figure. Mean total health care costs (reported in 2005 dollars) by month, adjusted for all of the variants in the regression models, specifically, index hospitalization; patient age, race, and sex; whether the patient received the delirium prevention intervention; Charlson comorbidity score; whether the patient had dementia; the number of impairments in activities of daily living; whether the patient died during follow-up; and the interaction of the Charlson comorbidity score with whether the patient died.

As shown in **Table 3**, adjusted total costs were significantly higher for the delirium group than for the nondelirium group. Total costs per day survived were more than 2½ times higher for patients with delirium than for patients without delirium. In the model that ignores the right-censoring problem (method 1), costs for patients with delirium were $16 303 higher than for those without delirium. Costs attributable to delirium were higher in the 2 models that accounted for the fact that the data were right-censored (methods 2 and 3), ranging from $60 516 to $64 421. Ninety-five percent of the difference in costs was due to inpatient and nursing home care.

COMMENT

This study documents the considerable direct health care costs associated with delirium in the United States. We estimate that delirium is responsible for between $60 516 and $64 421 in additional health care costs per delirious patient per year. Following Inouye et al[2] and assuming that delirium complicates hospital stays for 20% of the 11.8 million persons 65 years and older who are hospitalized each year, our results imply that total direct 1-year health care costs attributable to delirium range from $143 billion to $152 billion nationally. These estimates are adjusted for the difference in survival time. Even when we use our most conservative estimate, which ignores the right-censoring problem, costs associated with delirium exceed $38 billion per year. Given that a number of effective interventions have been developed to prevent or treat delirium,[18,30-35] at least some of these costs may be avoidable.

We took great care not to underestimate costs associated with delirium due to more patients with delirium dying before the end of the study period than patients without delirium. However, costs may also be underestimated if patients with delirium die quietly, ie, without additional diagnostic or therapeutic intervention. To explore this possibility, we compared average daily costs for patients with and without delirium stratified by whether they survived the entire study period. Average

Table 3. Adjusted Total 1-Year Health Care Costs[a]

Measure	Costs, Mean (SD), $			*P* Value
	Delirium Group	Nondelirium Group	Difference (Delirium–Nondelirium)	
Total costs per survival day	461 (570)	166 (195)	295	<.001
Total costs, method 1[b]	65 755 (58 247)	49 452 (43 806)	16 303	.005
Total costs, method 2[c]	117 620 (109 530)	53 199 (54 698)	64 421	<.001
Total costs, method 3[d]	120 349 (181 274)	59 833 (55 155)	60 516	<.001

[a] Costs are adjusted for inflation and are reported in 2005 dollars.
[b] Based on ordinary least-squares (OLS) regression model of log-transformed total costs.
[c] Based on OLS regression model of log-transformed daily costs multiplied by average days survived.
[d] Based on partitioned estimator of Bang and Tsiatis.[29]

daily costs were significantly higher for the patients with delirium regardless of whether they died during the study period (Table 2). Although in our secondary data analysis we did not demonstrate the cost savings for delirious patients who die quietly, this remains a possibility for a subset of patients, which may bias our results toward underestimating the costs associated with delirium.

National annual health care costs have been estimated for a number of conditions, including hip fracture ($7 billion),[36] nonfatal falls ($19 billion),[37] diabetes mellitus ($91.8 billion),[38] and cardiovascular disease ($257.6 billion).[39] While we acknowledge the difficulty and limitations in comparing across conditions owing to differences in study methods, diagnostic overlap, and shared comorbidities, our results suggest that the economic burden of delirium is substantial, even relative to other conditions.

The pattern of costs over time is interesting. As previous studies have shown,[8,10,40-42] delirium increases hospital length of stay and costs, so the large initial costs associated with delirium are not surprising. The increased costs later in the period may be due to recurrence of delirium or terminal care costs, although more research is needed to explore the sources of these costs.

We included patients in the study sample who had received the delirium prevention intervention to have the largest possible sample size. Although these patients had lower rates of delirium than patients in the control group, receipt of the delirium prevention intervention did not significantly affect costs in the multivariate models. To the extent that including these patients biases our results, we would argue that the bias would be conservative, because, if anything, delirium in the intervention group would have been anticipated to be less costly. Moreover, as a sensitivity analysis, when the sample was limited to just the usual-care patients who did not receive the intervention, the costs associated with delirium were not substantially different (data not shown).

Although previous studies have demonstrated the increased hospital and nursing home costs associated with delirium,[5,41,42] this study is the first, to our knowledge, to document the costs associated with delirium across such a wide range of services (inpatient, intensive care unit, emergency department, outpatient, nursing home, home health, rehabilitation, and other services) and during such a long period. While the study has a number of strengths, such as the availability of detailed clinical information and comprehensive service use and cost data from multiple sources, some limitations of the analysis deserve comment. First, although our cost estimates are adjusted for a number of patient sociodemographic and clinical characteristics, there may be residual confounding due to inherent differences between the delirium and nondelirium groups that might affect costs. However, we believe that any bias introduced by such residual confounding would be small because we are able to include a number of detailed clinical measures in our models. Second, cost estimates are derived from a single site only, and hence the generalizability of the results may be limited. In addition, cost estimates include direct health care costs only and do not take into account important indirect costs associated with caregiver burden or reduced quality of life. Finally, follow-up was truncated at 1 year; therefore, any costs associated with delirium that accrue more than 1 year after discharge are not included.

Despite these limitations, it is clear that the economic burden of delirium is substantial. It is our hope that these results draw attention to delirium as a serious condition with significant long-term clinical and economic implications. Future research will need to focus on the specific sources of the increased health care costs associated with delirium. Given that the condition is costly, increasing in magnitude with the aging population, and potentially preventable, increased efforts to prevent, detect, and treat delirium are urgently needed.

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Screening for Delirium in the Emergency Department: A Systematic Review

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Older adults who visit emergency departments (EDs) often experience delirium, but it is infrequently recognized. A systematic review was therefore conducted to identify what delirium screening tools have been used in ED-based epidemiologic studies of delirium, whether there is a validated set of screening instruments to identify delirium among older adults in the ED or prehospital environments, and an ideal schedule during an older adult's visit to perform a delirium evaluation. MEDLINE/EMBASE, Cochrane, PsycINFO, and CINAHL databases were searched from inception through February 2013 for original, English-language research articles reporting on the assessment of older adults' mental status for delirium. Twenty-two articles met all study inclusion criteria. Overall, 7 screening instruments were identified, though only 1 has undergone initial validation for use in the ED environment and a second instrument is currently undergoing such validation. Minimal information was identified to suggest the ideal scheduling of a delirium assessment process to maximize the recognition of this condition in the ED. Study results indicate that several delirium screening tools have been used in investigations in the ED, though validation of these instruments for this particular environment has been minimal to date. The ideal interval(s) during which a delirium screening process should take place has yet to be determined. Research will be needed both to validate delirium screening instruments to be used for investigation and clinical care in the ED and to define the ideal timing and form of the delirium assessment process for older adults. [Ann Emerg Med. 2014;63:551-560.]

Please see page 552 for the Editor's Capsule Summary of this article.

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INTRODUCTION

Background

Delirium is a syndrome of acute change in mental status accompanied by inattention and marked by a fluctuating course.[1] The condition is estimated to occur in 11% to 42% of hospitalizations,[2] is believed to add between $38 billion and $152 billion to health care expenditures annually in the United States,[3] and is a common complication of the care of acutely ill older adults. Delirium causes distress to caregivers and places patients at higher risk for institutionalization, readmission to the hospital, and death.[4,5] Because patients discharged home from the emergency department (ED) with unidentified delirium have 6-month mortality rates almost 3-fold greater (30.8% versus 11.8%) than their counterparts in whom delirium is detected,[6] unrecognized delirium in the acute care setting presents a major health challenge to older adults.

Importance

On average, delirium has been estimated to be present in approximately 7% to 10% of older ED visitors during their ED stay[7-9] but often goes undetected. Studies consistently show that emergency providers identify delirious patients in only 16% to 35% of cases.[7,8,10,11] Consequently, the Society for Academic Emergency Medicine's Geriatric Task Force has called for mental status screening to be a standard component of the evaluation of every senior in the ED.[12] Members of the Geriatric Task Force have also articulated a need for further investigation into delirium assessment,[13] including the identification of an optimal screening tool and window during which patient evaluations should be performed.[14]

Goals of This Investigation

During the last several decades, several screening instruments have been developed to identify delirious patients in a variety of venues for either research, clinical care, or both.[15,16] The ED, however, represents a unique environment with intense time demands on providers and high volumes of patients that can make caring for older adults more challenging[17] and where it will be necessary as a result to separately evaluate screening instruments for delirium.[14] Therefore, in this systematic review, we sought to answer the following questions: what delirium assessment tools have been used in epidemiologic studies of delirium in the ED and out-of-hospital environment, is there a set of validated screening instruments that should be used to identify delirium among elderly ED patients, and is there evidence for when delirium screening

Editor's Capsule Summary

What is already known on this topic

Although delirium is estimated to be present in 7% to 10% of older patients in the emergency department (ED), it frequently goes undetected.

What question this study addressed

What is the evidence that delirium screening instruments are feasible and valid in the ED and when should they be used?

What this study adds to our knowledge

Data about delirium screening are scarce.

How this is relevant to clinical practice

Despite there being a need to identify delirium in ED geriatric patients, there are no validated instruments and there is a paucity of data on this topic.

should be performed during the course of a patient's ED encounter?

MATERIALS AND METHODS

We conducted a search through February 2013 of MEDLINE/EMBASE from 1946, the Cochrane Library from inception, the PsycINFO database from 1941, and the CINAHL database from 1965. Search terms included the words "delirium" or "acute confusional state" AND "emergency," "emergency room," or "emergency department." We limited the results of the CINAHL and PsycINFO searches to those articles that were peer reviewed. The reference lists of included articles were reviewed by 2 people (M.A.L., a geriatrician, and F.C.M., an emergency physician) to ascertain any further potential studies for inclusion. Additional articles were identified from our own libraries. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[18] for the conduct and reporting of systematic reviews and meta-analyses, whenever possible.

Selection of Participants

Using the PICOT framework[19] (Table 1), we established study selection criteria before conducting any database searches. This approach required us to name the population, intervention, comparison groups, outcomes, and time frame for articles that would be potentially included in our review. There was no preferred study design type. In brief, articles in English studying the prospective evaluation of patients aged 65 years and older for delirium in the ED or out-of-hospital environments and describing the test characteristics of delirium assessment instruments were eligible. A study member (M.A.L.) reviewed and assessed each title and each abstract evaluated in this article, whereas articles submitted for full review were evaluated by 2 reviewers (M.A.L. and F.C.M.). At title review, articles were excluded if they were clearly not relevant. Articles and abstracts were excluded at later stages from this review for the following reasons: the article did not meet predetermined inclusion criteria, the evaluation of delirium did not occur in the ED or out-of-hospital environment, the article was not in English, or the presented abstract was from a scientific meeting presentation and was not published as a separate, peer-reviewed article.

Table 1. PICOT criteria and search strategy.

Criterion	Search strategy
Population of interest	Aged 65 y or above and in the ED or out-of-hospital (ie, EMS) environment
Intervention of interest	Inclusion: Assessment of mental status for delirium Exclusion: Evaluation takes place outside of ED/out-of-hospital environment or assessment deals with patients who are delirious as a result of illicit drug consumption or ethanol intake/withdrawal
Comparison	No comparison group specified or required
Outcomes	Any outcome considered that quantifies delirium presence or development
Time frame	Intervention/assessment performed at any point in the course of the patient's ED stay or in the out-of-hospital environment (under care by EMS)

PICOT, Population, intervention, comparison groups, outcomes, and time frame.

Data Collection and Processing

Two reviewers (M.A.L. and F.C.M.) abstracted data from each eligible study submitted for full review to a standardized collection instrument, recording study type, population, intervention, comparison group, and results. Additional information was collected about study methodology and whether the study reported on the validation, timing, or application of a delirium screening instrument. Original study authors were contacted, whenever needed, to clarify study details. The 2 reviewers resolved any differences of opinion about which articles to include in the final review, details of data extraction, and quality reviews among themselves through discussion; no residual disagreements required external adjudication.

Each study was independently assessed by the 2 reviewers with the Grading of Recommendations Assessment, Development and Evaluation approach.[20] Within this framework, articles were determined to provide "grade I"–level evidence if they reported data from a randomized, placebo-controlled trial with allocation concealment; "grade II"–level evidence if they reported data from a randomized, placebo-controlled trial without adequate allocation concealment; "grade III"–level evidence if they presented data from an observational study; and "grade IV"–level evidence if they presented data from a case series or case report. Additionally, among the validation studies, the 2 reviewers independently assessed for bias in reporting of diagnostic test results, using the Quality Assessment of Diagnostic Accuracy Studies tool[21] as recommended in the

Standards for the Reporting of Diagnostic Accuracy statement.[22] Among the validation studies, the 2 reviewers also independently determined quality ratings according to the following criteria described by Wei et al[23]: "adequacy of the reference standard rating (ie, comprehensive assessment for delirium), blinded assessment (ie, no shared information between CAM [Confusion Assessment Method] rater and reference standard), close proximity of assessments between CAM rater and the reference standard assessment (≤8 hours), inclusion of false-positive challenges (eg, dementia, depression, and other psychiatric conditions), and inclusion of false-negative challenges (eg, patients with normal mental status, without psychiatric conditions)." According to this methodology, we assigned 1 point for each met criterion, whereas we allowed one-half point for each partially met criterion. Criteria scores were then combined for each validation study. Any disagreements on scoring were discussed between reviewers until consensus on final criteria scores was achieved.

RESULTS

In our initial search of the databases, we identified 2,666 titles (Figure). In this process, we found that the same titles emerged from different sources, suggesting saturation of all available articles. After full review, 22 articles ultimately met all of the inclusion criteria and were included in this systematic review. All of these articles described studies that provided information that addressed the use of screening instruments for delirium identification within the ED, whereas 3 of these articles simultaneously provided information about the optimal timing of a delirium screening process in the ED. Among the articles providing information about the identification of delirium in the ED, 2 were validation studies of a screening instrument in the ED, whereas 20 were application studies of screening tools.

Among the reviewed articles, delirium was identified among ED patients with 7 different instruments: the CAM,[24] the Confusion Assessment Method–ICU (CAM-ICU),[25] the Confusion Assessment Method–Emergency Department (CAM-ED),[23] the Organic Brain Syndrome Scale,[26] the Diagnostic and Statistical Manual criteria, the Delirium Rating Scale,[27] and the NEECHAM Confusion Scale.[28] The CAM was the most frequently used instrument (11 studies), whereas the CAM-ICU was the second most commonly used (6 studies). The CAM requires raters to assess 9 delirium elements and takes approximately 5 minutes to complete. The CAM-ICU is an adaptation of the CAM that includes nonverbal items, requires assessment of 4 cardinal features of delirium, and has been validated in the ICU population. The CAM-ED is another adaptation of the CAM and adds attention tasks to the original CAM instrument. The Organic Brain Syndrome Scale consists of 2 subscales with 15 questions and 39 clinical items. The Delirium Rating Scale requires the completion of a 10-item scale based on all information available to the rater. The NEECHAM Confusion Scale consists of 3 subscales and assesses patients on their cognitive status, observed behavior and performance at tasks, and their "vital status."

The CAM has been used extensively in the ED literature to identify older adults with delirium (Table 2). In these applications, the tool has been used to establish the prevalence of delirium among seniors,[5,8,9] to identify the proportion of older adults with delirium who arrive by EMS,[29] to assess documentation rates for delirium and the effect of delirium screening on those rates,[9,10] to determine whether routine mental status screening can identify delirium early in an ED visit,[30] and to identify the long-term sequelae of delirium.[6,31]

In these studies using the CAM, investigators reported delirium prevalence rates in the ED among elderly adults ranging from 0.6% to 24%. In the case of the study[29] that reported a delirium prevalence rate of 0.6%, the authors noted that this number may be "artificially low" and raised the possibility that other screening tools, such as the CAM-ICU, may be more appropriate for the ED environment.

In a series of studies, Han et al[11,32-35] investigated the prevalence, associated characteristics, and consequences of delirium in the ED among older adults with the second most frequently used screening instrument, the CAM-ICU. In a separate study, Carpenter et al[36] evaluated the performance of a battery of screening tests to detect cognitive impairment among seniors, including an assessment for delirium with the CAM-ICU. A validation of the CAM-ICU for use in the ED among older adults was not presented in any of these investigations. In their studies, Han et al[11,32-35] reported delirium prevalence rates between 8.3% and 37.9% among selected subsets of older ED visitors. By comparison, Carpenter et al[36] found that 5.5% of their ED study population experienced delirium.

In one study,[7] a separate group of investigators used a third instrument, the CAM-ED, to establish the prevalence of delirium among older adults in the ED and to assess the sensitivity of an emergency physician's documentation of the condition. With the CAM-ED, 10% of patients were judged to have delirium or "probable" delirium. A validation of this instrument, however, was not presented in this original study, nor was one identified in this systematic review.

Finally, in a Turkish study, investigators used the evaluation by an emergency medicine resident and neurologist applying the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) criteria to investigate the clinical characteristics of older (≥65 years) and younger (≤65 years) adults with delirium.[37] No data were provided in this article to calculate a delirium prevalence rate, though delirium was found in equal numbers of patients between the 2 groups, with 21 cases among older adults and 22 cases among younger adults.

In 4 articles, delirium screening tools were used to identify patients for further study, but not to evaluate either delirium screening test performance or delirium prevalence rates. In the first article,[38] as part of their efforts to identify prospectively those factors that extend hospital length of stay, investigators screened older adults in the ED for delirium, using the Delirium Rating Scale. Though a prevalence rate of delirium in the ED was not presented, the authors demonstrated a connection between

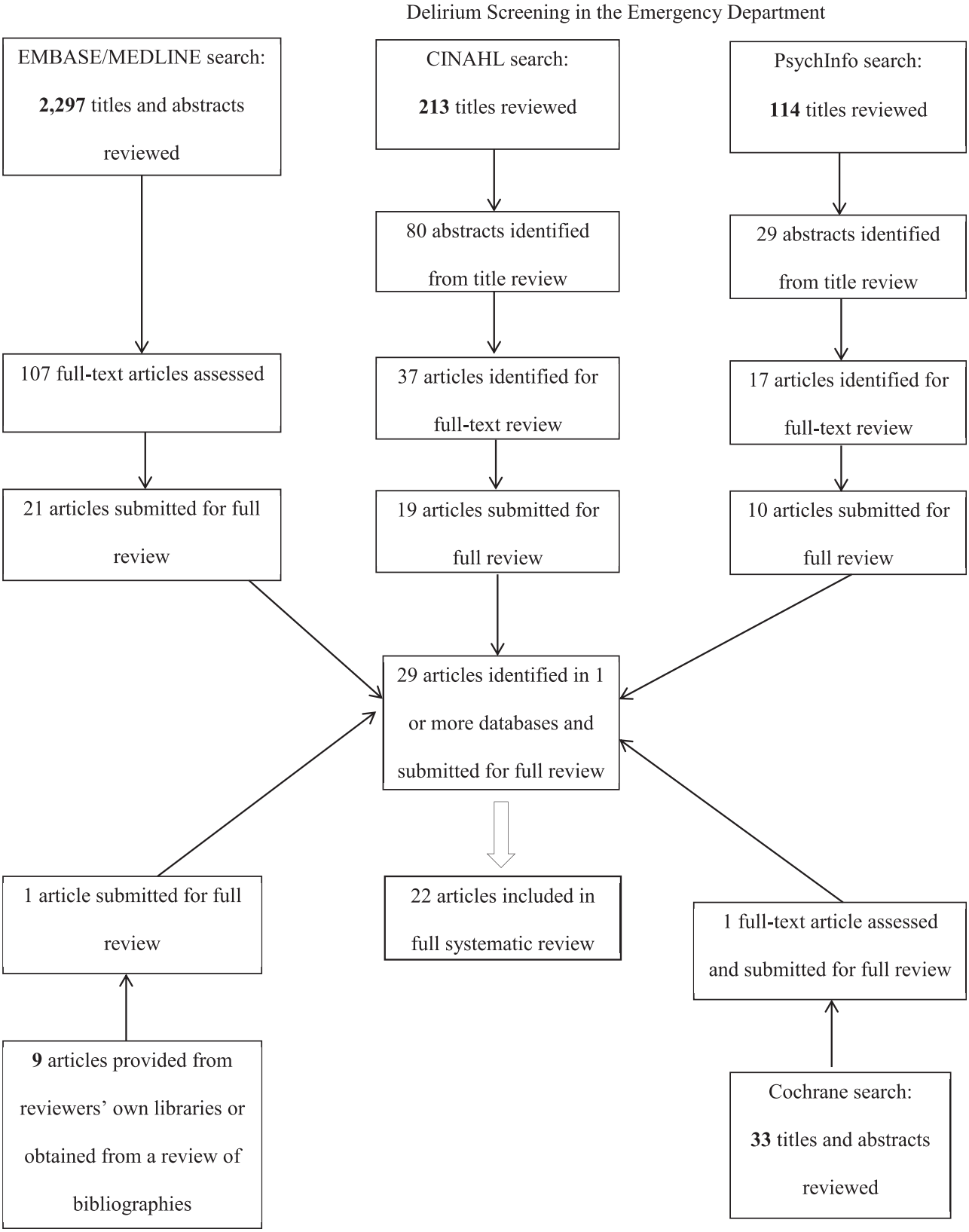

Figure. Search results and selection of studies for systematic review.

Table 2. Application studies of delirium screening instruments.

Instrument	Study	Publication Date	Country	Use	Finding
Prospective identification of delirium					
CAM	Elie et al	2000	Canada	Establish prevalence of delirium in ED. CAM administered by research psychiatrist.	Delirium prevalence 9.6% (95% CI 6.9%–12.4%)
	Hare et al	2008	Australia	Evaluate whether routine mental status screening can identify delirium early in an ED visit. CAM administered by research nurse.	Nurse-led assessment of cognition is feasible; delirium was present in 3 of 28 patients (10.7%)
	Hustey and Meldon	2002	United States	Establish prevalence and documentation rate of delirium in ED. CAM administered by research assistants.	10% of patients were delirious (95% CI 7%–14%); 17% had cognitive impairment noted (95% CI 9%–27%)
	Hustey et al	2003	United States	Assess documentation rates for delirium and effect of delirium screening on its recognition. CAM assessment performed by research assistant.	7% of patients were delirious (95% CI 4%–11%); 16% of delirious patients were recognized (95% CI 3%–40%); screening changed management plans in no cases
	Kakuma et al	2003	Canada	Establish whether prevalent delirium is risk factor for mortality. CAM assessment performed by research assistant.	Patients discharged from ED with delirium undetected have higher mortality
	Naughton et al	1995	United States	Determine prevalence of delirium in ED. CAM assessment performed by research assistant.	24% of patients >70 y were delirious
	Shah et al	2011	United States	Establish rate of delirium and other cognitive impairment among older adults arriving by EMS. CAM assessment performed by study staff.	0.6% of patients were found to be delirious
	Vida et al	2006	Canada	Establish relationship between delirium and later ADLs, basic ADLs, IADLs. CAM assessment performed by research assistant.	Delirium alone is not a predictor of poorer functional outcome
CAM-ICU	Carpenter et al	2011	United States	Identify delirious patients during evaluation of several other cognitive screening instruments. CAM-ICU assessment performed by research assistant.	5.5% of patients had delirium
	Han et al	2009	United States	Establish recognition, risk factors, and subtypes of delirium. CAM-ICU assessment performed by research assistant.	8.3% of patients were delirious; delirium was missed in 76% of cases
	Han et al	2009	United States	Evaluate whether nursing home patients are at greater risk for delirium in the ED. CAM-ICU assessment performed by research assistant.	37.9% of nursing home patients were delirious vs 5.7% of non–nursing home patients
	Han et al	2010	United States	Evaluate whether delirium is an independent predictor of death within 6 mo. CAM-ICU assessment performed by research assistant.	17.2% of patients were delirious; delirium is an independent predictor of 6-mo mortality
	Han et al	2011	United States	Assess whether delirium is predictor of hospital length of stay. CAM-ICU assessment performed by research assistant.	17% of patients were delirious; delirium is an independent predictor of hospital length of stay
	Han et al	2011	United States	Analyze the effect of delirium on accuracy of chief complaint and understanding of discharge instructions. CAM-ICU assessment performed by research assistant.	Patients with delirium superimposed on dementia had less accurate chief complaints and understood their discharge instructions less frequently
CAM-ED	Lewis et al	1995	United States	Evaluate the sensitivity of a conventional assessment for detecting delirium. CAM-ED assessment performed by research assistant.	10% of patients had delirium or probable delirium; 17% of cases were identified by emergency physicians' records
DSM-IV criteria	Duran and Aygün	2012	Turkey	Classify delirium according to its cause in older and younger adult populations. DSM criteria applied by emergency resident and neurologist.	Metabolic disorders were the most common cause of delirium in the 21 older adults and 22 younger adults with delirium.

Table 2. Continued.

Delirium identification used to identify patients for further study					
Instrument	**Study**	**Publication Date**	**Country**	**Study Aim**	**Notes**
OBS Scale	Bjorkelund et al	2010	Sweden	Evaluate whether a multifactorial program can reduce delirium among elderly hip fracture patients. OBS performed by research investigator.	Patients with delirium at admission excluded from study
NEECHAM	Milisen et al	2001	Belgium	Test the effect of nurse-led program for delirium on patient outcomes. NEECHAM performed by nurses.	Screening of patients for delirium occurred in ED
Delirium Rating Scale	Saravay et al	2004	United States	Identify cause of extended length of stay in elderly hospitalized patients. Unclear who administered DRS.	Delirium identified at admission in the ED is associated with greater length of stay
CAM	Shapiro et al	2001	United States	To assess functional decline for older adults after minor traumatic injury. Unclear who administered CAM.	Patients with delirium were excluded from the study

ADLs, activities of daily living; *IADLs*, instrumental activities of daily living; *OBS*, Organic Brain Syndrome Scale.

delirium in the ED, clinical and behavioral complications during a patient's hospitalization, and longer hospital length of stay.

In a second study,[39] investigators from Scandinavia identified delirium among patients admitted with hip fracture from the ED, using the Organic Brain Syndrome scale. No specific numbers for delirium identification with the scale in the ED were presented. In a similar manner, investigators from Belgium used the NEECHAM Confusion Scale to identify delirium among older adults who had experienced a hip fracture.[40] In this study, the primary nurse screened for delirium with the NEECHAM Confusion Scale, whereas the CAM was used to confirm the diagnosis of delirium. The proportion of cases of delirium that were identified within the ED, however, was not presented.

One final study[41] used the CAM to exclude older adults with delirium who presented with trauma to a US ED. The study investigated functional decline after minor injury in older adults but did not present data on the number of adults who were excluded from the study or who were identified with delirium.

The studies analyzed in this systematic review were of heterogenous design. The studies were judged to provide level III evidence according to the Grading of Recommendations Assessment, Development and Evaluation criteria.

The studies identified in this review reported delirium rates ranging between 0.6% in the general population of older adults treated in one ED[29] to 37.9% among nursing home patients treated in another ED.[34] Delirium, however, was most frequently reported as occurring in 7% to 10% of older adults assessed in the ED.[7-11,25] In the studies in which provider recognition of delirium was assessed, providers identified between 16% and 17%[7,10] and 35%[8] of cases of delirium in older adults.

Though 7 tools were identified in this review, only 1 instrument, the CAM, was validated in a population of seniors visiting the ED, first in a Canadian study and later in a Brazilian study (Table 3). In the Canadian study (21 patients considered delirious of 110 screened),[42] the investigators first compared the results of CAMs performed by lay interviewers to geriatricians' CAM results. Then, the investigators further compared the geriatrician's CAM to his or her evaluation of the patient, using the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised* (*DSM-III-R*) and *DSM-IV* criteria, as well as with his or her clinical judgment of whether delirium was present. Using the geriatrician's CAM as the reference standard, the sensitivity and specificity, respectively, of a lay interviewer's CAM assessment were 0.86 and 1.00. κ Statistics were reported for the agreement of the geriatrician's CAM with the *DSM-III-R* (0.86; 95% confidence interval [CI] 0.43 to 1.12), *DSM-IV* (0.97; 95% CI 0.78 to 1.16), and clinical impression (0.94; 95% CI 0.76 to 1.13).

In the Brazilian study (17 patients considered delirious of 100 screened),[43] the results of the Portuguese-language version of the CAM administered by a geriatrician were compared with the results of an independent evaluation by a psychiatrist, who applied the *DSM-IV* criteria within 2 hours of the geriatrician's assessment. In this analysis, the CAM displayed a sensitivity of 0.94 and specificity of 0.96. In a second analysis, the

Table 3. Validation studies of delirium screening instruments.

Instrument	Study	Publication Date	Country	Performance Characteristics	Quality Rating*
CAM	Monette et al	2001	Canada	κ Scores for reliability between CAM and *DSM-III-R* (0.86; 95% CI 0.43–1.12), *DSM-IV* (0.97; 95% CI 0.78–1.16), and clinical impression (0.94; 95% CI 0.76–1.13). CAM performed by geriatrician and lay interviewer.	4.5 of 5 quality points
CAM (Portuguese)	Fabbri et al	2008	Brazil	CAM displayed a sensitivity of 0.94 and specificity of 0.96 compared with a psychiatrist's evaluation with the *DSM-IV* criteria. CAM was administered by a geriatrician.	2.5 of 5 quality points

*Quality points assigned according to methodology of Wei et al[23]: 1 point each for "adequacy of the reference standard, blinded assessment, close proximity of assessments between CAM rater and the reference standard assessment, inclusion of false-positive challenges, and inclusion of false-negative challenges."

investigators sought to establish the interobserver reliability of the CAM by comparing a subset of evaluations by the geriatrician with a second clinician's evaluation performed concurrently. Among the 24 patients evaluated in this manner, the geriatrician and clinician agreed in their delirium assessments in 22 of 24 cases, yielding a κ score of 0.70.

Because of the small number of validation studies, the differences in study designs, and the potential differences between these 2 ED environments, we did not calculate pooled sensitivity and specificity statistics for the CAM. In our analysis, we found the studies' validation procedures to be of heterogeneous quality, with the Canadian study earning 4.5 validation quality points and the Brazilian study earning 2.5 validation quality points (out of 5 maximum). These 2 studies were determined to constitute grade III evidence, applying the Grading of Recommendations Assessment, Development and Evaluation methodology, and each had 10 of 14 positive responses to the questions used in the Quality Assessment of Diagnostic Accuracy Studies assessment tool (Appendix E1, available online at http://www.annemergmed.com).

Three studies provided information to assess the optimal screening interval(s) during which a delirium screening process might be timed. In a pair of studies, Han et al[11,34] evaluated patients for delirium at arrival and then 3 hours later, using the CAM-ICU. In the first of these studies, 32 of 341 patients (9.4%) who sought care in the ED had positive CAM-ICU assessments initially, whereas 6 of 90 patients (6.7%) who underwent an assessment at 3 hours were subsequently found to have newly identified delirium.[30] In the second study,[11] 21 of 376 older adults (6.9%) initially had a positive CAM-ICU test result. Among the 82 (27.1%) patients who then underwent a second assessment with the CAM-ICU at 3 hours, an additional 4 patients (4.9%) were newly found to be delirious.

The third study used a different design to evaluate the effect of mental status screening on the care plans for delirious older adults in the ED.[10] Though the study did not use serial evaluations of patients for delirium as the previous studies had, it did provide information on the effect of the disclosure of delirium screening results to emergency physicians at the end of a visit. During the investigation, the research team assessed for delirium at enrollment in the ED but did not share these assessments with the patients' emergency physicians until after a disposition and care plan had been developed. Following this protocol, the authors found that ED providers recognized delirium in only 3 of 19 (16%) patients identified by CAM testing, but that when the results of the investigators' delirium testing were shared with providers, none of the original management or discharge plans were changed. Following through on their original management plans, the emergency providers discharged home 5 of the 19 patients who were discovered to be delirious by the research team. This finding suggests that delirium screening results may need to be provided earlier in the ED stay to affect provider behavior.

LIMITATIONS

Our study may be limited by its search strategy, its inclusion of articles printed only in English, and publication bias. Additionally, our review was conducted without the involvement of a research librarian, though a member of our research team has conducted previous systematic reviews. To limit these potential biases, we hand-searched reference lists for potential additional articles and searched multiple scientific databases. Our review deviated from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines as applied to systematic reviews in that we did not register our systematic review and have not placed a copy of our review protocol online, though our methods are described in this article. Finally, the reports identified in this systematic review provide details on the efficacy of these screening tools' use during clinical investigations, though their effectiveness and performance characteristics in daily clinical use have yet to be demonstrated.

DISCUSSION

This review provides a comprehensive outline of the use of delirium screening instruments in studies conducted in EDs and the out-of-hospital environment, both nationally and internationally, during the last several decades. Furthermore,

it identifies those screening tools that have been used in epidemiologic studies of delirium, those delirium screening instruments that have been validated for use in the ED, and the body of evidence that exists to support when a delirium screening process should be conducted during the course of an older adult's ED visit. Our review identifies that there is a lack of delirium assessment tools that have been validated for use in the ED and a paucity of evidence to guide practitioners on the optimal timing of a delirium screening assessment, despite a call by geriatric emergency medicine experts more than 10 years ago for brief delirium assessments to be developed for the ED and for further research to be conducted in this area.[13]

From this review, it is clear that older adults in the ED are frequently delirious and also that emergency providers' recognition of delirium has not appeared to improve much despite an increase in literature on the topic. It is possible, though not proven, that delirium frequently goes unrecognized among older adults in the ED in part because of the lack of a validated and brief instrument for delirium identification there, as well as a lack of recognition among providers of the potential consequences of a missed delirium diagnosis. As this review highlights, there are dangers associated with undetected delirium. Initial evidence shows that older adults who are discharged from the ED with their delirium unidentified are at greater risk of death in the next 6 months than those patients whose delirium is recognized[6] and that delirium is an independent predictor of death among older adults seeking care in the ED.[35] These findings, demonstrating a link between delirium and mortality, are consistent with results observed in other populations of individuals affected by delirium in the hospital setting.[44,45] Consequently, this systematic review underscores opportunities to improve the quality and organization of ED and out-of-hospital care that is provided to older adults with delirium.

A variety of tools have been used to identify delirium among older adults in ED research studies, though to date only 1, the CAM, has undergone initial validation, albeit in relatively small study populations and in studies that did not strictly follow the Standards for the Reporting of Diagnostic Accuracy criteria. Indeed, the CAM is extensively used and has gained wide acceptance in the research community for use in multiple clinical venues,[23] though it is unclear how frequently it is used in clinical practice within the ED. More recently, it has been argued by some that the CAM-ICU may be the preferred standard for delirium identification in the ED,[36] though the CAM-ICU's validation in the ED is still ongoing.[46] Given its ease of use and its short length, the CAM-ICU may indeed be well suited for use by ED providers.[46] However, in light of recent evidence suggesting that the CAM-ICU may not perform as well as expected outside of the ICU setting,[47] we believe the separate validation of the CAM-ICU for use in the ED is necessary.

Beyond the CAM and the CAM-ICU, other promising delirium assessments exist, including the Delirium Diagnostic Tool–Provisional and the Single Question in Delirium. These instruments were investigated in patients with traumatic brain injury and in hospitalized patients, respectively,[48,49] and may deserve evaluation in the ED, given their brevity and performance characteristics in initial studies. More recently, other delirium assessment tools, including the Emergency Department Delirium Triage Screen and the Brief Confusion Assessment Method, have been presented at scientific conferences,[50,51] though their assessments have not been published yet, to our knowledge, in peer-reviewed journal article formats. Beyond these, a randomized controlled trial from Australia will evaluate new criteria for the diagnosis of delirium against the CAM among patients receiving care in an ED.[52] Criteria that may aid in the refinement of delirium assessment tools have been described in the literature[53] and may be useful during the development of new delirium screening tools for the ED and out-of-hospital environments.

Even with a validated screening instrument, the performance of delirium assessment may still be influenced by timing considerations, including when the syndrome is most readily detected and when the results are most useful to emergency providers. By definition, delirium is a condition that is marked by fluctuations in mental status over time. In the majority of studies evaluated in this review, investigators assessed patients' mental status at one time only. In 2 studies, though, a set of investigators made repeated patient observations to demonstrate that a small but significant proportion of adults who were not initially identified as delirious were found to be so when testing was repeated 3 hours later. These findings suggest a potential benefit to screening for delirium at multiple points during the course of a patient's ED visit to maximize the syndrome's identification. However, inadequate evidence exists to define the ideal schedule for conducting the repeated testing. The optimal frequency and manner of delirium testing will ultimately need to be established, of course, with sensitivity to time, personnel, and resource allocation considerations of the busy ED environment. New research should seek to identify the critical junctures in care when delirium testing could be performed to improve its recognition. If delirium is detected, there are a variety of interventions that have been developed and applied in other areas of the hospital, including the Delirium Room and the Hospital Elder Life Program, that in concept might be adapted to the ED environment and affect patient-oriented outcomes.[54-56]

The timing of any delirium assessment should also take into account when its results might be most useful to the clinician. The findings of Hustey et al[10] suggest that emergency physicians are not influenced in their management decisions by the results of standardized cognitive testing for delirium if that testing is shared after a patient's disposition and plan of care have been determined. It remains possible, yet untested, that standardized delirium assessments that are shared with providers earlier in the course of an ED visit will positively influence patient management and outcomes. Research will be needed to answer this question conclusively.

In summary, the recognition of delirium by providers appears to be central to the management and provision of appropriate care to affected older adults in the ED. Two delirium screening

tools have been identified as being most frequently used in the literature, though only 1 tool, the CAM instrument, has undergone initial validation for use in the ED environment. Minimal evidence exists to suggest the optimal timing of delirium assessment(s) to maximize its identification, though repeated delirium testing appears necessary. To move the field of delirium identification and management forward within the ED, we believe a series of concrete steps will be needed. As identified by others, a brief tool for delirium screening that has been appropriately validated in the ED will likely be needed, as well as further education of emergency professionals about the importance of delirium recognition. In particular, delirium identification has been identified by emergency medicine and geriatric educators as a potential core competency for graduating emergency medicine residents.[57] However, given that practice change requires more than just education[58] and occurs most effectively when multifaceted strategies are used,[59] the adoption of an improved system of care for the management of potentially delirious patients may be needed. Multicomponent, proactive systems of care that work to mitigate the impact of delirium on patient's health and health care use have been shown to be effective in other areas of the hospital outside of the ED.[54,60] Future research on the identification and management of delirium in the ED should build on the important work conducted to date in this field and should potentially occur under the purview of a national body that may promote coordinated efforts with validated patient-oriented outcome instruments across a variety of sites. Patients who are at high risk of poor outcomes from the sequelae of delirium, including seniors and other vulnerable adults, should be targeted for study within this research program.

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Appendix E1.

Quality Assessment of Diagnostic Accuracy Studies tool results

Study: Fabrri, 2008

Item	Reviewer 1 Response (M.A.L.)	Reviewer 2 Response (F.C.M.)	Final Response After Discussion
Was the spectrum of patients representative of the patients who will receive the test in practice?	Yes	Yes	Yes
Were selection criteria clearly described?	Yes	Yes	Yes
Is the reference standard likely to correctly classify the target condition?	Yes	Yes	Yes
Is the period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the 2 tests?	Yes	Yes	Yes
Did the whole sample or a random selection of the sample receive verification using a reference standard of diagnosis?	Yes	Yes	Yes
Did patients receive the same reference standard regardless of the index test result?	Yes	Yes	Yes
Was the reference standard independent of the index test (ie, the index test did not form part of the reference standard)?	Yes	Yes	Yes
Was the execution of the index test described in sufficient detail to permit replication of the test?	Yes	Yes	Yes
Was the execution of the reference standard described in sufficient detail to permit its replication?	Yes	Yes	Yes
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	Unclear	Unclear
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes	Unclear	Unclear
Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	Yes	Yes
Were uninterpretable/intermediate test results reported?	Unclear	Unclear	Unclear
Were withdrawals from the study explained?	Yes	Unclear	Unclear
Calculated κ score	0.32		

Quality Assessment of Diagnostic Accuracy Studies tool results.

Study: Monette, 2001

Item	Reviewer 1 Response (M.A.L.)	Reviewer 2 Response (F.C.M.)	Final Response After Discussion
Was the spectrum of patients representative of the patients who will receive the test in practice?	Yes	Yes	Yes
Were selection criteria clearly described?	Yes	Yes	Yes
Is the reference standard likely to correctly classify the target condition?	Yes	Unclear	Yes
Is the period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the 2 tests?	Yes	Yes	Yes
Did the whole sample or a random selection of the sample receive verification using a reference standard of diagnosis?	Yes	No	No
Did patients receive the same reference standard regardless of the index test result?	Yes	No	No
Was the reference standard independent of the index test (ie, the index test did not form part of the reference standard)?	Yes	Yes	Yes

Appendix E1. Continued.

Quality Assessment of Diagnostic Accuracy Studies tool results.

Study: Monette, 2001

Item	Reviewer 1 Response (M.A.L.)	Reviewer 2 Response (F.C.M.)	Final Response After Discussion
Was the execution of the index test described in sufficient detail to permit replication of the test?	Yes	Yes	Yes
Was the execution of the reference standard described in sufficient detail to permit its replication?	Yes	Yes	Yes
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	Unclear	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes	Unclear	Yes
Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	Yes	Yes
Were uninterpretable/intermediate test results reported?	Unclear	Unclear	Unclear
Were withdrawals from the study explained?	Yes	No	No
Calculated κ score	0.17		

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A MULTICOMPONENT INTERVENTION TO PREVENT DELIRIUM IN HOSPITALIZED OLDER PATIENTS

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ABSTRACT

Background Since in hospitalized older patients delirium is associated with poor outcomes, we evaluated the effectiveness of a multicomponent strategy for the prevention of delirium.

Methods We studied 852 patients 70 years of age or older who had been admitted to the general-medicine service at a teaching hospital. Patients from one intervention unit and two usual-care units were enrolled by means of a prospective matching strategy. The intervention consisted of standardized protocols for the management of six risk factors for delirium: cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment, and dehydration. Delirium, the primary outcome, was assessed daily until discharge.

Results Delirium developed in 9.9 percent of the intervention group, as compared with 15.0 percent of the usual-care group (matched odds ratio, 0.60; 95 percent confidence interval, 0.39 to 0.92). The total number of days with delirium (105 vs. 161, P=0.02) and the total number of episodes (62 vs. 90, P=0.03) were significantly lower in the intervention group. However, the severity of delirium and recurrence rates were not significantly different. The overall rate of adherence to the intervention was 87 percent, and the total number of targeted risk factors per patient was significantly reduced. Intervention was associated with significant improvement in the degree of cognitive impairment among patients with cognitive impairment at admission and with a significant reduction in the rate of use of sleep medications among all patients. Among the other risk factors, there were trends toward improvement in immobility, visual impairment, and hearing impairment.

Conclusions The risk-factor intervention strategy that we studied resulted in significant reductions in the number and duration of episodes of delirium in hospitalized older patients. The intervention had no significant effect on the severity of delirium or on recurrence rates; this finding suggests that primary prevention of delirium is probably the most effective treatment strategy. (N Engl J Med 1999;340:669-76.)

DELIRIUM, also known as acute confusional state, is a common, serious, and potentially preventable source of morbidity and mortality among hospitalized older patients.[1-3] Delirium has particular importance because patients over 65 years of age account for more than 48 percent of all days of hospital care.[4] Each year, delirium complicates hospital stays for more than 2.3 million older people, involves more than 17.5 million inpatient days, and accounts for more than $4 billion (in 1994 dollars) of Medicare expenditures.[5] Substantial additional costs accrue after discharge from the hospital, because of the increased need for institutionalization, rehabilitation, and home care.[6,7] Moreover, the incidence of delirium will probably increase with the aging of the population.[8]

Previous interventional studies of delirium have focused on four types of intervention: general geriatric approaches,[9-14] nursing care,[15-19] family interventions,[20] and anesthesia.[21-23] Although in most of the studies there were trends toward a reduction in delirium in the intervention group, in most cases the reduction was not statistically significant. Many studies had methodologic limitations, such as small samples, use of nontargeted interventions, and use of relatively insensitive outcome measures (e.g., screening mental-status tests or confusion checklists). Finally, most previous studies focused on the treatment of delirium rather than on primary prevention, which was the goal of the present study.

Rarely is delirium caused by a single factor; rather, it is a multifactorial syndrome, resulting from the interaction of vulnerability on the part of the patient

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(i.e., the presence of predisposing conditions, such as cognitive impairment, severe illness, or visual impairment) and hospital-related insults (i.e., medications and procedures).[1,24] The risk of delirium increases with the number of risk factors present.[24,25] Therefore, a multicomponent approach targeted to the patient's risk factors is the most clinically relevant and potentially effective intervention for delirium.

We conducted a controlled clinical trial of a multicomponent strategy to reduce the number of risk factors for delirium with the goal of preventing delirium in hospitalized older patients. Our aims were to compare the effectiveness of a multicomponent strategy for reducing the risk of delirium with that of a usual plan of care for hospitalized older patients, to determine the level of adherence to the intervention protocol, and to measure the effect of the intervention on the targeted risk factors.

METHODS

Study Design

This controlled clinical trial used prospective, individual matching to compare patients admitted to one intervention and two usual-care (control) units at a teaching hospital. Random assignment of subjects to the intervention or usual-care units was not possible because of the large number of patients in all medical units during the time of the study. A pilot study confirmed that randomization was not feasible, because beds in the units intended for study were often unavailable.

The prospective, individual matching strategy was chosen as an alternative to randomization that would ensure that patients in our study groups were comparable at base line. This strategy has been described in detail previously.[26] In brief, all the subjects in the intervention unit who met the eligibility criteria were enrolled. Concurrently, eligible patients from two usual-care units were identified, so that the subject pool was sufficiently large to permit the use of a computerized algorithm[27] designed to match patients according to age within five years, sex, and base-line risk of delirium (intermediate or high) as defined by our previously developed predictive model.[25] The predictive model included four of the risk factors for delirium: visual impairment, severe illness, cognitive impairment, and a high ratio of blood urea nitrogen to creatinine. Intermediate risk was defined as the presence of one or two risk factors at base line, and high risk as the presence of three or four risk factors at base line. The matching factors were selected because previous work had established them as important predictors of the development of delirium.[25,28] To control for changing patterns of care over time, patients in the intervention group and matched usual-care patients were required to have been admitted within 180 days of each other. The computerized algorithm matched patients prospectively, strictly on the basis of their characteristics at admission.

Setting and Patients

Potential participants in the study were consecutive patients admitted to the general-medicine service (non-intensive care) at Yale–New Haven Hospital from March 25, 1995, through March 18, 1998. Yale–New Haven Hospital, an 800-bed urban teaching hospital with 200 medical beds, serves a large number of patients from the community as well as a population of referred patients. A total of 2434 patients were potentially eligible to participate: they were admitted to one of three general-medicine units, were at least 70 years old, had no delirium at the time of admission, and were at intermediate or high risk for delirium at base line. Of these, 1265 patients were excluded because of inability to participate in interviews (because of profound dementia that precluded verbal communication [154 patients], a language barrier [92], profound aphasia [38], or intubation or respiratory isolation [14]), coma or terminal illness (69 patients), a hospital stay of 48 hours or less (219), prior enrollment in this study (324), or other reasons (e.g., unavailability of an interviewer or unavailability of the patient because of examinations or procedures elsewhere in the hospital) (355). Of the remaining 1169 eligible patients, the patient, family, or physician refused enrollment in 250 cases and a matching patient could not be found in 67 cases. Thus, the final study sample included 852 patients, who were matched as 426 pairs of patients receiving the study intervention and usual care.

The 1265 patients who were excluded did not differ significantly from the 852 patients who were enrolled in terms of age, sex, or base-line risk of delirium; however, a larger proportion of patients receiving usual care were excluded (63 percent, vs. 50 percent in the intervention group; $P=0.001$), mainly because more patients were available for screening in the two usual-care units. The 250 patients who declined to participate did not differ significantly from the 852 who enrolled in terms of age, sex, base-line risk of delirium, or group assignment. Of the 919 qualified patients who agreed to enroll, 67 (7 percent) could not be matched (24 in the intervention group and 43 in the usual-care group). These 67 unmatched patients, as compared with the 852 enrolled patients, were significantly older (mean age, 84 and 80 years, respectively), had a higher risk of delirium at base line (high risk, 42 percent vs. 28 percent), and were more likely to be admitted to a usual-care unit (64 percent vs. 50 percent). These differences were due to the inherent difficulty of finding matches for patients who were at extreme ends of the matching criteria (e.g., extremely old); patients receiving usual care predominated because of the matching algorithm, which kept a pool of unmatched patients receiving usual care available to facilitate subsequent matching.

Informed consent for participation was obtained orally from the patients or, for those with substantial cognitive impairment, from a proxy (usually the closest relative), according to procedures approved by the institutional review board of the Yale University School of Medicine.

Assessments

All the assessments were carried out by members of a research staff who had no role in the intervention and who were unaware of the nature of the study and of the patients' group assignments. The staff was composed of research nurses and experienced clinical researchers, all of whom underwent intensive training and followed standard procedures outlined in a detailed training and coding manual. At base line, standardization of assessments and measurements of interrater reliability verified the consistency of ratings among all the staff members. Subsequently, researchers met monthly to review procedural and coding issues. Quality checks of interviews and assessments of the interrater reliability with respect to the primary outcomes and targeted risk factors were performed every six months. All the data were collected on standardized, precoded forms, and the data were entered twice into a computerized data base and underwent extensive checks of error and validity.

The screening interview included the Mini–Mental State Examination,[29] the Digit Span Test,[30] evaluation by the Confusion Assessment Method,[31] assessment of Katz's Activities of Daily Living,[32] the standard Jaeger test for vision, and chart review to determine the Acute Physiology, Age, and Chronic Health Evaluation (APACHE II) score.[33] The Mini–Mental State Examination measures cognitive functioning on a scale of 0 (poor) to 30 (excellent), with a score of less than 24 indicating cognitive impairment. The orientation score consists of the 10 orientation items on the Mini–Mental State Examination, each scored on a scale of 0 to 10, with a score of less than 8 indicating disorientation. The Digit Span Test measures attention span on a scale of 0 to 7, with lower scores indicating inattention. Evaluation of Katz's

Activities of Daily Living assesses the ability to perform seven basic-care skills (feeding, bathing, grooming, dressing, using the toilet, transferring between bed and chair, and walking) on a scale of 0 to 14, with lower scores indicating functional impairment.

Eligible patients then underwent the base-line assessment, which included the collection of demographic data, assessment of instrumental activities of daily living,[34] the Whisper Test[35] for hearing, and assessment of sleep. Visual impairment was defined as binocular near vision, after correction, worse than 20/70 as measured by the standard Jaeger test. The APACHE II score measures severity of illness on a scale of 0 to 71, with higher scores indicating increased severity. The instrumental Activities of Daily Living scale assesses the ability to perform seven complex activities (using the telephone, grocery shopping, using transportation, cooking, housekeeping, taking medications, and handling finances) on a scale of 0 to 14, with lower scores indicating functional impairment. The Whisper Test measures hearing according to the number of 12 whispers heard, with 6 or fewer indicating hearing impairment. A family member was interviewed at the time of admission and asked to describe the patient's cognitive functioning before admission and any recent cognitive changes and to complete the modified Blessed Dementia Rating Scale,[36,37] an observer-rated score that correlates directly with the number of neuritic plaques found on postmortem examination of the brain. The modified (shortened) version has been tested[37]; scores greater than 2 on the modified Blessed Dementia Rating Scale indicate possible dementia. A ratio of blood urea nitrogen to creatinine (both measured in milligrams per deciliter) of 18 or greater was used as an index of dehydration. Screening and base-line assessments were completed within 48 hours after admission.

Subsequently, patients were evaluated daily until discharge with a structured interview consisting of the Digit Span Test, Mini–Mental State Examination, and Confusion Assessment Method rating. On hospital day 5 or at discharge (if discharge was before day 5), patients were reassessed for risk factors for delirium (Table 1). After discharge, medical records were reviewed for evidence of delirium, final diagnoses, medications, laboratory results, and destination after discharge.

Intervention

The intervention strategy, called the Elder Life Program, was implemented by a trained interdisciplinary team, which consisted of a geriatric nurse-specialist, two specially trained Elder Life specialists, a certified therapeutic-recreation specialist, a physical-therapy consultant, a geriatrician, and trained volunteers. The performance of each staff member, including volunteers, was evaluated quarterly, with completion of checklists to ensure competency and consistent and complete adherence to all intervention protocols.

Six risk factors for delirium were targeted for intervention: cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment, and dehydration.[24,25,28,38] These factors were selected on the basis of evidence of their association with the risk of delirium and because they were amenable to intervention strategies considered feasible in the context of current hospital practice. Table 1 describes the risk group that received each intervention, the standardized intervention protocols for each risk factor, and the targeted outcome for each intervention protocol.

Usual Care

Usual care consisted of standard hospital services provided by physicians, nurses, and support staff (e.g., physical therapists, pharmacists, and nutritionists) in the other general-medicine units. Members of the intervention team did not provide services

TABLE 1. RISK FACTORS FOR DELIRIUM AND INTERVENTION PROTOCOLS.

TARGETED RISK FACTOR AND ELIGIBLE PATIENTS	STANDARDIZED INTERVENTION PROTOCOLS	TARGETED OUTCOME FOR REASSESSMENT
Cognitive impairment*	Orientation protocol: board with names of care-team members and day's schedule; communication to reorient to surroundings	Change in orientation score
All patients, protocol once daily; patients with base-line MMSE score of <20 or orientation score of <8, protocol three times daily	Therapeutic-activities protocol: cognitively stimulating activities three times daily (e.g., discussion of current events, structured reminiscence, or word games)	
Sleep deprivation	Nonpharmacologic sleep protocol: at bedtime, warm drink (milk or herbal tea), relaxation tapes or music, and back massage	Change in rate of use of sedative drug for sleep†
All patients; need for protocol assessed once daily	Sleep-enhancement protocol: unit-wide noise-reduction strategies (e.g., silent pill crushers, vibrating beepers, and quiet hallways) and schedule adjustments to allow sleep (e.g., rescheduling of medications and procedures)	
Immobility	Early-mobilization protocol: ambulation or active range-of-motion exercises three times daily; minimal use of immobilizing equipment (e.g., bladder catheters or physical restraints)	Change in Activities of Daily Living score
All patients; ambulation whenever possible, and range-of-motion exercises when patients chronically non-ambulatory, bed or wheelchair bound, immobilized (e.g., because of an extremity fracture or deep venous thrombosis), or when prescribed bed rest		
Visual impairment	Vision protocol: visual aids (e.g., glasses or magnifying lenses) and adaptive equipment (e.g., large illuminated telephone keypads, large-print books, and fluorescent tape on call bell), with daily reinforcement of their use	Early correction of vision, ≤48 hr after admission
Patients with <20/70 visual acuity on binocular near-vision testing		
Hearing impairment	Hearing protocol: portable amplifying devices, earwax disimpaction, and special communication techniques, with daily reinforcement of these adaptations	Change in Whisper Test score
Patients hearing ≤6 of 12 whispers on Whisper Test		
Dehydration	Dehydration protocol: early recognition of dehydration and volume repletion (i.e., encouragement of oral intake of fluids)	Change in ratio of blood urea nitrogen to creatinine
Patients with ratio of blood urea nitrogen to creatinine≥18, screened for protocol by geriatric nurse-specialist		

*The orientation score consisted of results on the first 10 items on the Mini–Mental State Examination (MMSE).

†Sedative drugs included standard hypnotic agents, benzodiazepines, and antihistamines, used as needed for sleep.

to patients assigned to usual care. However, the same attending and resident physicians provided care to patients in both study groups.

Outcomes

The primary outcome was delirium, defined according to the Confusion Assessment Method criteria,[31] which consisted of acute onset and a fluctuating course of symptoms of delirium, inattention, and either disorganized thinking or an altered level of consciousness. Each of these features was rated by the researchers on the basis of observations made during the daily interviews. The Confusion Assessment Method criteria provided a standardized rating of delirium, which has been validated against geropsychiatric diagnoses, with a sensitivity of 94 to 100 percent, a specificity of 90 to 95 percent, and high interobserver reliability.[31]

For the primary analysis of the effectiveness of the intervention, delirium was considered a binary outcome (present or absent) according to its earliest occurrence, and only one episode of delirium per patient was counted. We also counted the total number of days of delirium (the total person-days of all episodes of delirium) and the number of episodes of delirium in each study group, and we evaluated recurrence (two or more episodes) and severity. The severity of delirium was measured by an additive score for the four designated symptoms (symptom fluctuation, inattention, disorganized thinking, and an altered level of consciousness). Each symptom of delirium except fluctuation was rated by the interviewers as absent (0 points), mild (1 point), or marked (2 points); symptom fluctuation was rated as absent (0 points) or present (1 point). The sum of these ratings yielded a delirium-severity score, ranging from 0 to 7, with higher scores indicating increased severity.

Confusion Assessment Method ratings were completed in 4848 of 4857 daily interviews (99.8 percent). Interrater reliability for these ratings was confirmed in 16 paired observations that involved all the members of the research staff (kappa, 1.0). A total of 108 uncertain ratings, ratings with missing Confusion Assessment Method items, or possible episodes of delirium occurring between interviews were assessed for the presence or absence of delirium by two independent reviewers (a geriatrician and a neuropsychologist who were unaware of the patients' study-group assignments) on review of all interview data and medical records.

Adherence

The level of adherence to the intervention, with reasons for nonadherence, was recorded daily by the intervention staff. Daily adherence was complete if the patient received all parts of the assigned protocol for the total number of times it was to be given. Partial adherence indicated that the patient either received some but not all parts of the protocol or did not receive the protocol for the required number of times that day. Nonadherence indicated that none of the parts of the assigned protocol were received that day.

Statistical Analysis

Characteristics at admission were compared between patients within matched pairs by matched statistical analyses, either paired t-tests for continuous variables or McNemar's test for binary measures. These results were confirmed with unmatched analyses.

All analyses of the effectiveness of the intervention with regard to the primary outcome used the intention-to-treat approach. The effectiveness of the intervention strategy in reducing the incidence of delirium was evaluated by a method of conditional logistic regression developed by Holford et al.[39] for prospectively sampled, individually matched data. To identify potential confounders, all the base-line characteristics were examined in bivariate analyses, and factors associated at a level of $P=0.20$ with the type of treatment (intervention or usual care) were further examined. Each potential covariate was added individually to the model and was retained if its presence resulted in a modification of the log-linear parameter for an intervention effect of 10 percent or more.[40,41] Subsequently, unmatched analyses by means of traditional logistic regression for new cases of delirium during the hospital stay and Cox proportional-hazards analysis for the risk of delirium per hospital day, with adjustment for the matching factors, were carried out to provide comparisons and alternatives to the matched analyses, as advocated by previous investigators.[42] Kaplan–Meier analysis and the log-rank test were used to compare the cumulative incidence of delirium, defined as the proba-

TABLE 2. CHARACTERISTICS OF THE PATIENTS ON ADMISSION, ACCORDING TO STUDY GROUP.*

CHARACTERISTIC	INTERVENTION GROUP (N=426)	USUAL-CARE GROUP (N=426)
Age — yr	79.6±6.1	79.8±6.2
Female sex — no. (%)	259 (61)	259 (61)
White race — no. (%)	378 (89)	362 (85)
Married — no. (%)	163 (38)	144 (34)
Residence in nursing home — no. (%)	24 (6)	27 (6)
Education — yr	11.3±3.3	11.0±3.7
APACHE II score	15.5±4.0	15.6±4.1
Any impairment in activities of daily living — no. (%)	145 (34)	149 (35)
Any impairment in instrumental activities of daily living — no. (%)	350 (82)	336 (79)
MMSE		
Mean score	23.7±4.6	23.3±4.9
Patients with score of <24 — no. (%)	175 (41)	192 (45)
Modified Blessed Dementia Rating Scale		
Mean score	0.53±1.2	0.47±1.1
Patients with score of >2 — no. (%)	50 (12)	45 (11)
Base-line risk of delirium		
Intermediate — no. (%)	307 (72)	307 (72)
High — no. (%)	119 (28)	119 (28)
Targeted risk factors — no. (%)†		
Cognitive impairment	130 (31)	128 (30)
Immobility	97 (23)	98 (23)
Visual impairment	97 (23)	98 (23)
Hearing impairment	120 (28)	98 (23)
Dehydration	248 (58)	254 (60)
Total no. of risk factors	2.5±1.1	2.5±1.1
Principal diagnosis — no. (%)		
Pneumonia	51 (12)	46 (11)
Chronic lung disease	41 (10)	54 (13)
Congestive heart failure	43 (10)	48 (11)
Ischemic heart disease	33 (8)	38 (9)
Gastrointestinal disease	65 (15)	46 (11)
Diabetes mellitus or metabolic disorder	20 (5)	17 (4)
Cancer	12 (3)	12 (3)
Cerebrovascular disease	9 (2)	13 (3)
Renal failure	9 (2)	11 (3)
Anemia	7 (2)	6 (1)
Other	136 (32)	135 (32)

*Plus–minus values are means ±SD. There were no significant differences in any of these characteristics between the intervention and control groups in matched or unmatched analyses. APACHE II denotes the Acute Physiology, Age, and Chronic Health Evaluation, and MMSE Mini–Mental State Examination. Because of rounding, percentages may not total 100.

†Sleep deprivation is not included here since all the patients were considered to be at risk for this factor. Targeted risk factors were defined as follows: cognitive impairment, orientation score of <8; immobility, Activities of Daily Living score of ≤12; visual impairment, visual acuity of <20/70 on binocular near-vision testing; hearing impairment, score of ≤6 on the Whisper Test; dehydration, ratio of blood urea nitrogen to creatinine of ≥18.

TABLE 3. DELIRIUM-RELATED OUTCOMES DURING HOSPITALIZATION, ACCORDING TO STUDY GROUP.*

OUTCOME	STUDY GROUP		STATISTICAL ANALYSIS	
	INTERVENTION	USUAL CARE	MATCHED	UNMATCHED
All matched patients (n=852)				
First episode of delirium — no. of patients (%)	42 (9.9)	64 (15.0)	OR, 0.60 (95% CI, 0.39–0.92); P=0.02†	OR, 0.61 (95% CI, 0.40–0.93); P=0.02‡
Total days of delirium§	105	161	P=0.02¶	
No. of episodes of delirium‖	62	90	P=0.03¶	
Patients with delirium (n=106)				
Mean ±SD delirium-severity score	3.85±1.27	3.52±1.44		P=0.25**
Recurrence (two or more episodes) — no. of patients (%)	13 (31.0)	17 (26.6)		P=0.62††

*All analyses were based on the intention-to-treat strategy. OR denotes odds ratio, and CI confidence interval.

†This analysis was conducted with conditional logistic-regression models appropriate for matched analyses; 88 discordant pairs were used.

‡This analysis was conducted with unmatched logistic-regression analysis, with control for matching factors.

§For total days of delirium, the mean (±SE) value per patient was 0.25±0.05 in the intervention group and 0.38±0.06 in the usual-care group. The mean within-pair difference was 0.13±0.08 fewer day in the intervention group.

¶For this matched analysis, the sign test was applied on within-pair differences.

‖For the number of episodes of delirium, the mean (±SE) value per patient was 0.15±0.03 in the intervention group and 0.21±0.03 in the usual-care group. The mean within-pair difference was 0.07±0.04 fewer episode in the intervention group.

**The delirium-severity score ranged from 0 to 7 according to the presence and severity of four symptoms of delirium; higher scores indicate increased severity. This unmatched comparison was conducted with the t-test.

††This unmatched comparison was conducted with the chi-square test.

bility that delirium would develop by a specified time, between the study groups.

Total days of delirium, defined as the total number of days with delirium among all the patients in each study group, and the number of episodes of delirium in each group were calculated. Statistical comparisons were carried out in the matched analyses with use of the sign test to assess pairwise differences. The severity and rate of recurrence of delirium among patients with delirium were compared between study groups by means of appropriate statistical analyses for unmatched comparisons.

Adherence rates were calculated according to patient-day in the intervention group. Eligible patient-days were defined as those on which patients were assigned to receive the specified part of the intervention protocol. Changes in risk factors or targeted outcomes at the time of reassessment (on day 5 or at discharge, if earlier) were compared between the subgroups of patients in the intervention and usual-care groups who had the risk factor in question at base line by means of unmatched statistical analyses, including chi-square analysis for categorical variables. Adjusted mean scores at reassessment were calculated as least-squares means with use of analysis of covariance with adjustment for the base-line score.

All statistical tests were two-tailed, and a P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

The characteristics of the patients in each study group at the time of admission are shown in Table 2. The intervention and usual-care groups did not differ significantly in terms of any of the characteristics. Many patients with dementia were included in the study; scores on the Mini–Mental State Examination ranged from 7 to 30, with 25 percent of the patients having a score of 20 or less. The mean numbers of risk factors per patient at admission were similar in the two groups. The median lengths of stay were 7.0 and 6.5 days in the intervention and usual-care groups, respectively (P=0.95). Six patients in the intervention group (1.4 percent) and seven in the usual-care group (1.6 percent) died during hospitalization (P=0.78); complete information on delirium was available for these subjects.

Overall Effectiveness

The rate of incidence of delirium was significantly lower in the intervention group than in the usual-care group (9.9 percent vs. 15.0 percent, P=0.02). The matched odds ratio of 0.60 (95 percent confidence interval, 0.39 to 0.92) in matched multivariable analyses indicates that a substantial reduction in risk was associated with the intervention (Table 3). After examination of all the potential base-line covariates (Table 2), only a Mini–Mental State Examination score of less than 24 was significantly associated with outcome (P<0.01). Adjustment for the score, however, did not substantially affect the overall results, and thus we did not control for this variable in subsequent models. Unmatched multivariable analyses, including both logistic-regression and Cox proportional-hazards analyses, with adjustment for matching factors, confirmed the matched results. The cumulative incidence of delirium was significantly lower in the intervention group than in the usual-care group (Fig. 1).

The total number of days of delirium was significantly lower in the intervention group than in the

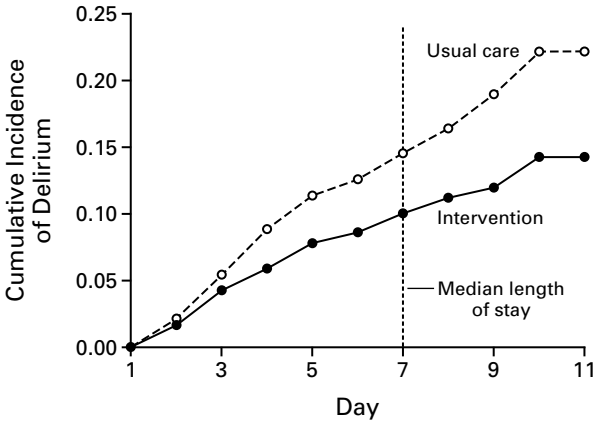

Figure 1. Cumulative Incidence of Delirium According to Study Group.

The cumulative incidence of delirium was defined as the probability of the development of delirium by a specified time. Data on patients were censored at the time of discharge or death. The difference between the groups was significant (chi-square = 4.77; P=0.03 by the log-rank test). Kaplan–Meier estimates of the incidence of delirium at the median length of the hospital stay (seven days, indicated by the dotted line) were 0.100 for the intervention group and 0.145 for the usual-care group.

group that received usual care (105 vs. 161 days, P=0.02) (Table 3). The total number of episodes of delirium was also significantly lower in the intervention group (62 episodes, vs. 90 in the usual-care group; P=0.03); however, this effect appeared to result primarily from the effects of the intervention on the first episode of delirium rather than on recurrent episodes. Among cases of delirium, severity scores and rates of recurrence did not differ significantly between the two study groups.

In matched-subgroup analyses, the intervention significantly reduced the rate of incidence of delirium in the group at intermediate risk for delirium at base line (odds ratio, 0.52; 95 percent confidence interval, 0.29 to 0.92). In the group at high risk for delirium at base line, the intervention was associated with a reduction in incidence (odds ratio, 0.73; 95 percent confidence interval, 0.38 to 1.38), but the reduction was not statistically significant.

Level of Adherence

The overall rate of adherence (complete and partial adherence) to all the intervention protocols was 87 percent (8716 of 10,056 patient-days). The overall adherence rates for the individual protocols were 96 percent for the orientation protocol (2443 of 2534 patient-days), 92 percent for the vision protocol (487 of 531 patient-days), 92 percent for the hearing protocol (514 of 561 patient-days), 86 percent for therapeutic activities (2188 of 2542 patient-days), 84 percent for early mobilization (2054 of 2452 patient-days), 81 percent for volume repletion (68 of 84 patient-days), and 71 percent for the nonpharmacologic sleep protocol (962 of 1352 patient-days). The most common reasons for nonadherence included refusal by the patient, lack of availability of the patient because of procedures elsewhere in the hospital, medical contraindications, and lack of availability of intervention staff members. No adverse effects were associated with the intervention protocols.

Effect on Targeted Risk Factors

The change in risk factors or targeted outcomes at the reassessment on day 5 or at discharge is shown in Table 4. At reassessment, there was significant improvement in the orientation score and a significant reduction in the rate of use of sedative drugs for sleep in the intervention group as compared with the usual-care group. The Activities of Daily Living score and the score on the Whisper Test demonstrated trends toward improvement in the intervention group. Receipt of early vision correction was also associated with a trend toward improvement in this group. Overall, there were significantly fewer risk factors present in the intervention group than in the usual-care group at reassessment.

Cost of Intervention

The total cost of the intervention, including staff time spent in intervention activities, equipment, supplies, and consultant costs, was $139,506, or an average of $327 per patient in the intervention group. The cost of intervention per case of delirium prevented was $6,341 ($139,506 for 22 cases prevented [64 cases of delirium occurred in patients receiving usual care, as compared with 42 cases in those receiving the intervention]).

DISCUSSION

This controlled clinical trial provides evidence that a multicomponent, targeted intervention strategy, the Elder Life Program, is effective for the prevention of delirium in hospitalized older medical patients. The intervention prevented the initial development of delirium and reduced the total number of days of delirium. It was most effective in patients who were at intermediate risk for delirium at base line. Once an initial episode of delirium had occurred, however, the intervention had no significant effect on the severity of delirium or on the likelihood of recurrence. This finding has an important implication for the treatment of delirium: primary prevention is probably the most effective strategy. Once delirium has occurred, our intervention strategy will be less effective and less efficient.

The strengths of this study include the daily assessment of patients for delirium with a standardized, validated instrument; the completeness of the

TABLE 4. CHANGE IN RISK FACTORS OR TARGETED OUTCOMES AT REASSESSMENT, ACCORDING TO STUDY GROUP.*

RISK FACTOR	INTERVENTION	USUAL CARE	P VALUE
Cognitive impairment			
No. (%) of patients assessed	128	125	
Improved by 2 points	51 (40)	33 (26)	0.04
Same	76 (59)	88 (70)	
Worse by 2 points	1 (1)	4 (3)	
Adjusted orientation score at reassessment	7.2±0.2	6.8±0.2	0.06
Sleep deprivation			
No. (%) of patients assessed	426	426	
Use of sedative drug for sleep during hospital stay	148 (35)	195 (46)	0.001
Immobility			
No. (%) of patients assessed	96	98	
Improved by 2 points	6 (6)	13 (13)	0.06
Same	68 (71)	54 (55)	
Worse by 2 points	22 (23)	31 (32)	
Adjusted Activities of Daily Living score at reassessment	9.7±0.3	9.3±0.3	0.34
Vision impairment			
No. (%) of patients assessed	57	62	
Early vision correction	21 (37)	17 (27)	0.27
Hearing impairment			
No. (%) of patients assessed	120	98	
Improved by 1 point	61 (51)	39 (40)	0.10
Same	37 (31)	44 (45)	
Worse by 1 point	22 (18)	15 (15)	
Adjusted Whisper Test score at reassessment	5.3±0.3	4.5±0.4	0.09
Dehydration			
No. (%) of patients assessed	240	254	
Improved by 5 points	107 (45)	98 (39)	0.40
Same	110 (46)	127 (50)	
Worse by 5 points	23 (9)	29 (11)	
Adjusted ratio of blood urea nitrogen to creatinine at reassessment	20.7±0.5	20.7±0.5	0.22
Total no. of risk factors			
No. (%) of patients assessed	426	426	
Improved (fewer risk factors)	272 (64)	236 (55)	0.02
Same	110 (26)	124 (29)	
Worse (more risk factors)	44 (10)	66 (15)	
Adjusted no. of risk factors per patient at reassessment	1.7±0.1	1.9±0.1	0.001

*Plus–minus values are means ±SD. These results are based on unmatched analyses. All the adjusted scores were calculated at reassessment (on day 5 or at discharge, if earlier). These scores were calculated as least-squares means with use of analysis of covariance with adjustment for the base-line score. Targeted risk factors were defined as follows: cognitive impairment, orientation score of <8; immobility, Activities of Daily Living score of ≤ 12; visual impairment, visual acuity of $<20/70$ on binocular near-vision testing; hearing impairment, score of ≤ 6 on the Whisper Test; and dehydration, ratio of blood urea nitrogen to creatinine of ≥ 18.

outcome data, with no losses to follow-up; the targeting of at-risk patients for intervention, an approach that maximizes the efficiency and clinical relevance of the intervention; and the detailed tracking of adherence to the intervention protocols. Moreover, the practical, realistic nature of the intervention protocols, designed to target well-documented risk factors for delirium, enhances their feasibility and the extent to which they can be applied in other settings.

These findings lend strong support to the use of a multicomponent intervention to prevent delirium. The positive trends in the reduction of risk factors at the time of reassessment validate the effectiveness of each intervention protocol. The significant reduction in the total number of risk factors with intervention as compared with usual care suggests that risk-factor reduction contributed at least in part to the effectiveness of the intervention strategy.

Several important limitations of this study deserve comment. Logistic constraints precluded random assignment of the patients to the two treatment groups. However, the prospective, individual-matching strategy allowed balanced assignment of the patients to the two groups. Furthermore, a contamination effect in the usual-care group probably decreased the overall rates of delirium. Contamination was evident in the rates of delirium, which were substantially lower than anticipated on the basis of earlier studies in the same study population,[24,25] and it was also evident in the substantial reduction in risk factors that occurred in the usual-care group. Although efforts were made to avoid contamination, some intervention protocols were disseminated by word of mouth to staff members in usual-care units. Moreover, although the intervention strategies most often involved the nursing staff, the physicians rotated on all hospital floors and carried over some intervention protocols to the usual-care group. Despite these contamination effects, which would have tended to bias the results toward the null hypothesis, the significant overall results substantiate the robustness of the effects of the intervention.

The estimated cost of $6,341 per case of delirium prevented compares favorably with the estimated costs in other studies of $7,727 to $11,834 (in 1996 dollars) per fall prevented[43] and $19,800 to $42,900 (in 1993 dollars) per myocardial infarction prevented.[44] Although a formal cost-effectiveness analysis was beyond the scope of this study, a complete analysis of health care costs related to delirium may demonstrate that the intervention yields a net savings.

This trial holds substantial promise for the prevention of delirium in hospitalized older patients. Further evaluation is needed to determine the cost effectiveness of the intervention; its effects on related outcomes, such as mortality, rehospitalization, institutionalization, use of home health care, and long-term cognitive functioning; and its effectiveness in other settings.

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