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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

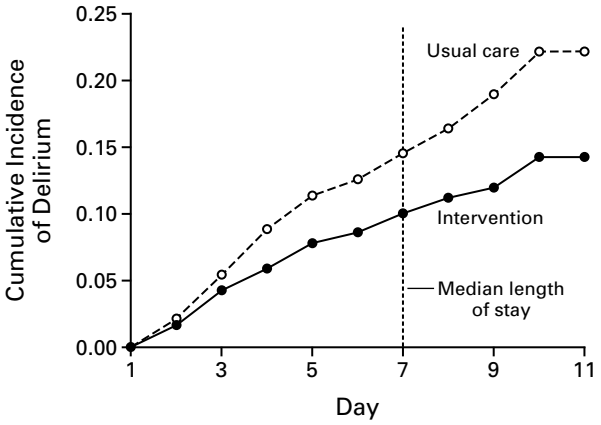

Figure 1. Cumulative Incidence of Delirium According to Study Group.

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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REFERENCES

1. Inouye SK. The dilemma of delirium: clinical and research controversies regarding diagnosis and evaluation of delirium in hospitalized elderly medical patients. Am J Med 1994;97:278-88.
2. Rummans TA, Evans JM, Krahn LE, Fleming KC. Delirium in elderly patients: evaluation and management. Mayo Clin Proc 1995;70:989-98.
3. Francis J, Kapoor WN. Delirium in hospitalized elderly. J Gen Intern Med 1990;5:65-79.
4. The Administration on Aging. A profile of older Americans. Washington, D.C.: American Association of Retired Persons, 1995.
5. Statistical abstract of the United States. Washington, D.C.: Bureau of the Census, 1996:116.
6. Inouye SK, Rushing JT, Foreman MD, Palmer RM, Pompei P. Does delirium contribute to poor hospital outcomes? A three-site epidemiologic study. J Gen Intern Med 1998;13:234-42.
7. Cole MG, Primeau FJ. Prognosis of delirium in elderly hospital patients. CMAJ 1993;149:41-6.
8. Hobbs FB, Damon BL. Special studies, 65+ in the United States. Current population reports. Series P23. No. 190. Washington, D.C.: Bureau of the Census, 1996.
9. Hogan DB, Fox RA, Gadley BWD, Mann OE. Effect of a geriatric consultation service on management of patients in an acute care hospital. CMAJ 1984;136:713-7.
10. Cole MG, Fenton FR, Englesmann F, Mansouri I. Effectiveness of geriatric psychiatry consultation in an acute care hospital: a randomized clinical trial. J Am Geriatr Soc 1991;39:1183-8.
11. Layne OL Jr, Yudofsky SC. Postoperative psychosis in cardiotomy patients: the role of organic and psychiatric factors. N Engl J Med 1971;284: 518-20.
12. Schindler JA, Shook J, Schwartz GM. Beneficial effects of psychiatric intervention on recovery after coronary artery bypass graft surgery. Gen Hosp Psychiatry 1989;11:358-64.
13. Cole MG, Primeau FJ, Bailey RF, et al. Systematic intervention for elderly inpatients with delirium: a randomized trial. CMAJ 1994;151:965-70.
14. Rubenstein LZ, Josephson KR, Wieland GD, English PA, Sayre JA, Kane RL. Effectiveness of a geriatric evaluation unit: a randomized clinical trial. N Engl J Med 1984;311:1664-70.
15. Wanich CK, Sullivan-Marx EM, Gottlieb GL, Johnson JC. Functional status outcomes of a nursing intervention in hospitalized elderly. Image J Nurs Sch 1992;24:201-7.
16. Nagley SJ. Predicting and preventing confusion in your patients. J Gerontol Nurs 1986;12:27-31.
17. Williams MA, Campbell EB, Raynor WJ, Mlynarczyk SM, Ward SE. Reducing acute confusional states in elderly patients with hip fractures. Res Nurs Health 1985;8:329-37.
18. Budd S, Brown W. Effect of a reorientation technique on postcardiotomy delirium. Nurs Res 1974;23:341-8.
19. Owens JF, Hutelmyer CM. The effect of preoperative intervention on delirium in cardiac surgical patients. Nurs Res 1982;31:60-2.
20. Chatham MA. The effect of family involvement on patients' manifestations of postcardiotomy psychosis. Heart Lung 1978;7:995-9.
21. Riis J, Lomholt B, Haxholdt O, et al. Immediate and long-term mental recovery from general versus epidural anesthesia in elderly patients. Acta Anaesthesiol Scand 1983;27:44-9.
22. Williams-Russo P, Urquhart RN, Sharrock NE, Charlson ME. Postoperative delirium: predictors and prognosis in elderly orthopedic patients. J Am Geriatr Soc 1992;40:759-67.
23. Gustafson Y, Brannstrom B, Berggren D, et al. A geriatric-anesthesiologic program to reduce acute confusional states in elderly patients treated for femoral neck fractures. J Am Geriatr Soc 1991;39:655-62.
24. Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized elderly persons: predictive model and interrelationship with baseline vulnerability. JAMA 1996;275:852-7.
25. Inouye SK, Viscoli CM, Horwitz RI, Hurst LD, Tinetti ME. A predictive model for delirium in hospitalized elderly medical patients based on admission characteristics. Ann Intern Med 1993;119:474-81.
26. Makuch RW, Zhang Z, Charpentier PA, Inouye SK. Prospective individual matching: covariate balance and power in a comparative study. Stat Med 1998;17:1517-26.
27. Charpentier PA, Inouye SK. Prospective individualized matching in a non-randomized geriatric intervention trial. Gerontologist 1995;35(Special Issue I):181.
28. Elie M, Cole MG, Primeau FJ, Bellavance F. Delirium risk factors in elderly hospitalized patients. J Gen Intern Med 1998;13:204-12.
29. Folstein MF, Folstein SE, McHugh PR. "Mini–Mental State": a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189-98.
30. Cummings JL. Clinical neuropsychiatry. Orlando, Fla.: Grune & Stratton, 1985:9.
31. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the Confusion Assessment Method: a new method for detection of delirium. Ann Intern Med 1990;113:941-8.
32. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of illness in the aged: the index of ADL, a standardized measure of biological and psychosocial function. JAMA 1963;185:914-9.
33. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985;13:818-29.
34. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 1969;9:179-86.
35. MacPhee GJ, Crowther JA, McAlpine CH. A simple screening test for hearing impairment in elderly patients. Age Ageing 1988;17:347-51.
36. Blessed G, Tomlinson BE, Roth M. The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. Br J Psychiatry 1968;114:797-811.
37. Uhlmann RF, Larson EB, Buchner DM. Correlations of Mini–Mental State and modified Dementia Rating Scale to measures of transitional health status in dementia. J Gerontol 1987;42:33-6.
38. Beresin EV. Delirium in the elderly. J Geriatr Psychiatry Neurol 1988; 1:127-43.
39. Holford TR, Bracken MB, Eskenazi B. Log-linear models for the analysis of matched cohort studies. Am J Epidemiol 1989;130:1247-53.
40. Greenland S. Modeling and variable selection in epidemiologic analysis. Am J Public Health 1989;79:340-9.
41. Mickey RM, Greenland S. The impact of confounder selection criteria on effect estimation. Am J Epidemiol 1989;129:125-37. [Erratum, Am J Epidemiol 1989;130:1066.]
42. Lynn HS, McCulloch CE. When does it pay to break the matches for analysis of a matched-pairs design? Biometrics 1992;48:397-409.
43. Rizzo JA, Baker DI, McAvay G, Tinetti ME. The cost-effectiveness of a multifactorial targeted prevention program for falls among community elderly persons. Med Care 1996;34:954-69.
44. Hall JP, Heller RF, Dobson AJ, Lloyd DM, Sanson-Fisher RW, Leeder SR. A cost-effectiveness analysis of alternative strategies for the prevention of heart disease. Med J Aust 1988;148:273-7.

REVIEW

Delirium in Elderly Patients and the Risk of Postdischarge Mortality, Institutionalization, and Dementia

A Meta-analysis

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Context Delirium is a common and serious complication in elderly patients. Evidence suggests that delirium is associated with long-term poor outcome but delirium often occurs in individuals with more severe underlying disease.

Objective To assess the association between delirium in elderly patients and long-term poor outcome, defined as mortality, institutionalization, or dementia, while controlling for important confounders.

Data Sources A systematic search of studies published between January 1981 and April 2010 was conducted using the databases of MEDLINE, EMBASE, PsycINFO, and CINAHL.

Study Selection Observational studies of elderly patients with delirium as a study variable and data on mortality, institutionalization, or dementia after a minimum follow-up of 3 months, and published in the English or Dutch language. Titles, abstracts, and articles were reviewed independently by 2 of the authors. Of 2939 references in the original search, 51 relevant articles were identified.

Data Extraction Information on study design, characteristics of the study population, and outcome were extracted. Quality of studies was assessed based on elements of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for cohort studies.

Data Synthesis The primary analyses included only high-quality studies with statistical control for age, sex, comorbid illness or illness severity, and baseline dementia. Pooled-effect estimates were calculated with random-effects models. The primary analysis with adjusted hazard ratios (HRs) showed that delirium is associated with an increased risk of death compared with controls after an average follow-up of 22.7 months (7 studies; 271/714 patients [38.0%] with delirium, 616/2243 controls [27.5%]; HR, 1.95 [95% confidence interval {CI}, 1.51-2.52]; I^2, 44.0%). Moreover, patients who had experienced delirium were also at increased risk of institutionalization (7 studies; average follow-up, 14.6 months; 176/527 patients [33.4%] with delirium and 219/2052 controls [10.7%]; odds ratio [OR], 2.41 [95% CI, 1.77-3.29]; I^2, 0%) and dementia (2 studies; average follow-up, 4.1 years; 35/56 patients [62.5%] with delirium and 15/185 controls [8.1%]; OR, 12.52 [95% CI, 1.86-84.21]; I^2, 52.4%). The sensitivity, trim-and-fill, and secondary analyses with unadjusted high-quality risk estimates stratified according to the study characteristics confirmed the robustness of these results.

Conclusion This meta-analysis provides evidence that delirium in elderly patients is associated with poor outcome independent of important confounders, such as age, sex, comorbid illness or illness severity, and baseline dementia.

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DELIRIUM IS A SYNDROME OF acutely altered mental status characterized by inattention and a fluctuating course.[1] With occurrence rates of up to half of older patients postoperatively, and even higher in elderly patients admitted to intensive care units, delirium is the most common complication in hospitalized older people.[2-4] Delirium causes distress to patients and caregivers, has been associated with increased morbidity and mortality, and is a major burden to health care services in terms of expenditures.[5]

Numerous studies have addressed the long-term prognosis of older individuals who experienced delirium during hospitalization. The evidence that these studies provide is not entirely consistent (eg, older patients with delirium experienced increased long-term mortality in one study,[6] but not in another[7]). Elements of study design, such as delirium and outcome ascertainment and time to follow-up, may affect conclusions. Whether delirium independently contributes to poor outcome or merely represents a marker of underlying disease is especially relevant. The long-term detrimental se-

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quelae of delirium are difficult to disentangle from the effects of specific characteristics of the study population, such as the extent of medical illness and the presence or absence of dementia.

These issues preclude drawing reliable conclusions regarding the long-term prognosis after delirium, which could be instrumental in assessing the value of prevention and treatment[8] and in counseling patients and caregivers. Therefore, we systematically reviewed and summarized data regarding the risk of long-term poor outcome (defined as mortality, institutionalization, or dementia) after delirium. Our main objective was to assess the association between delirium and long-term poor outcomes in elderly patients while controlling for important confounders.

METHODS

We followed the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[9] We conducted a comprehensive literature search of MEDLINE, EMBASE, PsycINFO, and CINAHL databases for studies published between January 1981 and April 2010. We started our search in January 1981 because a formal nomenclature that differentiates delirium from dementia was first established with the *Diagnostic and Statistical Manual of Mental Disorders* (Third Edition) in 1980.[10] Search key words for delirium (ie, delirium, confusion, acute confusional state, acute confusional syndrome) were cross-referenced to citations pertinent to outcome (ie, mortality, prognos*, predict*, course). Studies that met each of the following criteria were considered eligible: (1) mean or median age of the study population of 65 years or older; (2) delirium as a study variable; (3) presentation of quantitative data (ie, event rates, odds ratios [ORs] or hazard ratios [HRs]) reflecting the association between delirium and outcome (ie, mortality, institutionalization, or dementia); (4) hospital or postacute care setting; and (5) follow-up assessment at 3 months or later. Searches were restricted to articles published in the English or Dutch language. Articles were excluded if they recruited (1) delirium patients only and no controls; (2) homogeneous populations of terminally ill patients (eg, patients with end-stage cancer); and (3) homogeneous populations of patients with central nervous system disease (eg, only patients with stroke or Parkinson disease). After exclusion of case studies and case series, the database searches identified 2939 articles. Reviews were hand searched for additional references but yielded no additional articles. Title and abstract review of all articles was completed by 3 of the authors (J.W., L.S.M.E., W.A.vG.). Full reports of 162 potentially relevant articles were independently reviewed by at least 2 investigators (J.W., L.S.M.E., W.A.vG.) to establish eligibility according to the inclusion criteria.

A standardized, piloted data extraction form was used for recording information. Data extraction was completed by 3 of the authors (J.W., L.S.M.E., W.A.vG.) using the following approach. For the primary analyses, we obtained statistically adjusted ORs and HRs with corresponding 95% confidence intervals (CIs) and noted the type of statistical adjustment (ie, the variables that were examined as possible covariates in relation with the outcomes of interest). For the secondary analyses, we extracted the number of events relative to the total number of participants in the delirium and control groups (ie, event rates). Because of our interest in the long-term outcomes after delirium, we preferentially extracted event rates that considered only postdischarge mortality and incident cases of institutionalization (or dementia). Therefore, if specified, event rates for mortality were corrected for death during the index hospitalization and event rates for institutionalization (and dementia) were corrected for baseline rates of institutionalization (or dementia).

Study populations were characterized as surgical, medical, or mixed and the following information was recorded: primary author, publication year, country of origin, study design, criteria for delirium and dementia ascertainment, duration of follow-up, average or median age, and (if applicable) the proportion of in-hospital mortality, baseline institutionalization, and dementia. Additional information such as separate event rates for patients with and without dementia were requested from 33 authors and 26 authors responded. Disagreement between reviewers during the selection and extraction process was resolved through consensus.

To limit heterogeneity resulting from differences in study design, we only included high-quality articles in the primary and secondary analyses. Lesser-quality articles were not included in any of our analyses. The quality of the studies was assessed based on elements from the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for cohort studies.[11] High-quality articles were defined as studies that diagnosed delirium prospectively, as opposed to, for example, retrospective chart review, and used a validated method for delirium ascertainment.

Studies were included in the primary analyses only if adequate statistical control was provided to account for the effect of important covariates on the association between delirium and poor outcome. Adequate adjustment was defined as statistical control for the covariables of age, sex, comorbid illness or illness severity, and baseline dementia. We selected these variables because they are risk factors for delirium in elderly patients that can themselves be associated independently with poor outcome.[2,5]

Secondary analyses were performed on a much larger sample of studies to examine the robustness of results from our primary analyses. In these secondary analyses, the studies' unadjusted ORs were stratified according to source of the study population, age (<80 years vs ≥80 years), country of origin (United States vs Europe), length of follow-up, and whether individuals who were

institutionalized or had dementia were included in the study population.

Finally, an exploratory secondary analysis was conducted to specifically examine the association of baseline dementia with the long-term prognosis after delirium. This analysis was performed using studies that allowed separate calculation of effect estimates among homogeneous populations of individuals with and without dementia.

Mortality, institutionalization, and dementia were examined as separate outcomes. In primary analyses, we pooled adjusted ORs and HRs across all studies based on the extracted risk estimates and corresponding 95% CIs. In secondary analyses, we combined ORs and 95% CIs that we recalculated based on event rates in the delirium and control groups.[12] If recalculation was not possible, the reported unadjusted ORs and 95% CIs were used.

Each study contributed only 1 effect size per analysis. If data were duplicated between studies, the largest study was used. If studies reported data on several follow-up assessments, we included only data from the latest follow-up. If necessary, different subgroups (eg, based on age) were combined to create 1 estimate per study.

The pooled ORs and HRs were calculated as the weighted average and weighting was assigned according to the inverse of the variance. An OR or HR greater than 1 indicates an increased risk of an outcome among delirium patients compared with controls. The I^2 statistic was used to examine the heterogeneity of effect sizes in the overall aggregations. The I^2 values of 25% or less indicate low heterogeneity, values near 50% indicate moderate heterogeneity, and values near 75% or greater indicate high heterogeneity.[13] Unless otherwise specified, random-effects models were used in all analyses.[14] Fixed-effects models were only used in sensitivity analyses that examined if these models yielded similar results.

Publication bias was evaluated with a combination of 2 funnel plot–based methods: the Egger regression asymmetry test[15] to investigate funnel plot asymmetry and the trim-and-fill method[16] to estimate the number of missing studies and to calculate a corrected OR as if these studies were present. Because 5 studies are usually too few to detect an asymmetrical funnel, only aggregated analyses with more than 5 studies were subjected to trim-and-fill analysis.[17] The effect of potential outliers was examined by comparing the pooled estimate with estimates obtained after iterations using $k-1$ findings. Studies were treated as statistical outliers when the $k-1$ estimate produced a 95% CI that did not overlap with the 95% CI of the aggregated estimate.

Sensitivity analyses were performed on our primary and secondary data sets to examine if risk estimates using postdischarge mortality only (excluding in-hospital or postacute care deaths) provided a more conservative estimate of the association between delirium and mortality and if the strength of the relationship between delirium and institutionalization was affected by including only risk estimates that were based on incident cases of institutionalization. Furthermore, we performed a sensitivity analysis to examine if studies that used different methods to diagnose baseline dementia (eg, chart review) and incident dementia at follow-up (eg, cognitive testing) overestimated the association between delirium and dementia. Studies with the same method to diagnose dementia at baseline and follow-up and that thus included only incident cases of dementia were pooled in these analyses.

Statistical analyses were performed using Comprehensive Meta-Analysis software (Englewood, New Jersey) version 2.2.048. *P* values of less than .05 were considered statistically significant.

RESULTS

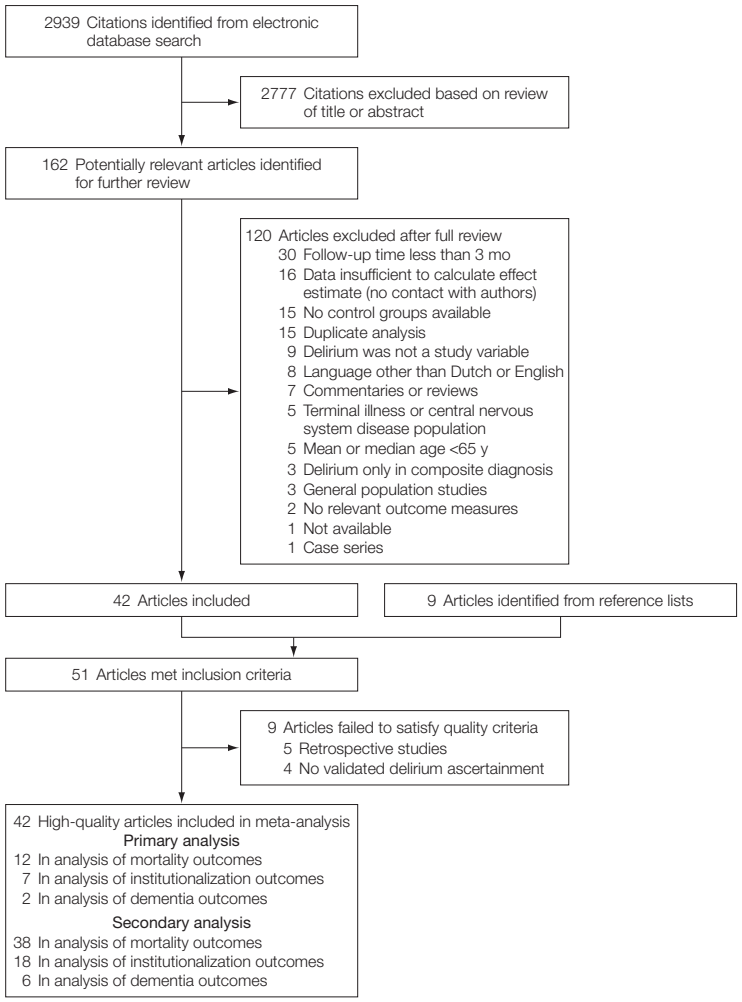
Our literature search yielded 2939 articles, of which we identified 162 for further review. Fifty-one studies met our inclusion criteria (see eTable 1, eTable 2, and eTable 3 at http://www.jama.com). Most excluded studies lacked either follow-up assessment, sufficient data to extract a risk estimate, a control group, or original data. Of the 51 studies that met our inclusion criteria, 9 studies[18-26] did not satisfy our quality criteria and were not included in the primary or secondary analyses (FIGURE 1).

Of the remaining 42 high-quality studies,[6,7,27-66] 23 studies* reported statistically adjusted effect estimates for the outcome of mortality and 16 studies† fulfilled criteria for adequate adjustment. Four studies[27,29,30,48] did not report sufficient information to extract an adjusted risk estimate for the latest follow-up assessment. The remaining 12 studies‡ provided 7 HRs and 7 ORs for the primary analysis of the association between delirium and mortality. Eight studies[6,7,30,32,40,43,61,63] reported adjusted ORs for the association between delirium and institutionalization, of which 7 studies[6,7,30,32,40,43,63] were adequately adjusted and provided 9 ORs for the primary analysis. Three studies presented adjusted ORs for the dementia outcome, of which 2 studies[32,54] were adequately adjusted and their ORs are included in our primary analysis.

For the secondary analyses with unadjusted ORs, 38 studies§ provided 40 ORs on mortality, 18 studies‖ provided 20 ORs on institutionalization, and 6 studies[32,41,47,49,54,65] provided 6 ORs on dementia. In 2 instances, ORs were recalculated based on the data supplied by the authors because nursing home residents had been excluded[6,63] and data had been provided on a substantially larger sample.[48] Four sets of studies[28-30,38,52,54,57] reported data on the same group of patients; the studies that reported postdischarge mortality[54] or presented data of the largest sample[29,30,52] were included.

*References 6, 7, 27-30, 32, 34, 35, 40, 41, 44, 45, 48, 51, 52, 55, 56, 60, 61, 63-65.
†References 6, 7, 27, 29, 30, 32, 35, 40, 41, 45, 48, 51, 52, 60, 63, 65.
‡References 6, 7, 32, 35, 40, 41, 45, 51, 52, 60, 63, 65.
§References 6, 7, 27, 29, 31-37, 39-56, 58-66.
‖References 6, 7, 30, 32, 33, 37, 40, 42, 43, 46, 47, 49, 55, 57, 61-63, 66.

Figure 1. Identification, Review, and Selection of Articles Included in the Meta-analysis



In our exploratory secondary analyses, we examined to what extent baseline dementia affected the association between delirium and poor outcome. A total of 18 studies¶ provided 18 ORs on mortality and 5 ORs on institutionalization in a homogeneous population of individuals with dementia, and 17 ORs on mortality and 6 ORs on institutionalization in a homogeneous population of individuals without dementia. Descriptive information regarding the studies that were included from each analysis is listed in eTables 1-3 and information on excluded studies is listed in eTable 4 at http://www.jama.com.

¶References 6, 27, 28, 35, 37-39, 41, 43, 45, 47-49, 59, 62, 63, 65, 66.

Mortality

The primary analysis of adequately adjusted HRs included a total of 2957 participants. After a mean (SD) follow-up of 22.7 (15.5) months (range, 3-48 months) in 7 studies, 271 of 714 patients with delirium (38%) had an increased risk of death compared with 616 of 2243 controls (27.5%) (HR, 1.95 [95% CI, 1.51-2.52]; I^2, 44.0%; FIGURE 2). There was no evidence of publication bias according to the Egger regression asymmetry test ($\beta = 0.16$; $P = .94$) or the trim-and-fill method and outliers were not identified. The aggregated analysis of adequately adjusted ORs included a total of 2066 participants and also showed a significant association between delirium and mortality after a mean (SD) follow-up of 11.4 (14.0) months (range, 3-38 months) in 183 of 483 participants with delirium (37.9%) vs 316 of 1583 controls (20.0%) (OR, 1.71 [95% CI, 1.27-2.30]; I^2, 0%). No evidence of publication bias (Egger $\beta = -0.37$; $P = .43$) or outliers was found.

A sensitivity analysis with adjusted HRs showed that the association between delirium and death remained significant when only studies for which postdischarge mortality could be determined were included (TABLE 1). Secondary analyses with unadjusted ORs (see the eFigure at http://www.jama.com) were consistent with the results of the primary analyses. Additional stratified analyses with these unadjusted data revealed that excess mortality was present among patients who had experienced delirium regardless of the source of the study population, inclusion of nursing home residents or individuals with dementia, age, country of origin, and follow-up time (see eTable 5).

Our exploratory secondary analysis showed that the association of delirium with mortality persisted independent of preexisting dementia. Delirium remained significantly associated with mortality when 222 of 643 patients with delirium superimposed on dementia (34.5%) were compared with 135 of 564 patients with dementia only (23.9%) (OR, 1.75 [95% CI, 1.30-2.36]; I^2, 0.7%), and when 168 of 575 patients with delirium only (29.2%) were compared with 266 of 1620 patients with neither delirium nor dementia (16.4%) (OR, 2.36 [95% CI, 1.82-3.05]; I^2, 2.1%; TABLE 2).

Institutionalization

The primary analysis of adjusted ORs included 2579 participants in 7 studies. Delirium was associated with an increased risk of institutionalization after a mean (SD) follow-up of 14.6 (12.0) months (range, 3-38 months) in 176 of

527 participants with delirium (33.4%) vs 219 of 2052 controls (10.7%) (OR, 2.41 [95% CI, 1.77-3.29]; I^2, 0%; (Figure 2). No evidence of publication bias was identified using the Egger regression asymmetry test (β=0.45; P=.65) but the trim-and-filled method simulated 1 missing study (OR, 2.32 [95% CI, 1.69-3.21]). No evidence of outliers was found. A sensitivity analysis showed that the association between delirium and institutionalization remained when only cases who had not resided in an institution at baseline were considered (Table 1).

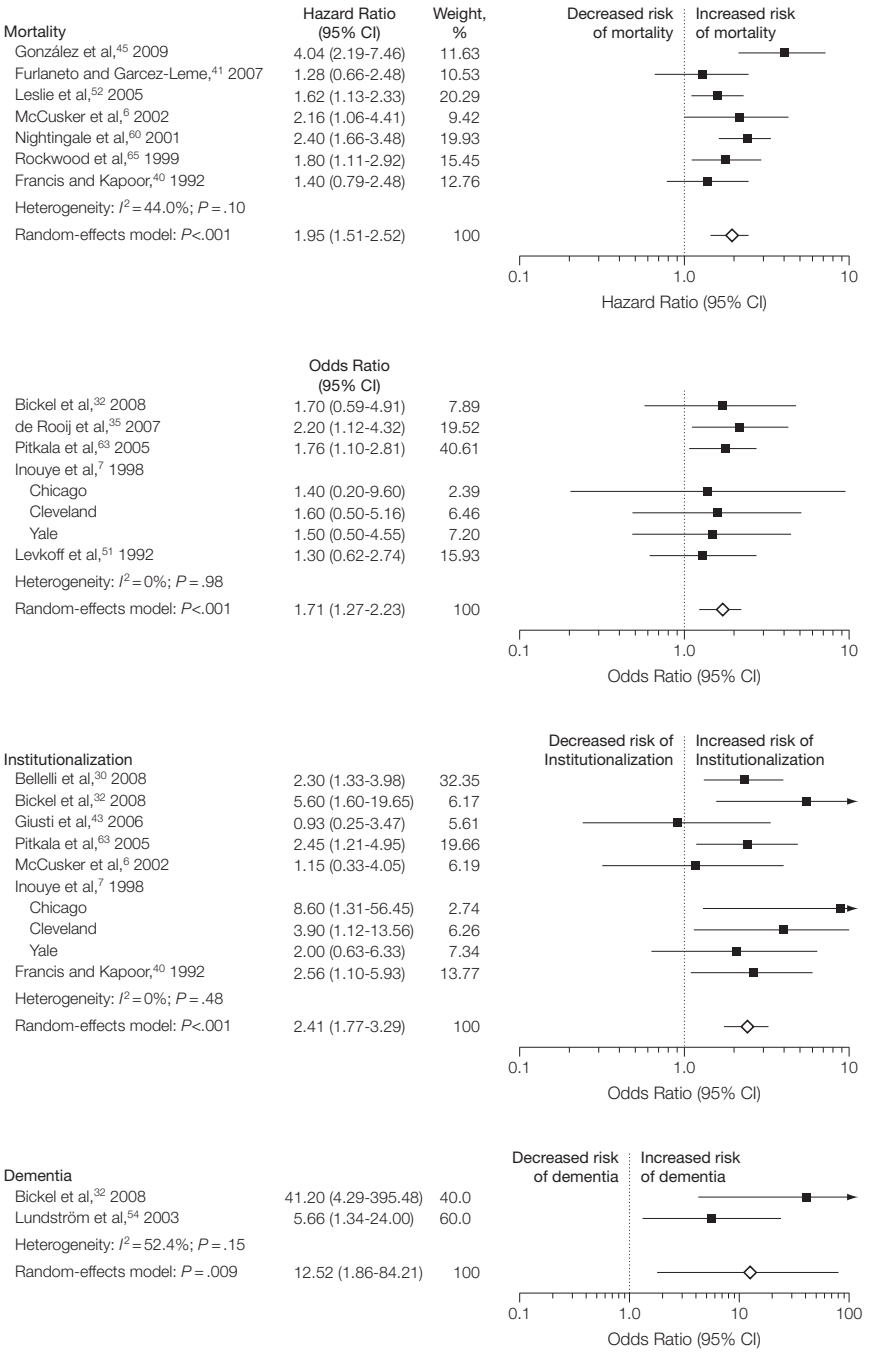
Secondary analyses with unadjusted ORs produced similar results (see the eFigure). Additional stratified analyses with unadjusted ORs showed that higher rates of institutionalization were present among individuals who experienced delirium regardless of the source of the study population (ie, inclusion of individuals with dementia, age, country of origin, and follow-up time; see eTable 5).

Our exploratory secondary analyses showed that delirium remained significantly associated with institutionalization when 80 of 174 patients with delirium superimposed on dementia (46.0%) were compared with 42 of 208 patients with dementia only (20.2%) (OR, 2.55 [95% CI, 1.56-4.18]; I^2, 0%), but the association was not significant when 24 of 108 patients with delirium only (22.2%) were compared with 29 of 237 patients with neither delirium nor dementia (12.2%) (OR, 3.25 [95% CI, 0.85-12.45]; I^2, 66.5%), although the number of patients in these study categories were small and power was limited (Table 2).

Dementia

The primary analysis of adequately adjusted ORs summarized the results of 2 studies and included 241 participants. Thirty-five of 56 patients with delirium (62.5%) had an increased risk of dementia at follow-up compared with 15 of 185 controls (8.1%) after 3.2 and 5.0 years of follow-up (OR, 12.52 [95% CI, 1.86-84.21]; I^2, 52.4%; Figure 2). Because only 2 studies were available for this primary analysis of adjusted risk estimates, no sensitivity or trim-and-fill analyses were performed. The secondary analysis confirmed the results of the primary analysis and showed that the association remained significant

Figure 2. Primary Analyses



Analyses of the association between delirium and mortality, institutionalization, and dementia adjusted for age, sex, comorbid illness or illness severity, and baseline dementia. CI indicates confidence interval. Weighting was assigned according to the inverse of the variance. Hazard ratios and odds ratios larger than 1 indicate increased risk of mortality, institutionalization, or dementia among participants who experienced delirium.

when only incident cases of dementia (from studies that had the same method of ascertainment at baseline and follow-up) were included (see eTable 5).

COMMENT

The results of this meta-analysis provide evidence that delirium in elderly patients is associated with an increased risk of death, institutionalization, and dementia, independent of age, sex, comorbid illness or illness severity, and presence of dementia at base-

Table 1. Primary Analyses of the Association Between Delirium and Mortality, Institutionalization, and Dementia in Studies Adjusted for Age, Sex, Comorbid Illness or Illness Severity, and Baseline Dementia

	Delirium, No.		No Delirium, No.					
	Events	Total Patients[a]	Events	Total Patients[a]	*k*[b]	References	HR (95% CI)[c]	I^2, %
Mortality								
Fixed effects	271	714	616	2243	7	6, 40, 41, 45, 52, 60, 65	1.95 (1.62-2.34)	44.0
Random effects	271	714	616	2243	7	6, 40, 41, 45, 52, 60, 65	1.95 (1.51-2.52)	44.0
Postdischarge mortality only	160	414	318	1298	5	6, 40, 41, 52, 65	1.62 (1.29-2.04)	0
							OR (95% CI)	
Fixed effects	183	483	316	1583	7	7, 32, 35, 51, 63	1.71 (1.27-2.30)	0
Random effects	183	483	316	1583	7	7, 32, 35, 51, 63	1.71 (1.27-2.30)	0
Postdischarge mortality only	15	41	17	158	1	32	1.70 (0.59-4.91)	NA
Institutionalization								
Fixed effects	176	527	219	2052	9	6, 7, 30, 32, 40, 43, 63	2.41 (1.77-3.29)	0
Random effects	176	527	219	2052	9	6, 7, 30, 32, 40, 43, 63	2.41 (1.77-3.29)	0
Incident cases only	89	302	161	1829	7	6, 7, 30, 32, 40, 43, 63	2.37 (1.63-3.45)	12.7
Dementia								
Fixed effects	35	56	15	185	2	32, 54	10.06 (2.98-34.0)	52.4
Random effects	35	56	15	185	2	32, 54	12.52 (1.86-84.21)	52.4
Incident cases only	21	30	9	48	1	54	5.66 (1.34-24.0)	NA

Abbreviations: CI, confidence interval; HR, hazard ratio; NA, data not applicable; OR, odds ratio.
[a]The sum total of participants in each subgroup is an estimate because the event rates entered in statistically adjusted analyses were not consistently reported for all studies.
[b]Indicates the number of individual effect estimates in aggregated analyses.
[c]The HRs and ORs that are greater than 1 indicate increased risk of mortality, institutionalization, and dementia among participants who experienced delirium.

Table 2. Primary Risk-Adjusted Analyses and Secondary Unadjusted Analyses

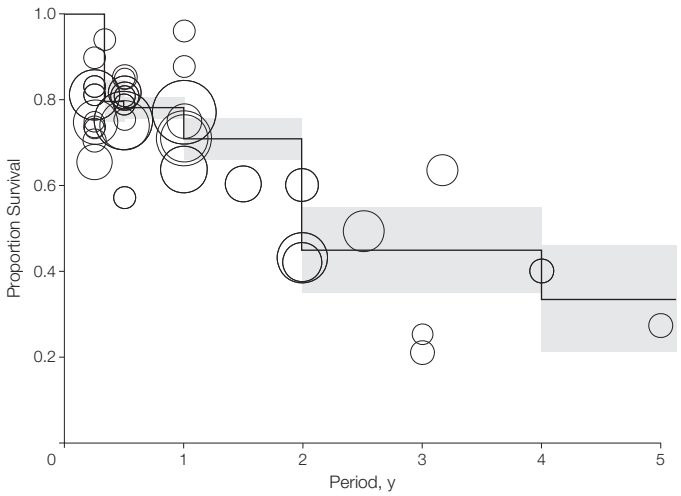
	Delirium, No.		No Delirium, No.		Summary Estimates				Trim-and-Fill Estimates	
	Events	Total Patients	Events	Total Patients	*k*[a]	RR (95% CI)[b]	*P* Value	I^2, %	Missing Studies, No.	Adjusted OR (95% CI)[b]
Primary Analyses[c]										
Mortality										
HR	271	714	616	2243	7	1.95 (1.51-2.52)	<.001	44.0	0	1.95 (1.51-2.52)
OR	183	483	316	1583	7	1.71 (1.27-2.30)	<.001	0	0	1.71 (1.27-2.30)
Institutionalization	176	527	219	2052	9	2.41 (1.77-3.29)	<.001	0	1	2.32 (1.69-3.21)
Dementia	35	56	15	185	2	12.52 (1.86-84.21)	.009	52.4	NA	NA
Secondary Analyses										
Mortality[d]	783	2615	1015	7225	40	2.65 (2.34-3.01)	<.001	2.5	7	2.41 (2.08-2.80)
Institutionalization	331	869	338	2826	20	4.73 (3.46-6.47)	<.001	45.2	7	3.61 (2.57-5.07)
Dementia	38	70	66	381	6	9.42 (4.26-20.87)	<.001	23.8	0	9.42 (4.26-20.87)
With dementia										
Mortality	222	643	135	564	18	1.75 (1.30-2.36)	<.001	0.7	2	1.61 (1.16-2.24)
Institutionalization	80	174	42	208	5	2.55 (1.56-4.18)	<.001	0	0	2.55 (1.55-4.18)
Without dementia										
Mortality	168	575	266	1620	17	2.36 (1.82-3.05)	<.001	2.1	4	2.16 (1.56-3.00)
Institutionalization	24	108	29	237	6	3.25 (0.85-12.45)	.04	66.5	0	3.25 (0.85-12.45)

Abbreviations: CI, confidence interval; HR, hazard ratio; NA, data not applicable; OR, odds ratio; RR, risk ratio.
[a]Indicates the number of individual effect estimates in aggregated analyses.
[b]The HRs and ORs that are greater than 1 indicate increased risk of mortality, institutionalization, and dementia among participants who experienced delirium.
[c]The sum total of participants in each subgroup is an estimate because the event rates entered in the statistically adjusted analyses were not consistently reported for all studies.
[d]Edelstein et al[36] did not report event rates for the delirium and no delirium group. Therefore, this study was omitted in the sum total of participants for each subgroup.

line. Moreover, our stratified models confirm that this association persists when excluding studies that included in-hospital deaths and patients residing in an institution at baseline.

The results of this meta-analysis can be instrumental in patient care. The low rate of survival and the high rates of institutionalization and dementia indicate that older people who experience delirium should be considered an especially vulnerable population (see FIGURE 3 and Table 2). The results of this meta-analysis gain special clinical relevance considering that delirium in some cases can be prevented.[8] However, once delirium is present, management of delirium has not been found to improve long-term mortality or need for institutional care.[67] Thus, identifying patients at high risk for delirium and implementing strategies aimed at preventing delirium may help to avert some of the delirium–associated poor outcomes these patients experience.

Figure 3. Meta-analytic Survival Curve



Based on mortality rates among patients that experienced delirium during hospitalization from studies listed in the eFigure at http://www.jama.com. Circles are proportional to study size and depict the proportion of surviving individuals. For specified periods, aggregated weighted estimates for survival are depicted by a horizontal line with corresponding 95% confidence intervals (gray area). For example, 2 to 4 years after delirium, 45% of individuals are still alive.

This, to our knowledge, is the first study to systematically summarize the risk of poor outcome in elderly patients who experienced delirium. We used a comprehensive search strategy and systematic review method, following recommendations from the MOOSE guidelines.[9] In our meta-analysis, we limited heterogeneity and potential sources of bias by including only high-quality studies in elderly patients in the hospital or postacute care settings, excluding population studies. We identified high-quality studies using individual methodological aspects because summary scores to identify trials of high quality can be problematic.[68] Furthermore, our approach subdivided poor outcome into several categories, thereby avoiding potential heterogeneity that may arise when a single summary estimate is used. Our primary analyses controlled for selected covariates that may influence the association between delirium and poor outcome. We also performed secondary analyses of unadjusted effect estimates and demonstrated that the associations persisted regardless of the study population, the inclusion of nursing home residents or patients with dementia, age, country of origin, and time of follow-up. Heterogeneity, potential outliers, and publication bias were examined and were not responsible for the associations identified.

There are several methodological limitations to our study. Given the nature of delirium, all studies in our meta-analysis are observational; diverse study designs and patient characteristics make interpretation of aggregated estimates challenging and causality cannot be inferred.[9] Nevertheless, delirium was associated with poor outcomes even after controlling for important covariates. Moreover, heterogeneity was low to moderate in the analyses of longer-term outcomes, suggesting that variations in findings are compatible with chance alone and not likely to be caused by genuine differences between studies.[13]

In our meta-analysis, studies were pooled irrespective of their definition of delirium. In most studies, delirium was diagnosed by experts based on criteria derived from the *Diagnostic and Statistical Manual of Mental Disorders*[1,10,69,70]; thus, broadly similar methods were used. With regard to the ascertainment of dementia, more variety was present. For instance, because of the high prevalence of delirium at hospital admission,[71] evaluation of cognitive function based on patient interviews may have overestimated the number of participants with preexisting dementia. Although no significant heterogeneity emerged when we pooled studies that adopted alternative definitions of delirium or dementia, differences in case ascertainment may have introduced some random error.

Only a small number of studies examined the risk of dementia after delirium. Importantly, sensitivity analyses restricted to incident cases of dementia yielded somewhat more conservative estimates of the association between delirium and dementia. Only 1 study[54] provided an adjusted OR based on incident cases, so no meta-analysis could be performed in this most stringent subgroup.

We restricted our search to English- and Dutch-language sources and we did not search gray literature or blind the data abstractors to the data sources. However, we believe that the

magnitude and consistency of the observed effects render an important effect of bias unlikely in this respect. Moreover, we rigorously controlled for publication bias and used random-effects models that are generally better suited when studies are only gathered from the published literature.[14]

Several important clinical findings emerge from our meta-analysis. The persistence of the association between delirium and poor outcome years after the occurrence of delirium and presumably resolution of the precipitating factors suggests that delirium is not merely a marker of underlying disease. This is substantiated by our finding that the increased risk of poor outcome after delirium cannot readily be explained by predisposing factors, such as age, sex, comorbid illness or illness severity, and presence of baseline dementia. Moreover, the results of our stratified analyses suggest that even patients without the given risk factor analyzed experience adverse outcomes after delirium at least as often as do those with the risk factor. This somewhat counterintuitive finding may be because for vulnerable (eg, older, cognitively impaired) patients, relatively mild precipitating factors suffice to precipitate delirium, whereas in relatively healthier patients, a greater insult is required,[72] and those kinds of insults may be associated with a poorer long-term prognosis. Alternatively, the long-term detrimental effects of delirium in vulnerable populations may compete with other risks for poor outcome. Furthermore, delirium may be more difficult to detect in patients with dementia, resulting in misclassification and bias toward the null.

A number of potential explanations for the observed association between delirium and poor outcome can be hypothesized. Delirium may persist and a protracted course of delirium may contribute to increased morbidity and complications, exemplified by the association between delirium and the new concept of postoperative cognitive dysfunction.[73] In turn, the increased morbidity and complications may lead to poor outcome.[74] Persistence of symptoms can also be an indication that the underlying medical illness is still active or has deteriorated during the follow-up period. Alternatively, the factors that precipitated delirium may incite a detrimental sequence of events in the brain. Through overactivation of microglia and an aberrant stress response, the resulting uncontrolled neuroinflammation, elevation of cortisol levels, and neurotransmitter imbalances can persist for months, reducing the threshold for new episodes of delirium and potentially causing prolongation of neuropsychiatric symptoms.[75,76]

Delirium is a serious and common neuropsychiatric syndrome that may markedly affect outcome and long-term prognosis of elderly patients. Future studies will have to establish what exact mechanisms are responsible for the long-term poor outcomes after delirium and whether clinical characteristics of delirium itself (eg, duration or subtype) differentially influence prognosis. Moreover, clinical trials are needed to investigate whether the long-term sequelae associated with delirium can be averted.

Authors Contributions: Mr Witlox had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: van Gool, Witlox.
Acquisition of data: Witlox, Eurelings.
Analysis and interpretation of data: van Gool, Witlox, Eurelings, Eikelenboom, de Jonghe, Kalisvaart.
Drafting of the manuscript: Witlox, van Gool.
Critical revision of the manuscript for important intellectual content: van Gool, Witlox, Eikelenboom, de Jonghe, Eurelings, Kalisvaart.
Statistical analysis: Witlox, van Gool.
Administrative, technical, or material support: Witlox, van Gool, Eurelings.
Study supervision: van Gool, Eikelenboom, de Jonghe, Kalisvaart.
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Online-Only Material: The eFigure and eTables 1-5 are available at http://www.jama.com.
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REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 4th ed, text rev. Washington, DC: American Psychiatric Association; 2000.
2. Dasgupta M, Dumbrell AC. Preoperative risk assessment for delirium after noncardiac surgery. *J Am Geriatr Soc*. 2006;54(10):1578-1589.
3. Morandi A, Jackson JC, Ely EW. Delirium in the intensive care unit. *Int Rev Psychiatry*. 2009;21(1):43-58.
4. Siddiqi N, House AO, Holmes JD. Occurrence and outcome of delirium in medical in-patients. *Age Ageing*. 2006;35(4):350-364.
5. Young J, Inouye SK. Delirium in older people. *BMJ*. 2007;334(7598):842-846.
6. McCusker J, Cole M, Abrahamowicz M, et al. Delirium predicts 12-month mortality. *Arch Intern Med*. 2002;162(4):457-463.
7. Inouye SK, Rushing JT, Foreman MD, Palmer RM, Pompei P. Does delirium contribute to poor hospital outcomes? *J Gen Intern Med*. 1998;13(4):234-242.
8. Holroyd-Leduc JM, Khandwala F, Sink KM. How can delirium best be prevented and managed in older patients in hospital? *CMAJ*. 2010;182(5):465-470.
9. Stroup DF, Berlin JA, Morton SC, et al; Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of observational studies in epidemiology. *JAMA*. 2000;283(15):2008-2012.
10. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 3rd ed. Washington, DC: American Psychiatric Association; 1980.
11. von Elm E, Altman DG, Egger M, et al; STROBE Initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement. *BMJ*. 2007;335(7624):806-808.
12. Bland JM, Altman DG. Statistics notes. *BMJ*. 2000;320(7247):1468.
13. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-560.
14. Borenstein M, Hedges LV, Higgins JPT, et al. Fixed-effect versus random-effects models. In: *Introduction to Meta-analysis.* Chichester, West Sussex, England: John Wiley & Sons Ltd; 2009:77-85.

15. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629-634.
16. Duval S, Tweedie R. Trim and fill. *Biometrics*. 2000; 56(2):455-463.
17. Sutton AJ, Duval SJ, Tweedie RL, et al. Empirical assessment of effect of publication bias on meta-analyses. *BMJ*. 2000;320(7249):1574-1577.
18. Dolan MM, Hawkes WG, Zimmerman SI, et al. Delirium on hospital admission in aged hip fracture patients. *J Gerontol A Biol Sci Med Sci*. 2000; 55(9):M527-M534.
19. Harjola VP, Follath F, Nieminen MS, et al. Characteristics, outcomes, and predictors of mortality at 3 months and 1 year in patients hospitalized for acute heart failure. *Eur J Heart Fail*. 2010;12(3):239-248.
20. Heijmeriks JA, Dassen W, Prenger K, Wellens HJ. The incidence and consequences of mental disturbances in elderly patients post cardiac surgery. *Clin Cardiol*. 2000;23(7):540-546.
21. Iwata M, Kuzuya M, Kitagawa Y, et al. Underappreciated predictors for postdischarge mortality in acute hospitalized oldest-old patients. *Gerontology*. 2006;52(2):92-98.
22. Loponen P, Luther M, Wistbacka JO, et al. Postoperative delirium and health related quality of life after coronary artery bypass grafting. *Scand Cardiovasc J*. 2008;42(5):337-344.
23. Poór G, Atkinson EJ, O'Fallon WM, Melton LJ III. Determinants of reduced survival following hip fractures in men. *Clin Orthop Relat Res*. 1995;(319): 260-265.
24. Rudolph JL, Marcantonio ER, Culley DJ, et al. Delirium is associated with early postoperative cognitive dysfunction. *Anaesthesia*. 2008;63(9):941-947.
25. Satish S, Winograd CH, Chavez C, Bloch DA. Geriatric targeting criteria as predictors of survival and health care utilization. *J Am Geriatr Soc*. 1996; 44(8):914-921.
26. Wacker P, Nunes PV, Cabrita H, Forlenza OV. Postoperative delirium is associated with poor cognitive outcome and dementia. *Dement Geriatr Cogn Disord*. 2006;21(4):221-227.
27. Adamis D, Treloar A, Darwiche FZ, et al. Associations of delirium with in-hospital and in 6-months mortality in elderly medical inpatients. *Age Ageing*. 2007;36(6):644-649.
28. Bellelli G, Frisoni GB, Turco R, et al. Delirium superimposed on dementia predicts 12-month survival in elderly patients discharged from a postacute rehabilitation facility. *J Gerontol A Biol Sci Med Sci*. 2007; 62(11):1306-1309.
29. Bellelli G, Morghen S, Turco R, Trabucchi M. Delirium in older people. *Age Ageing*. 2008;37(3): 353-354.
30. Bellelli G, Magnifico F, Trabucchi M. Outcomes at 12 months in a population of elderly patients discharged from a rehabilitation unit. *J Am Med Dir Assoc*. 2008;9(1):55-64.
31. Berggren D, Gustafson Y, Eriksson B, et al. Postoperative confusion after anesthesia in elderly patients with femoral neck fractures. *Anesth Analg*. 1987; 66(6):497-504.
32. Bickel H, Gradinger R, Kochs E, Förstl H. High risk of cognitive and functional decline after postoperative delirium. *Dement Geriatr Cogn Disord*. 2008; 26(1):26-31.
33. Brännström B, Gustafson Y, Norberg A, Winblad B. Problems of basic nursing care in acutely confused and non-confused hip-fracture patients. *Scand J Caring Sci*. 1989;3(1):27-34.
34. Curyto KJ, Johnson J, TenHave T, et al. Survival of hospitalized elderly patients with delirium. *Am J Geriatr Psychiatry*. 2001;9(2):141-147.
35. de Rooij SE, Buurman BM, Korevaar JC, et al. Comorbidity in acutely hospitalised older patients as a risk factor for death in hospital or within 3 months after discharge [in Dutch]. *Ned Tijdschr Geneeskd*. 2007; 151(36):1987-1993.
36. Edelstein DM, Aharonoff GB, Karp A, et al. Effect of postoperative delirium on outcome after hip fracture. *Clin Orthop Relat Res*. 2004;(422):195-200.
37. Edlund A, Lundström M, Lundström G, et al. Clinical profile of delirium in patients treated for femoral neck fractures. *Dement Geriatr Cogn Disord*. 1999; 10(5):325-329.
38. Edlund A, Lundström M, Brännström B, et al. Delirium before and after operation for femoral neck fracture. *J Am Geriatr Soc*. 2001;49(10):1335-1340.
39. Edlund A, Lundström M, Karlsson S, et al. Delirium in older patients admitted to general internal medicine. *J Geriatr Psychiatry Neurol*. 2006;19 (2):83-90.
40. Francis J, Kapoor WN. Prognosis after hospital discharge of older medical patients with delirium. *J Am Geriatr Soc*. 1992;40(6):601-606.
41. Furlaneto ME, Garcez-Leme LE. Impact of delirium on mortality and cognitive and functional performance among elderly people with femoral fractures. *Clinics (Sao Paulo)*. 2007;62(5):545-552.
42. George J, Bleasdale S, Singleton SJ. Causes and prognosis of delirium in elderly patients admitted to a district general hospital. *Age Ageing*. 1997;26 (6):423-427.
43. Giusti A, Barone A, Oliveri M, et al. An analysis of the feasibility of home rehabilitation among elderly people with proximal femoral fractures. *Arch Phys Med Rehabil*. 2006;87(6):826-831.
44. González M, de Pablo J, Valdés M, et al. Delirium. *Eur J Psychiatry*. 2005;19(3):165-171.
45. González M, Martínez G, Calderón J, et al. Impact of delirium on short-term mortality in elderly inpatients. *Psychosomatics*. 2009;50(3):234-238.
46. Gustafson Y, Berggren D, Brännström B, et al. Acute confusional states in elderly patients treated for femoral neck fracture. *J Am Geriatr Soc*. 1988; 36(6):525-530.
47. Isaia G, Astengo MA, Tibaldi V, et al. Delirium in elderly home-treated patients. *Age (Dordr)*. 2009; 31(2):109-117.
48. Kakuma R, du Fort GG, Arsenault L, et al. Delirium in older emergency department patients discharged home. *J Am Geriatr Soc*. 2003;51(4):443-450.
49. Kat MG, Vreeswijk R, de Jonghe JF, et al. Long-term cognitive outcome of delirium in elderly hip surgery patients. *Dement Geriatr Cogn Disord*. 2008; 26(1):1-8.
50. Koster S, Hensens AG, van der Palen J. The long-term cognitive and functional outcomes of postoperative delirium after cardiac surgery. *Ann Thorac Surg*. 2009;87(5):1469-1474.
51. Levkoff SE, Evans DA, Liptzin B, et al. Delirium. *Arch Intern Med*. 1992;152(2):334-340.
52. Leslie DL, Zhang Y, Holford TR, et al. Premature death associated with delirium at 1-year follow-up. *Arch Intern Med*. 2005;165(14):1657-1662.
53. Lewis LM, Miller DK, Morley JE, et al. Unrecognized delirium in ED geriatric patients. *Am J Emerg Med*. 1995;13(2):142-145.
54. Lundström M, Edlund A, Bucht G, et al. Dementia after delirium in patients with femoral neck fractures. *J Am Geriatr Soc*. 2003;51(7):1002-1006.
55. Marcantonio ER, Flacker JM, Michaels M, Resnick NM. Delirium is independently associated with poor functional recovery after hip fracture. *J Am Geriatr Soc*. 2000;48(6):618-624.
56. Marcantonio ER, Kiely DK, Simon SE, et al. Outcomes of older people admitted to postacute facilities with delirium. *J Am Geriatr Soc*. 2005;53(6): 963-969.
57. McAvay GJ, Van Ness PH, Bogardus ST Jr, et al. Older adults discharged from the hospital with delirium. *J Am Geriatr Soc*. 2006;54(8):1245-1250.
58. Minden SL, Carbone LA, Barsky A, et al. Predictors and outcomes of delirium. *Gen Hosp Psychiatry*. 2005;27(3):209-214.
59. Milisen K, Foreman MD, Abraham IL, et al. A nurse-led interdisciplinary intervention program for delirium in elderly hip-fracture patients. *J Am Geriatr Soc*. 2001;49(5):523-532.
60. Nightingale S, Holmes J, Mason J, House A. Psychiatric illness and mortality after hip fracture. *Lancet*. 2001;357(9264):1264-1265.
61. O'Keeffe S, Lavan J. The prognostic significance of delirium in older hospital patients. *J Am Geriatr Soc*. 1997;45(2):174-178.
62. Olofsson B, Lundström M, Borssén B, et al. Delirium is associated with poor rehabilitation outcome in elderly patients treated for femoral neck fractures. *Scand J Caring Sci*. 2005;19(2):119-127.
63. Pitkala KH, Laurila JV, Strandberg TE, Tilvis RS. Prognostic significance of delirium in frail older people. *Dement Geriatr Cogn Disord*. 2005;19(2-3):158-163.
64. Pompei P, Foreman M, Rudberg MA, et al. Delirium in hospitalized older persons. *J Am Geriatr Soc*. 1994;42(8):809-815.
65. Rockwood K, Cosway S, Carver D, et al. The risk of dementia and death after delirium. *Age Ageing*. 1999;28(6):551-556.
66. Zakriya K, Sieber FE, Christmas C, et al. Brief postoperative delirium in hip fracture patients affects functional outcome at three months. *Anesth Analg*. 2004; 98(6):1798-1802.
67. Pitkälä KH, Laurila JV, Strandberg TE, Tilvis RS. Multicomponent geriatric intervention for elderly inpatients with delirium. *J Gerontol A Biol Sci Med Sci*. 2006;61(2):176-181.
68. Jüni P, Witschi A, Bloch R, Egger M. The hazards of scoring the quality of clinical trials for meta-analysis. *JAMA*. 1999;282(11):1054-1060.
69. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 3rd ed, revised. Washington, DC: American Psychiatric Association; 1987.
70. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: American Psychiatric Association; 1994.
71. Juliebø V, Bjøro K, Krogseth M, et al. Risk factors for preoperative and postoperative delirium in elderly patients with hip fracture. *J Am Geriatr Soc*. 2009; 57(8):1354-1361.
72. Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized elderly persons. *JAMA*. 1996;275(11):852-857.
73. Moller JT, Cluitmans P, Rasmussen LS, et al; ISPOCD Investigators. Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. *Lancet*. 1998;351(9106):857-861.
74. Cole MG, Ciampi A, Belzile E, Zhong L. Persistent delirium in older hospital patients. *Age Ageing*. 2009;38(1):19-26.
75. van Gool WA, van de Beek D, Eikelenboom P. Systemic infection and delirium. *Lancet*. 2010;375 (9716):773-775.
76. Maclullich AM, Ferguson KJ, Miller T, et al. Unravelling the pathophysiology of delirium. *J Psychosom Res*. 2008;65(3):229-238.

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ACUTE GERIATRICS

Is delirium the medical emergency we know least about?

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An 87-year-old woman has been in your ED for an hour. Three weeks ago she fell at home and sustained a fractured humerus, before being discharged to a rehabilitation facility. She has been sent back to ED as staff are concerned she has uncontrolled pain, manifesting as distress, particularly at night, and refusal to cooperate with her rehab programme.

You become aware of her when a nursing colleague approaches and says 'You have to do something about that patient trying to climb out of bed'.

Delirium (acute brain failure) is a syndrome characterised by acute onset of disturbance in attention and orientation that fluctuates and is accompanied by cognitive deficits such as disturbance in memory, language, perception or consciousness.[1] Like other acute organ failures, it is a medical emergency. Patients with delirium have a 38% higher mortality and 200% higher rate of institutionalisation after hospitalisation.[2] The clinical presentation of delirium can be classified broadly into three subtypes – hypoactive, hyperactive and mixed – on the basis of psychomotor behaviour. In hypoactive delirium, there is global cognitive slowing that manifests as a quiet, withdrawn and confused patient.[3]

About 10% of Australians aged over 70 years have delirium at the time of presentation to ED, and a further 8% develop delirium during a hospital admission.[4]

Delirium has been identified by the Australian Commission on Safety and Quality in Healthcare as a high priority area for quality improvement.[5] The challenge for ED staff is to respond to this priority, despite the competition of other pressing demands.

Diagnosis

Delirium detection is clinical, not difficult, yet poorly executed in almost all EDs. The reasons for this are myriad, but in our view include gaps in ACEM training, lack of recognition of its importance and the perception that this is not core ED business. When a colleague tells you he or she can always spot a patient with delirium, do not believe them. Emergency physicians correctly diagnose delirium in only one quarter of cases.[6] What they usually mean is that they have seen agitated patients climbing out of bed and know they have to 'do something' about them. In fact, the hypoactive or mixed forms of delirium are collectively at least three times as common as the hyperactive form. But you are almost never asked to 'do something' about an older person lying quietly in bed.

Table 1 represents one method to diagnose delirium in ED, but there are many more.[7] As with most things in life, when there are numerous ways of doing something, no one method is clearly superior; otherwise, we would all be doing it. All measures to detect delirium represent a compromise between the sensitivity and specificity of the instrument, the amount of training required to use it, the time it takes to perform in a time-poor environment and its validity in the ED population. The authors cannot even agree among ourselves as to which instrument is best to use, but we all agree that any ED should have one instrument that is consistently and regularly taught to all relevant staff. Consistency with tools used by inpatient colleagues (if they are using any) is a good tactic where practical.

Prevention and non-pharmacological management

Strategies to manage the delirious patient, and prevent delirium developing, can be thought of together. We recommend attention to the structural, policy and staffing environment of the ED, although this is largely opinion based as few approaches have been experimentally tested.

From a structural perspective, designing a new ED will allow for incorporation of specific gerontic elements that improve exposure to natural light, enhance independent orientation, navigation and mobility of elders through the environment and reduce noise.[8]

But assuming you would not be building a new ED any time soon, some simple measures in existing EDs can be optimised:

1. Improve orientation
   a. In cubicles install high visibility clocks, calendars and patient orientation charts that state clearly

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TABLE 1. *The Confusion Assessment Method (adapted from Inouye et al.[22])*

Feature 1: Acute onset and fluctuating course	Is there evidence of an acute change in the patient's cognition from baseline? Does it fluctuate over the day?
Feature 2: Inattention	Does the patient have difficulty focusing attention? Do they have difficulty keeping track of what is being said?
Feature 3: Disorganised thinking	Is the patient's thinking incoherent, rambling, irrelevant, unclear or illogical, switching from subject to subject?
Feature 4: Altered level of consciousness	Is the patient's level of consciousness altered, that is, drowsy, lethargic or stupor; hyper alert

A diagnosis of delirium requires the presence of both Feature 1 and 2 with at least one of Feature 3 or 4.

where the patient is and what they are awaiting.[9–11]

b. Fit clear signage using colours and fonts that are easily recognisable by older persons to facilitate independent navigation through the ED.

2. Encourage safe mobilisation and navigation within ED.

a. Keep corridors free of clutter.

b. Use colour contrast (e.g. in wall/door painting) to ensure that features such as toilets are easily distinguished and recognised.

Policy and staffing changes can contribute to delirium prevention, and their implementation can be seen as 'doing something about that patient' without progressing to pharmacological restraint.

1. Patient flow

a. Preferentially triage older persons to, where available, areas where daylight is visible or single rooms to aid rest and avoid the extremes of sensory stimulation commonly found in the ED.[9]

b. Minimise room and staffing changes for those at risk of, or with, delirium.[10]

2. Staffing approach

a. Adopt a TADA approach (tolerate, anticipate, do not agitate).[12]

i. Tolerate behaviours where these are not a threat to patient or staff safety.

ii. Anticipate behaviour where clinically appropriate by not tethering older persons to beds by intravenous lines, oxygen, monitoring and bladder catheters.[10–12]

iii. Do not agitate, for example, avoid unnecessary medical procedures.

b. Transition from the custodial (and even punitive) model of staff–patient interaction, where staff physically restrain or simply supervise at risk elders, to a therapeutic model,[10,12–15] train staff to actively encourage mobility and patient participation in their care and engage elders in cognitively meaningful activities.

c. Actively involve family and caregivers to encourage patient sense of security and reinforce orientation cues.[10]

3. Clinical approach

a. Prevent dehydration by frequent offering of food and fluids (where appropriate).[9]

b. Assess and treat pain using cognition-appropriate pain assessment tools.[16]

c. Promote a structured approach to assessment for and management of underlying causes for delirium.

d. Avoid drugs implicated in delirium.

e. Regularly toilet.

f. Ensure access to patient's hearing and visual aids.[9,10]

Finally, given the delirium risk inherent to the ED and hospital environment, ED physicians should champion emergency avoidance and hospital substitutive care programmes that provide frail, older persons the option to have their acute healthcare needs addressed in the community where possible.[17,18]

Pharmacological management

Pharmacological management of the agitated patient should only be utilised when non-pharmacological methods have failed and the attendant risk is outweighed by the potential patient safety benefits.

The aim of medication is not to obtund the patient but to treat patient (not staff) distress, enhance safety and to create a setting wherein the underlying cause of delirium can be sought and treated. Common sedation protocols used for acutely disturbed younger adults in ED should not be used in this population. We strongly recommend the 'start low, go slow' approach: start medications at a low dose and with sufficiently long intervals between doses based on the pharmacokinetics and pharmacodynamics of the drug. Do not expect immediate effects or respond to their absence by frequent escalating dosing. Particular attention should be given when choosing medications when treating patients with possible Parkinsons or Lewy Body Dementia. Haloperidol should be avoided in this group of patients. Having a departmental approach formulated with your inpatient colleagues, such as geriatricians or psychogeriatricians, who are usually responsible for managing the complications of over sedation, is often useful. If family or carers are comfortable, they can be used as allies in offering drug therapy to frightened patients.

The main drugs used for managing acutely agitated delirious older patients are haloperidol, risperidone, olanzapine and quetiapine.

Haloperidol has been extensively used in this population and is effective but comes with a significant adverse effect profile including extrapyramidal symptoms, which can be life-threatening.[19]

Recently, risperidone has emerged as an equivalent alternative with a better adverse effect profile.[20] There is no intravenous form available in Australasia, but it comes in sublingual, quicklets and tablet presentations.

Either haloperidol or risperidone should be started at a dose of 0.25 mg for frail elders or in patients that are naïve to the drug (or 0.5 mg otherwise). Avoid re-dosing within 4 h. Risperidone quicklets can be offered dissolved in juice or sublingually.

Olanzapine[21] has a comparatively good safety profile and is being increasingly used in delirium. It comes

in i.m., i.v., oral or sublingual form. Olazapine may be commenced at 1.25 mg orally or i.m. in frail elders (or 2.5 mg otherwise), with no re-dosing within 6 h.

Quetiapine should at present be considered a second line agent unless haloperidol, risperidone or olanzapine are contraindicated. However, for patients with Parkinsons or Lewy Body Dementia, quetiapine has been pitched as an alternative. Quetiapine is well absorbed and has been shown to be as effective as haloperidol in appropriate circumstances. The commencing dose is 25 mg.

The use of benzodiazepines outside the setting of alcohol or benzodiazepine withdrawal is controversial and best avoided.

Prior to initiating any of the above pharmacotherapies ensure that contributors to delirium such as pain have been adequately addressed and that non-pharmacologic approaches have been exhausted.

Summary

Delirium is a medical emergency common in older patients presenting to ED, with a high risk of morbidity and mortality. ED physicians fail to identify delirium in three out of four patients. The hypoactive subtype is more common than the hyperactive subtype, which most people associate with delirium. As well as identifying and managing delirium present on arrival, the ED needs processes in place to prevent iatrogenic delirium. To make this cultural change requires clear commitment and education of the whole multidisciplinary ED team. Non-pharmacological interventions such as attention to toileting, feeding, analgesia and re-orientation are important for both prevention and management of distress. When using pharmacological agents, remember 'start low, go slow'. Unless contraindicated, risperidone is a reasonable first choice where drug management is required.

Competing interests

None declared.

References

1. Neufeld KJ, Thomas C. Delirium: definition, epidemiology, and diagnosis. *J. Clin. Neurophysiol.* 2013; **30**: 438–42.
2. Witlox J, Eurelings LS, de Jonghe JF, Kalisvaart KJ, Eikelenboom P, van Gool WA. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis. *JAMA* 2010; **304**: 443–51.
3. Lipowski ZJ. Transient cognitive disorders (delirium, acute confusional states) in the elderly. *Am. J. Psychiatry* 1983; **140**: 1426–36.
4. Travers C, Byrne G, Pachana N, Klein K, Gray L. Prospective observational study of dementia and delirium in the acute hospital setting. *Intern. Med. J.* 2013; **43**: 262–9.
5. Australian Commission on Safety and Quality in Health Care. Delirium clinical care standard. ASC-QHC. 2016. [Cited 22 Jun 2016.] http://www.safetyandquality.gov.au/our-work/clinical-care-standards/delirium-clinical-care-standard/
6. Han JH, Zimmerman EE, Cutler N *et al.* Delirium in older emergency department patients: recognition, risk factors, and psychomotor subtypes. *Acad. Emerg. Med.* 2009; **16**: 193–200.
7. De J, Wand AP. Delirium screening: a systematic review of delirium screening tools in hospitalized patients. *Gerontologist* 2015; **55**: 1079–99.
8. Schnitker LM, Martin-Khan M, Burkett E *et al.* Structural quality indicators to support quality of care for older people with cognitive impairment in emergency departments. *Acad. Emerg. Med.* 2015; **22**: 273–84.
9. Inouye SK, Bogardus ST Jr, Charpentier ST *et al.* A multicomponent intervention to prevent delirium in hospitalized older patients. *N. Engl. J. Med.* 1999; **340**: 669–76.
10. McCusker J, Cole M, Abrahamowicz M, Han L, Podoba JE, Ramman-Haddad L. Environmental risk factors for delirium in hospitalized older people. *J. Am. Geriatr. Soc.* 2001; **49**: 1327–34.
11. Martinez FT, Tobar C, Beddings CI, Vallejo G, Fuentes P. Preventing delirium in an acute hospital using a non-pharmacological intervention. *Age Ageing* 2012; **41**: 629–34.
12. Flaherty JH, Little MO. Matching the environment to patients with delirium: lessons learned from the delirium room, a restraint-free environment for older hospitalized adults with delirium. *J. Am. Geriatr. Soc.* 2011; **59**: S295–300.
13. Moyle W, Borbasi S, Wallis M, Olorenshaw R, Gracia N. Acute care management of older people with dementia: a qualitative perspective. *J. Clin. Nurs.* 2011; **20**: 420–8.
14. Dewing J. Special observation and older persons with dementia/delirium: a disappointing literature review. *Int. J. Older People Nurs.* 2013; **8**: 19–28.
15. Graham F. A new frontier: improving nursing care for people with dementia and delirium in hospitals. *J. Nurs. Adm.* 2015; **45**: 589–91.
16. Schreier AM. Nursing care, delirium, and pain management for the hospitalized older adult. *Pain Manag. Nurs.* 2010; **11**: 177–85.
17. Burkett E, Scott I. CARE-PACT: a new paradigm of care for acutely unwell residents in aged care facilities. *Aust. Fam. Physician* 2015; **44**: 204–9.
18. Conway J, Dilworth S, Hullick C, Hewitt J, Turner C, Higgins I. A multi-organisation aged care emergency service for acute care management of older residents in aged care facilities. *Aust. Health Rev.* 2015; **39**: 514–6.
19. Suh G, Greenspan A, Choi S. Comparative efficacy of risperidone versus haloperidol on behavioural and psychological symptoms of dementia. *Int. J. Geriat. Psychiatry* 2007; **22**: 494–5.
20. Brodaty H, Ames D, Snowdon J *et al.* A randomized placebo-controlled trial of risperidone for the treatment of aggression, agitation, and psychosis of dementia. *J. Clin. Psychiatry* 2003; **64**: 134–43.
21. Street JS, Clark WS, Gannon KS *et al.* Olanzapine treatment of psychotic and behavioral symptoms in patients with Alzheimer disease in nursing care facilities: a double-blind, randomized, placebo-controlled trial. The HGEU Study Group. *Arch. Gen. Psychiatry* 2000; **57**: 968–76.
22. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann. Intern. Med.* 1990; **113**: 941–8.

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How can we identify patients with delirium in the emergency department?☆ A review of available screening and diagnostic tools

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ABSTRACT

Delirium is a widespread and serious but under-recognized problem. Increasing evidence argues that emergency health care providers need to assess the mental status of the patient as the "sixth vital sign". A simple, sensitive, time-efficient, and cost-effective tool is needed to identify delirium in patients in the emergency department (ED); however, a stand-alone measurement has not yet been established despite previous studies partly because the differential diagnosis of dementia and delirium superimposed on dementia (DSD) is too difficult to achieve using a single indicator. To fill up the gap, multiple aspects of a case should be assessed including inattention and arousal. For instance, we proposed the 100 countdown test as an effective means of detecting inattention. Further dedicated studies are warranted to shed light on the pathophysiology and better management of dementia, delirium and/or "altered mental status". We reviewed herein the clinical questions and controversies concerning delirium in an ED setting.

1. Introduction

Delirium is a widespread and serious but under-recognized problem. Approximately 8–10% of older patients visiting the emergency department (ED) present with delirium, which is overlooked by emergency health care providers in 75% of the cases [1]. Delirium basically represents a decompensation of cerebral function in response to pathophysiological stressors [2]. The patient with delirium typically has adverse outcomes including mortality [3] and cognitive decline [4]. A previous study recommended that mental status be included as the "sixth vital sign" [5] along with the respiratory rate (respiratory system), pulse rate, blood pressure (cardiac system), temperature (immune system), and pain (neurological system).

Herein we reviewed the clinical questions and controversies concerning delirium in an ED setting based on previous systematic reviews [6,7]. This article includes: 1) a summary of previous studies of delirium in the ED; 2) delirium superimposed on dementia (DSD); 3) inattention as a component of consciousness; and 4) future prospects for better understanding of dementia, delirium and "altered mental status".

2. Summary of previous studies of delirium in the ED

Table 1 shows a list of previous studies of delirium in the ED setting, which validated and reported the diagnostic value of various screening tests used in the ED. The tests were found to have good sensitivity and specificity; however, Han et al. showed that ED health care providers were often busy and reluctant to adopt a delirium assessment tool into their routine clinical practice, even if such a procedure required < 2 min [1,8]. These studies underscore the need for much more simple, sensitive, time-efficient and cost-effective tool for identifying delirium in the ED setting such as those currently used for other diseases [9,10].

In this volume, Grossmann et al. [11] discussed whether the modified Richmond Agitation-Sedation Scale (mRASS), which requires only about 30 s implement, was effective in identifying delirium in consecutive patients in the ED with this symptom. The sensitivity, specificity, and the positive and negative predictive values were shown to be 0.70, 0.93, 0.44, and 0.98, respectively (see [11] for details including the 95% confidence interval). Grossmann et al. also performed a relevant subclass analysis, allocating subjects to either a group with or without dementia [11]. The aforementioned parameters in patients with dementia were 0.55, 0.83, 0.55 and 0.83, respectively, leading the authors to conclude that the mRASS was not sensitive enough to identify delirium in the ED setting especially in patients with dementia [11]. However, the same parameters were 0.89, 0.94, 0.38 and 1.00, respectively, in patients without dementia [11], a finding which seems sufficient to

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Table 1
Selective reports of delirium screening tests used in the emergency department.
This Table was modified from Mariz et al. [7].

Author	Ref.	Year	Tool	Country	Number of item	Administration time	Sensitivity; specificity
Almató et al.	[21]	2012	NEECHAM	Spain	9-Step assessment	10 min	95%; 78% (originally reported [22])
Han et al.	[23]	2013	DTS (Delirium Triage Screen)	USA	2-Step assessment	20 s	98%; 55%
Han et al.	[23]	2013	bCAM	USA	4 criteria	2 min	78–84%; 96–97%
Han et al.	[24]	2014	CAM-ICU	USA	4 criteria	2–5 min	68–72%; 98.6%
Hare et al.	[25]	2014	CAM	Australia	9 criteria	20 min	87%; 70%
Grosmann et al.	[8]	2014	mCAM-ED	Switzerland	3-Step assessment	4–6 min	In preparation (personal communication)
Han et al.	[1]	2015	RASS	USA	10-Step assessment	30–60 s	82–84%; 85–88%
Bo et al.	[26]	2016	4AT	Italy	4 criteria	1–2 min	90%; 84% (originally reported [27])
Morandi et al.	[12]	2016	Case-by-case	Multinational			

integrate mRASS into routine ED practice for patients with no previous history of dementia.

3. Delirium superimposed on dementia

One of crucial clinical questions is the differential diagnosis of dementia and DSD [12,13]. The Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) lists the five diagnostic criteria for delirium [14] as follows:

A) Disturbance in attention and awareness
B) Acute onset and fluctuation in severity during the course of a day
C) An additional disturbance in cognition (e.g. memory deficit, disorientation, language, visuospatial ability, or perception.)
D) The disturbances in Criteria A and C are not better explained by a pre-existing, established or evolving neuro-cognitive disorder and do not occur in the context of a severely reduced level of arousal such as coma.
E) Evidence that the disturbance is a direct physiological consequence of another medical condition or substance effects.

These criteria suggest that delirium cannot be correctly identified based on any one of these aspects alone, and that multiple aspects should be assessed using a systematic battery of tests (even in basic science, a battery of behavioral tests has been used to study post-operative delirium in mice [15]).

4. Inattention as a component of consciousness

Consciousness includes a function of awareness (content), arousal/wakefulness (level), and attention (tentatively considered as content) [2,16]. The European Delirium Association and American Delirium Society criticized the definition of delirium in the DSM-5 [2], proposing instead that attention and arousal are hierarchically related and that the level of arousal must be sufficient before attention can be reasonably assessed [2]. The DSM-5 defines awareness as reduced orientation to the environment; however, this definition might be too vague and the DSM-5 has not suggested how awareness might be assessed. Because the assessment of awareness is complicated and requires time, arousal and attention may be more suitable as assessment targets on a screening test. Previous studies concluded that inattention as well as arousal should be assessed to detect delirium [2,7,13]. We assumed that mRASS allowed assessment of arousal, but which of the attention subtypes – sustained attention, selective attention, switching attention, divided attention, or working memory [13] – should be assessed, and which test should be used for assessment, remain unclear.

Several assessment techniques are currently in use. The "months of the year backwards" (MOYB) is a widely used assessment technique. The Brief Confusion Assessment Method (bCAM) utilizes an abbreviated version of MOYB (December to July). Both these methods are useful in an English-language context, but the names of the months and the difficulty of reciting them backwards differ according to language. For example, in Japanese or Chinese, the names of months are number-based, presumably making the task easier. Thus, the evidence using English-language context cannot apply the real-world setting in such countlies. We have therefore proposed the "100 countdown" method as a simple, sensitive, time-efficient, and cost-effective means of detecting inattention [17]. An examiner simply asks a patient to count backwards from 100 to 70 in a manner similar to that used in Wechsler's mental control, in which the patient is asked to count backwards from 20 to 1, although the 100 countdown method has much higher sensitivity. Comparative studies based on the concurrent use of the various tests for detecting inattention will help to identify which subtype of attention should be tested to identify delirium.

5. Future prospects for better understanding of dementia, delirium and "altered mental status"

Quick Sequential Organ Failure Assessment (qSOFA) comprises only the respiratory rate (≥22/min), systolic blood pressure (≤100 mm Hg), and "altered mental status" [18] and actually has better prognostic value outside the ICU [19]. Given this fact, we may be justified in reconsidering what "altered mental status" means in clinical terms [20]. Even if mental status were to be accepted as the sixth vital sign, it remains to be solved whether the Glasgow Coma Scale is the best way to detect "altered mental status". Hence further studies dedicated to shedding light on the pathophysiology and better management of dementia, delirium, and/or "altered mental status" are warranted.

In this paper, we reviewed some of the clinical questions and controversies surrounding delirium in the ED setting. A screening test for delirium needs to have reasonably high sensitivity, but a stand-alone measurement for this purpose has yet to be established. In the interim, multiple aspects of a patient's symptomatology including inattention and arousal should be assessed. Together with other researchers who have examined this issue, we believe that a screening method for inattention and parameters for assessing dementia and delirium in the ED setting are desirable.

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References

[1] Han JH, Vasilevskis EE, Schnelle JF, Shintani A, Dittus RS, Wilson A, et al. The diagnostic performance of the Richmond Agitation Sedation Scale for detecting delirium in older emergency department patients. Acad Emerg Med 2015;22(7):878–82.
[2] European Delirium Association and American Delirium Society. The DSM-5 criteria, level of arousal and delirium diagnosis: inclusiveness is safer. BMC Med 2014; 12(141).
[3] Han JH, Shintani A, Eden S, Morandi A, Solberg LM, Schnelle J, et al. Delirium in the emergency department: an independent predictor of death within 6 months. Ann Emerg Med 2010;56(3):244–52.
[4] Gross AL, Jones RN, Habtemariam DA, Fong TG, Tommet D, Quach L, et al. Delirium and long-term cognitive trajectory among persons with dementia. Arch Intern Med 2012;172(17):1324–31.

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[5] Flaherty JH, Rudolph J, Shay K, Kamholz B, Boockvar KS, Shaughnessy M, et al. Delirium is a serious and under-recognized problem: why assessment of mental status should be the sixth vital sign. J Am Med Dir Assoc 2007;8(5):273–5.
[6] LaMantia MA, Messina FC, Hobgood CD, Miller DK. Screening for delirium in the emergency department: a systematic review. Ann Emerg Med 2014;63(5):551–60.
[7] Mariz J, Costa Castanho T, Teixeira J, Sousa N, Correia Santos N. Delirium diagnostic and screening instruments in the emergency department: an up-to-date systematic review. Geriatrics 2016;1(3):22.
[8] Grossmann FF, Hasemann W, Graber A, Bingisser R, Kressig RW, Nickel CH. Screening, detection and management of delirium in the emergency department - a pilot study on the feasibility of a new algorithm for use in older emergency department patients: the modified Confusion Assessment Method for the Emergency Department (mCAM-ED). Scand J Trauma Resusc Emerg Med 2014;22(19).
[9] Tamune H, Takeya H, Suzuki W, Tagashira Y, Kuki T, Nakamura M. Absence of jolt accentuation of headache cannot accurately rule out meningitis in adults. Am J Emerg Med 2013;31(11):1601–4.
[10] Tamune H, Takeya H, Suzuki W, Tagashira Y, Kuki T, Honda H, et al. Cerebrospinal fluid/blood glucose ratio as an indicator for bacterial meningitis. Am J Emerg Med 2014;32(3):263–6.
[11] Grossmann FF, et al. Performance of the Richmond agitation sedation scale in identifying delirium in older emergency department patients (AJEM15500). Am J Emerg Med 2017 [in press].
[12] Morandi A, Han JH, Meagher D, Vasilevskis E, Cerejeira J, Hasemann W, et al. Detecting delirium superimposed on dementia: evaluation of the diagnostic performance of the richmond agitation and sedation scale. J Am Med Dir Assoc 2016;17(9):828–33.
[13] Rudolph JL. Arousal, attention, and an abundance of opportunity to advance delirium care. J Am Med Dir Assoc 2016 Sep 1;17(9):775–6.
[14] American Psychiatric Association. Diagnostic and statistical manual of mental disorders5th ed. ; 2013, Arlington, VA.
[15] Peng M, Zhang C, Dong Y, Zhang Y, Nakazawa H, Kaneki M, et al. Battery of behavioral tests in mice to study postoperative delirium. Sci Report 2016;6:29874.
[16] Morandi A, Davis D, Bellelli G, Arora RC, Caplan GA, Kamholz B, et al. The diagnosis of delirium superimposed on dementia: an emerging challenge. J Am Med Dir Assoc 2017;18(1):12–8.
[17] Tamune H, Yasugi D, Narushima K. Diagnostic approach to the mental clouding–100 countdown and attention deficit–(in Japanese). Jpn J Psychiatr Treat 2016;31(3):381–6.
[18] Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016;315(8):801–10.
[19] Freund Y, Lemachatti N, Krastinova E, Van Laer M, Claessens YE, Avondo A, et al. Prognostic accuracy of Sepsis-3 criteria for in-hospital mortality among patients with suspected infection presenting to the emergency department. JAMA 2017;317(3):301–8.
[20] Han JH, Wilber ST. Altered mental status in older patients in the emergency department. Clin Geriatr Med 2013;29(1):101–36.
[21] Fontova Almató A, Basurto Oña X, Congost Devesa L. Prevalence of delirium in emergency department observation areas. (in Spanish). Rev Esp Geriatr Gerontol 2012;47(1):39–40.
[22] Neelon VJ, Champagne MT, Carlson JR, Funk SG. The NEECHAM confusion scale: construction, validation, and clinical testing. Nurs Res 1996;45(6):324–30.
[23] Han JH, Wilson A, Vasilevskis EE, Shintani A, Schnelle JF, Dittus RS, et al. Diagnosing delirium in older emergency department patients: validity and reliability of the delirium triage screen and the brief confusion assessment method. Ann Emerg Med 2013;62(5):457–65.
[24] Han JH, Wilson A, Graves AJ, Shintani A, Schnelle JF, Dittus RS, et al. Validation of the confusion assessment method for the intensive care unit in older emergency department patients. Acad Emerg Med 2014 Feb;21(2):180–7.
[25] Hare M, Arendts G, Wynaden D, Leslie G. Nurse screening for delirium in older patients attending the emergency department. Psychosomatics 2014;55(3):235–42.
[26] Bo M, Bonetto M, Bottignole G, Porrino P, Coppo E, Tibaldi M, et al. Length of stay in the emergency department and occurrence of delirium in older medical patients. J Am Geriatr Soc 2016;64(5):1114–9.
[27] Bellelli G, Annoni G, MacLullich AMJ, et al. Validation of the 4AT, a new instrument for rapid delirium screening: a study in 234 hospitalised older people. Age Ageing 2014;43:496–502.

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Delirium in the Emergency Department and Its Extension into Hospitalization (DELINEATE) Study: Effect on 6-month Function and Cognition

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BACKGROUND: The natural course and clinical significance of delirium in the emergency department (ED) is unclear.

OBJECTIVES: We sought to (1) describe the extent to which delirium in the ED persists into hospitalization (ED delirium duration) and (2) determine how ED delirium duration is associated with 6-month functional status and cognition.

DESIGN: Prospective cohort study.

SETTING: Tertiary care, academic medical center.

PARTICIPANTS: ED patients ≥65 years old who were admitted to the hospital.

MEASUREMENTS: The modified Brief Confusion Assessment Method was used to ascertain delirium in the ED and hospital. Premorbid and 6-month function were determined using the Older American Resources and Services Activities of Daily Living (OARS ADL) questionnaire which ranged from 0 (completely dependent) to 28 (completely dependent). Premorbid and 6-month cognition were determined using the short form Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) which ranged from 1 to 5 (severe dementia). Multiple linear regression was performed to determine if ED delirium duration was associated with 6-month function and cognition adjusted for baseline OARS ADL and IQCODE, and other confounders.

RESULTS: A total of 228 older ED patients were enrolled. Of the 105 patients who were delirious in the ED, 81 (77.1%) patients' delirium persisted into hospitalization. For every ED delirium duration day, the 6-month OARS ADL decreased by 0.63 points (95% CI: −1.01 to −0.24), indicating poorer function. For every ED delirium duration day, the 6-month IQCODE increased 0.06 points (95% CI: 0.01–0.10) indicating poorer cognition.

CONCLUSIONS: Delirium in the ED is not a transient event and frequently persists into hospitalization. Longer ED delirium duration is associated with an incremental worsening of 6-month functional and cognitive outcomes. **J Am Geriatr Soc 65:1333–1338, 2017.**

Key words: delirium; emergency department; long-term function; long-term cognition

Delirium is a form of acute brain failure that affects 8% to 17% of older emergency department (ED) patients,[1,2] and is associated with higher mortality[1] and prolonged hospitalizations.[3] The ED plays a central role in the US healthcare system and is the gateway for the majority of hospital admissions,[4] yet several knowledge gaps about delirium's impact in this unique setting exist. First, it is unclear how frequently delirium in the ED persists into hospitalization. Most delirium studies conducted in the ED typically assess for delirium at a single point in time.[5] Second, the effect of delirium in the ED on long-term outcomes is unclear especially as it relates to long-term function and cognition, which are critical components to the older patient's quality life. Most delirium outcome studies have been conducted in the inpatient setting and may have limited generalizability to the ED. The ED is a much more diverse environment representing patients with a wide variety of disease states (including

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illness severity) across different subspecialties (e.g., surgery, neurology, orthopedic surgery, etc.). These studies also typically enrolled patients within the first 48 hours of hospitalization and the patient's delirium status at the time of enrollment may not have reflected the patient's ED delirium status.[6–10] Third, it is unclear if prolonged episodes of delirium are associated with poorer long-term function and cognition. Despite delirium's heterogeneity, most outcome studies conducted have dichotomized delirium as a present-absent event. As a result, this study sought to (1) describe the extent in which delirium in the ED persists into hospitalization (ED delirium duration) and (2) determine how ED delirium duration is associated with 6-month function and cognition.

METHODS

Study Design and Setting

This was a prospective cohort study conducted at a tertiary care, academic hospital. The local institutional review board reviewed and approved this study.

Selection of Participants

Patients were enrolled from the ED between March 2012 and November 2014. Consecutive enrollment occurred Monday through Friday at four randomly selected 4-hour blocks per week (8A–12P, 10A–2P, 12P–4P, 2P–6P). Patients were included if they were 65 years or older, in the ED for less than four hours at the time of enrollment, and unlikely to be discharged home according to the ED physician. Patients were excluded if they were non-English speaking, previously enrolled, deaf, comatose, non-verbal or unable to follow simple commands prior to their current illness, were considered unsuitable for enrollment by the treating physician or nurse, were unavailable for enrollment with the four-hour time limit, or were discharged home from the ED.

Because 83% to 92% of older ED patients are non-delirious,[1,2] all delirious and one out of six randomly selected non-delirious older ED patients were enrolled to maximize the feasibility of our study. Randomization was determined by a computerized random-number generator. Non-delirious ED patients were included to serve as controls, to represent the full spectrum of acute brain dysfunction, and to increase statistical power for analyses; 38.2% of non-delirious ED patients had features of delirium without meeting full criteria (subsyndromal delirium).

Methods of Measurement

Delirium was assessed in the ED at the time of enrollment (0 hours) and at 3 hours and daily during the hospitalization for seven consecutive days after the ED visit or until hospital discharge, whichever came first. A patient was considered to be delirious in the ED if either the 0- or 3-hour delirium assessment was positive. If the patient was hospitalized more than 7 days, another delirium assessment was performed at hospital discharge. In-hospital delirium assessments occurred daily (usually in the morning) 7 days a week. The primary independent variable was the total number of days a delirious ED patient remained delirious throughout the hospitalization (ED delirium duration); the ED delirium episode was considered resolved if the patient was non-delirious for two consecutive days. Patients who were initially non-delirious in the ED were assigned an ED delirium duration of 0 days even if they later developed delirium during hospitalization; those who subsequently developed delirium during hospitalization were considered to have incident delirium. Similarly, for those who were delirious in the ED, but had another episode of delirium after resolution, these patients were also considered to have incident delirium.

In non-mechanically ventilated patients, trained research assistants (RAs) ascertained delirium using a modified version of the Brief Confusion Assessment Method (bCAM) which is a brief (<2 minutes) delirium assessment designed for use by non-physicians in the ED setting.[11] In older ED patients, the modified bCAM is 82% to 86% sensitive and 93% to 96% specific for delirium as diagnosed by a psychiatrist and its kappa is 0.87 indicating excellent inter-observer reliability.[11] In mechanically ventilated patients, the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) was used to ascertain delirium, and is 93% to 100% sensitive, 98% to 100% specific for delirium, and has a kappa of 0.96 indicating excellent interobserver reliability.[12]

The primary outcome variables were 6-month function and cognition adjusted for their baseline. Function was assessed for using the Older American Resources and Services Activities of Daily Living (OARS ADL) questionnaire to establish premorbid (baseline) and 6-month functional status.[13] This scale ranged from 0 (completely dependent) to 28 (completely independent). This was preferably completed by an informant who knew the patient well, but the patient was allowed to complete the OARS ADL if no informant was available and if he/she was capable of providing informed consent. Premorbid (baseline) and 6-month cognition was measured using the short form Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE).[14] This informant-based cognitive screen was used because global tests of cognition would not accurately reflect premorbid cognition during a delirium episode. It has been previously used to assess for cognitive decline.[15] The IQCODE was only completed by informants who knew the patient for at least 10 years. The IQCODE ranged from 1 (markedly improved cognition) to 5 (markedly worse cognition, severe dementia), where a score of 3 represented no change in cognition. To establish premorbid measures, the OARS ADL and IQCODE were obtained in the ED at the time of enrollment; patients and/or their surrogates were asked to rate the patient's function or cognition 2 weeks prior to the ED visit. An RA who was blinded to the ED and hospital delirium assessments determined 6-month function and cognition using phone follow-up. Every attempt was made to obtain these 6-month assessments from the same person who completed the premorbid assessments. The RA and the person completing the 6-month OARS ADL and IQCODE did not have access to the premorbid assessments.

Average daily alcohol consumption prior to the acute illness was collected by patient or surrogate interview. Medical record review was performed to collect dementia

status, comorbidity burden, severity of illness, home benzodiazepine or opioid medication use, and the presence of a central nervous system diagnosis. A patient was considered to have dementia if they had: (1) documented dementia in the medical record, (2) a premorbid IQCODE greater than a cut-off of 3.38,[16] or (3) prescribed cholinesterase inhibitors prior to admission. The Charlson Comorbidity Index was used to quantify the patient's comorbid burden.[17] The Acute Physiology Score (APS) of the Acute Physiology and Chronic Health Evaluation II (APACHE II) score was used to quantify severity of illness.[18] The presence of a central nervous system (CNS) diagnosis (meningitis, seizure, cerebrovascular accident, intraparenchymal hemorrhage, etc.) was determined by two physician reviewers via medical record review. Any disagreement was adjudicated by a third physician reviewer.

Data Analysis

To determine if ED delirium duration days was independently associated with 6-month function and cognition, multiple linear regression was performed. The 6-month cognition analysis was only conducted in patients who had a baseline and 6-month IQCODE. For the 6-month function outcome, the primary dependent variable was the 6-month OARS ADL and the model was adjusted for premorbid OARS ADL, age, dementia, comorbidity burden (Charlson Comorbidity Index), severity of illness (APS), nursing home residence, incident delirium, and the presence of any CNS diagnosis. For the 6-month cognition model, the primary dependent variable was the 6-month IQCODE and the model was adjusted for premorbid IQCODE, premorbid OARS ADL, age, comorbidity burden (Charlson Comorbidity Index), severity of illness (APS), nursing home residence, incident delirium, and the presence of any CNS diagnosis. These covariates were chosen a priori based upon expert opinion, literature review, and our previous work. We limited the number of covariates incorporated in the multivariable model to avoid overfitting.[19]

To evaluate the robustness of our multiple linear regression models, we performed a series of sensitivity analyses. We re-ran the multivariable models in a subgroup of patients who were delirious in the ED and in patients whose OARS ADLs were completed by informants only. Because the median hospital length of stay, the proportion of females, non-whites, home ethanol use, and home opiate or benzodiazepine use were different between delirious and non-delirious ED patients, we incorporated these covariates into the regression models. To determine how death may have impacted our findings, we assigned these patients a 6-month OARS ADL of 0 or a 6-month IQCODE of 6, and re-ran the multivariable regression models. All statistical analyses were performed with SAS version 9.4 (SAS Institute, Carey, NC, USA) and open source R statistical software, version 3.0.2 (http://www.r-project.org/).

RESULTS

During the study period, 3,383 older ED patients were screened. We enrolled 105 delirious ED patients and a random selection of 123 non-delirious ED patients (Figure 1). Two older patients who were initially non-delirious in the ED became delirious at three hours; these patients were considered to delirious in the ED. Table 1 presents patient characteristics stratified by ED delirium status. Of the 105 older patients who were delirious in the ED, 81 (77.1%, 95% CI: 67.7–84.5%) remained delirious on hospital day one. The median (IQR) ED delirium duration was 3 (1, 6) days and 48 (45.7%, 95% CI: 36.1–55.7%) remained delirious at hospital discharge.

Of the 228 enrolled, all patients had a baseline OARS ADL, 42 (18.4%) patients died within 6 months, 13 (5.7%) patients opted out of the follow-up phone call, and 14 (6.1%) patients were lost to follow-up leaving 159 older ED patients available for the ED delirium duration and 6-month function analysis. For every ED delirium duration day, the patient's 6-month OARS ADL significantly decreased by 0.63 points (95% CI: −1.01 to −0.24, Figure 2A) after adjusting for premorbid OARS ADL and other confounders. This indicated that longer ED delirium duration was associated with poorer 6-month function.

Of the 228 enrolled, 198 (86.8%) patients had a baseline IQCODE, 41 (18.0%) died within 6 months, 10 (4.4%) opted out of follow-up, and 16 (7.0%) were lost to follow-up, and 15 (6.6%) did not have a 6-month IQCODE leaving 116 patients available for the ED delirium duration and 6-month IQCODE analysis. For every ED delirium duration day, the patient's 6-month IQCODE significantly increased by 0.06 points (95% CI: 0.01–0.10, Figure 2B) after adjusting for premorbid IQCODE and other confounders. This indicated that longer ED delirium duration was associated with poorer 6-month cognition.

The results of the sensitivity analyses can be seen in Supplemental Table S1. The β-coefficients for ED delirium duration for both the 6-month function and cognition models remained similar for all sensitivity analyses models.

DISCUSSION

Our data suggest that delirium in the ED is a significant and life-altering event for the older patient, potentially threatening their independence and quality of life. We observed that delirium in the ED is not transient event and persists into hospitalization in 77% of cases and lasts a median of 3 days. The longer the ED delirium episode persisted during hospitalization (ED delirium duration), there was an incremental worsening in 6-month function and cognition. Based upon our findings, EDs should routinely monitor for delirium which is currently missed in the majority of cases.[2] Furthermore, this data suggest that ED-based delirium treatment interventions should be developed to preserve the patient's long-term function and cognition.

To our knowledge, only one study to date has evaluated the natural course of delirium in the ED. In 260 older ED patients, Hsieh et al. similarly observed that ED delirium resolved within 24 hours in 28% of cases.[20] However, they were not able to quantify ED delirium duration or assess for delirium at hospital discharge as they followed these patients for 2 days. Most of what is known about delirium's natural course is based upon studies conducted in the hospital setting, many of which enrolled patients in

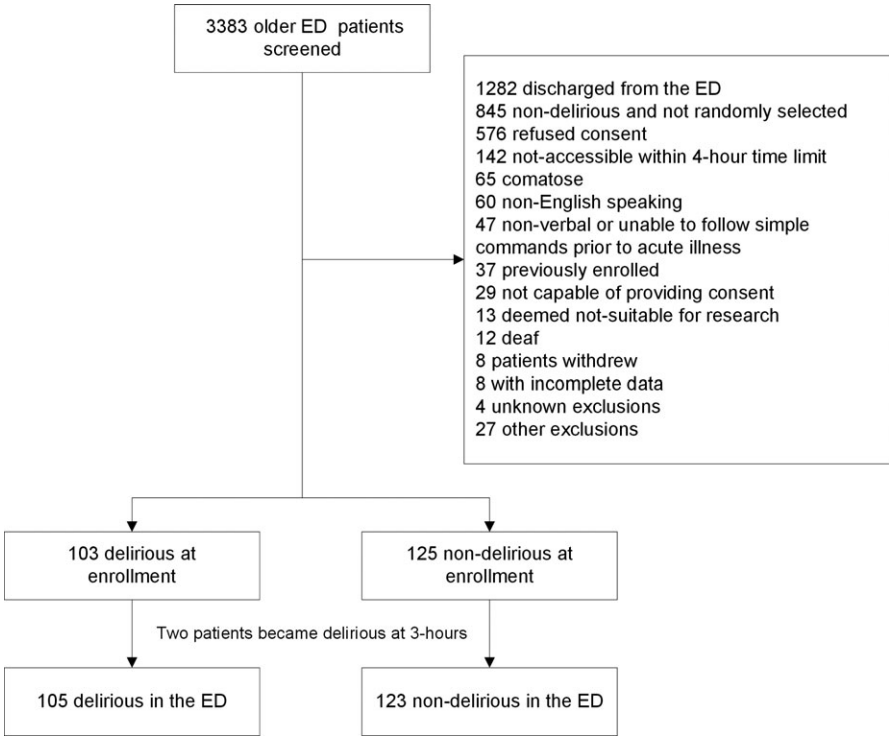

Figure 1. Enrollment flow diagram. ED = emergency department. Patients who were non-verbal or unable to follow simple commands prior to the acute illness were considered to have end-stage dementia.

Table 1. Patient Characteristics and Demographics

	Non-Delirious Patients n = 123	Delirious Patients n = 105
Median (IQR) Age	73 (69, 80)	75 (68, 83)
Female gender	58 (47.2%)	68 (64.8%)
Non-white race	12 (9.8%)	18 (17.1%)
Nursing home residence	2 (1.6%)	5 (4.8%)
Average # of daily alcoholic beverage consumption		
0	105 (85.4%)	100 (95.2%)
1	9 (7.3%)	2 (1.9%)
2	4 (3.3%)	1 (1.0%)
3	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)
5 or more	4 (3.3%)	1 (1.0%)
Home opioid or benzodiazepine use	41 (33.3%)	48 (45.7%)
Dementia	31 (25.2%)	77 (73.3%)
Median (IQR) OARS ADL	26 (21, 27)	16 (11, 23)
Median (IQR) IQCODE	3.19 (3.00, 3.56)	4.06 (3.38, 4.69)
Median (IQR) Charlson	3 (2, 5)	3 (2, 5)
Median (IQR) APS	4 (1, 6)	4 (2, 6)
Median (IQR) hospital LOS	3 (2, 5)	5 (3, 8)
[a]Incident delirium	12 (9.8%)	6 (5.7%)

APS = Acute Physiology Score; ED = emergency department; IQR = Interquartile range; LOS = length of stay.

[a]Incident delirium were delirium episodes that occurred after an episode of ED delirium resolved (two consecutive days with negative delirium assessments) or new onset delirium that occurred in those who were not delirious in the ED.

the hospital wards up to 48 hours after the admission. Based upon these studies, delirium can resolve within 24 hours in 40%[21] and can persist to hospital discharge in 45% of delirious patients,[22] with mean delirium duration of 7 days.[21] Taken these data as a whole, delirium, regardless of clinical setting, is not a transient event and frequently persists to hospital discharge.

There is a dearth of data regarding the effect of delirium in the ED on long-term functional status and cognition. Vida et al. reported that delirium in the ED was not associated with 18-month function,[23] and to our knowledge, no study has investigated ED delirium's effect on long-term cognition. Most of what is known about delirium's impact on these outcomes are from the in-hospital literature. The relationship between delirium and long-term function is equivocal as some of inpatient studies have observed a significant association[8,24,25] while others have not.[23,26,27] Such discordant observations may have occurred because these studies dichotomized delirium into a present-absent event and did not take into account delirium's variable clinical course. For this reason, we quantified ED delirium's duration and observed that it was significantly associated with poorer 6-month function. Studies have also shown that delirium during hospitalization is associated with accelerated cognitive decline in those who have baseline dementia[28] and are critically ill.[29] We also observed an association between delirium and poorer long-term cognition in more diverse older ED patient population who possess the full spectrum of pre-existing cognitive impairment and severity of illness.

Our study has several notable limitations. We did not enroll ED patients on the weekends or from 6 p.m. to 4 a.m., and this may have introduced selection bias. There was a significant number of patients who refused (n = 576) to participate in the study and these patients

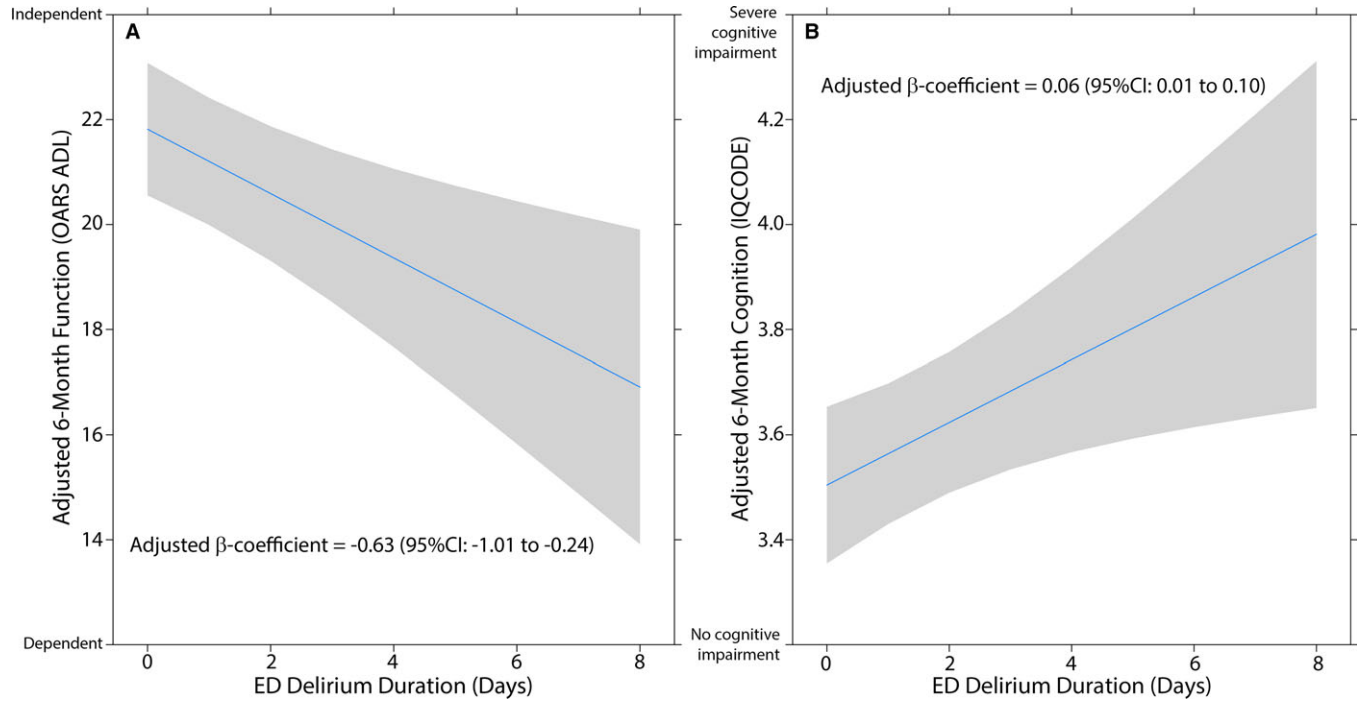

Figure 2. (A) Relationship between emergency department (ED) delirium duration and 6-month function as measured by the Older American Resources and Services Activities of Daily Living (OARS ADL) scale adjusted for baseline OARS ADL, age, dementia, comorbidity burden, severity of illness, nursing home residence, central nervous system diagnoses, and incident delirium. Lower OARS ADL scores indicated poorer function. For every additional ED delirium duration day, the OARS ADL decreased by 0.63 (95% CI: −1.01 to −0.24) points. (B) The relationship between ED delirium duration and 6-month cognition as measured by the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) adjusted for baseline IQCODE, age, baseline function, comorbidity burden, severity of illness, nursing home residence, central nervous system diagnoses, and incident delirium. Higher IQCODE scores indicated poorer cognition. For every ED delirium duration day, the patient's 6-month IQCODE significantly increased by 0.06 points (95% CI: 0.01–0.10) indicating poorer 6-month cognition. [Color figure can be viewed at wileyonlinelibrary.com]

were slightly older, were less likely to be non-white, and slightly more likely to reside in a nursing home (Table S2). Additionally, some of patients were excluded from the ED delirium duration and cognition analysis because of missing baseline or 6-month IQCODEs. These patients were probably more likely to be vulnerable, have underlying dementia, and be more functionally dependent, and their exclusion may have introduced additional selection bias. We used the modified bCAM which is 82% to 86% sensitive and only assessed for delirium once daily. This may have introduced misclassification bias, which can overestimate or underestimate our effect sizes. We also did not account for delirium severity or psychomotor subtypes, which may have further impacted 6-month function and cognition. The OARS ADL and IQCODE are informant-based questionnaires that were used to determine 6-month function and cognition, respectively. It is possible that informants who witnessed delirium episodes were more likely to rate the patient has having poorer 6-month function or cognition. However, delirium is frequently unrecognized in the ED and hospital settings,[2,30] and informants are unlikely to be familiar with the link between delirium and adverse outcomes mitigating this source of potential informant bias. Inherent to most prospective cohort studies, unmeasured (e.g., malnutrition, drug exposure during hospitalization) and residual confounding (e.g., dementia) may have still existed. This study was conducted in a single center, urban, academic hospital and enrolled patients who were 65 years or older. Our findings may not be generalizable to other settings and younger patients.

In conclusion, delirium in the ED is not a transient event and frequently persists into hospitalization in the majority of cases. Furthermore, longer ED delirium duration is associated with an incremental worsening of 6-month function and cognition.

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Author Contributions: JHH, EWE, JFS, and RDS conceived the trial and participated in the study design. JHH and EEV recruited patients and collected the data. RC, XL, and JHH analyzed the data. All authors participated in the interpretation of results. JHH drafted the manuscript, and all authors contributed to the critical review and revision of the manuscript. JHH takes responsibility for the manuscript as a whole.

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REFERENCES

1. Han JH, Shintani A, Eden S et al. Delirium in the emergency department: An independent predictor of death within 6 months. Ann Emerg Med 2010;56:244–252.
2. Han JH, Zimmerman EE, Cutler N et al. Delirium in older emergency department patients: Recognition, risk factors, and psychomotor subtypes. Acad Emerg Med 2009;16:193–200.
3. Han JH, Eden S, Shintani A et al. Delirium in older emergency department patients is an independent predictor of hospital length of stay. Acad Emerg Med 2011;18:451–457.
4. Schuur JD, Venkatesh AK. The growing role of emergency departments in hospital admissions. N Engl J Med 2012;367:391–393.
5. Lamantia MA, Messina FC, Hobgood CD et al. Screening for delirium in the emergency department: A systematic review. Ann Emerg Med 2014;63:551–560.
6. Pompei P, Foreman M, Rudberg MA et al. Delirium in hospitalized older persons: Outcomes and predictors. J Am Geriatr Soc 1994;42:809–815.
7. O'Keeffe S, Lavan J. The prognostic significance of delirium in older hospital patients. J Am Geriatr Soc 1997;45:174–178.
8. Inouye SK, Rushing JT, Foreman MD et al. Does delirium contribute to poor hospital outcomes? A three-site epidemiologic study. J Gen Intern Med 1998;13:234–242.
9. McCusker J, Cole M, Abrahamowicz M et al. Delirium predicts 12-month mortality. Arch Intern Med 2002;162:457–463.
10. Kelly KG, Zisselman M, Cutillo-Schmitter T et al. Severity and course of delirium in medically hospitalized nursing facility residents. Am J Geriatr Psychiatry 2001;9:72–77.
11. Han JH, Wilson A, Graves AJ et al. A quick and easy delirium assessment for nonphysician research personnel. Am J Emerg Med 2016;34:1031–1036.
12. Ely EW, Inouye SK, Bernard GR et al. Delirium in mechanically ventilated patients: Validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). JAMA 2001;286:2703–2710.
13. McCusker J, Bellavance F, Cardin S et al. Validity of an activities of daily living questionnaire among older patients in the emergency department. J Clin Epidemiol 1999;52:1023–1030.
14. Holsinger T, Deveau J, Boustani M et al. Does this patient have dementia? JAMA 2007;297:2391–2404.
15. Serrano S, Domingo J, Rodriguez-Garcia E et al. Frequency of cognitive impairment without dementia in patients with stroke: A two-year follow-up study. Stroke 2007;38:105–110.
16. Jorm AF. A short form of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): Development and cross-validation. Psychol Med 1994;24:145–153.
17. Murray SB, Bates DW, Ngo L et al. Charlson Index is associated with one-year mortality in emergency department patients with suspected infection. Acad Emerg Med 2006;13:530–536.
18. Knaus WA, Draper EA, Wagner DP et al. APACHE II: A severity of disease classification system. Crit Care Med 1985;13:818–829.
19. Harrell FE. Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression, and Survival Analysis. New York: Springer, 2001.
20. Hsieh SJ, Madahar P, Hope AA et al. Clinical deterioration in older adults with delirium during early hospitalisation: A prospective cohort study. BMJ Open 2015;5:e007496.
21. McCusker J, Cole M, Dendukuri N et al. The course of delirium in older medical inpatients: A prospective study. J Gen Intern Med 2003;18:696–704.
22. Cole MG, Ciampi A, Belzile E et al. Persistent delirium in older hospital patients: A systematic review of frequency and prognosis. Age Ageing 2009;38:19–26.
23. Vida S, Galbaud du Fort G, Kakuma R et al. An 18-month prospective cohort study of functional outcome of delirium in elderly patients: Activities of daily living. Int Psychogeriatr 2006;18:681–700.
24. Buurman BM, Hoogerduijn JG, de Haan RJ et al. Geriatric conditions in acutely hospitalized older patients: Prevalence and one-year survival and functional decline. PLoS ONE 2011;6:e26951.
25. Murray AM, Levkoff SE, Wetle TT et al. Acute delirium and functional decline in the hospitalized elderly patient. J Gerontol 1993;48:M181–M186.
26. Katz IR, Curyto KJ, TenHave T et al. Validating the diagnosis of delirium and evaluating its association with deterioration over a one-year period. Am J Geriatr Psychiatry 2001;9:148–159.
27. McCusker J, Cole M, Dendukuri N et al. Delirium in older medical inpatients and subsequent cognitive and functional status: A prospective study. CMAJ 2001;165:575–583.
28. Gross AL, Jones RN, Habtemariam DA et al. Delirium and long-term cognitive trajectory among persons with dementia. Arch Intern Med 2012;172:1–8.
29. Pandharipande PP, Girard TD, Jackson JC et al. Long-term cognitive impairment after critical illness. N Engl J Med 2013;369:1306–1316.
30. Collins N, Blanchard MR, Tookman A, et al. Detection of delirium in the acute hospital. Age Ageing. 2010;39:131–135.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Sensitivity Analyses.

Table S2. Comparison of Refusals and Enrolled Patients.

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CLINICAL INVESTIGATION

Rates of Delirium Diagnosis Do Not Improve with Emergency Risk Screening: Results of the Emergency Department Delirium Initiative Trial

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OBJECTIVES: To determine whether a bundled risk screening and warning or action card system improves formal delirium diagnosis and person-centered outcomes in hospitalized older adults.

DESIGN: Prospective trial with sequential introduction of screening and interventional processes.

SETTING: Two tertiary referral hospitals in Australia.

PARTICIPANTS: Individuals aged 65 and older presenting to the emergency department (ED) and not requiring immediate resuscitation (N = 3,905).

INTERVENTION: Formal ED delirium screening algorithm and use of a risk warning card with a recommended series of actions for the prevention and management of delirium during the subsequent admission

MEASUREMENTS: Delirium diagnosis at hospital discharge, proportion discharged to new assisted living arrangements, in-hospital complications (use of sedation, falls, aspiration pneumonia, death), hospital length of stay.

RESULTS: Participants with a positive risk screen were significantly more likely (relative risk = 6.0, 95% confidence interval = 4.9–7.3) to develop delirium, and the proportion of at-risk participants with a positive screen was constant across three study phases. Delirium detection rate in participants undergoing the final intervention (Phase 3) was 12.1% (a 2% absolute and 17% relative increase from the baseline rate) but this was not statistically significant ($P = .29$), and a similar relative increase was seen over time in participants not receiving the intervention

CONCLUSION: A risk screening and warning or action card intervention in the ED did not significantly improve rates of delirium detection or other important outcomes. **J Am Geriatr Soc 2017.**

Key words: delirium; screening; emergency medicine

Delirium is a clinical syndrome characterized by the rapid onset and fluctuating course of impaired attention, consciousness, and cognition.[1] Despite a clear case definition and the existence of many guidelines, delirium is frequently underdiagnosed and mismanaged. It is estimated that emergency department (ED) staff miss the diagnosis more than half of the time.[2] One important factor contributing to this is the lack of a structured, easily performed assessment protocol that can be used at the time of the decision to hospitalize an individual.

Delirium is sometimes assumed to be a transient disorder, but long-term complications are common, and the condition is associated with significantly higher rates of mortality and morbidity, dementia, institutional placement, and longer hospital stays.[3] In 2011, it was projected that total societal costs for delirium approached $150 billion.[4] Because delirium detection is poor and the condition is associated with negative outcomes, most consensus delirium guidelines recommend that two practices occur when an individual presents to the hospital: processes to prevent delirium developing in at-risk groups and screening at-risk individuals to detect delirium with a view to managing it.[5,6] Multicomponent interventions reduce development of delirium in at-risk hospitalized people undergoing surgery and in general medicine wards.[7,8] In contrast, whether because of unreported failed trials or lack of funding for ED delirium research, the evidence base for delirium prevention strategies having any effect on morbidity and mortality outcomes in hospital admissions through the ED is virtually nonexistent.[9] Furthermore, the negative consequences associated with delirium that are attributable to the delirium, as

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opposed to the underlying cause of the delirium, remain a subject for research and debate.[10]

A delirium screening tool that is simple and can be applied at the earliest sentinel point in an individual's hospitalization—the initial ED nurse assessment—was previously developed.[11] The current study was designed to explore the use of a modified version of this tool as part of a sequential series of interventions begun in the ED to test whether rates of delirium diagnosis could be improved and morbidity and mortality subsequently reduced in individuals with or at risk of developing delirium. These are objectives that align with many of the highest priorities of ED delirium research.[12]

METHODS

Ethics

The human research ethics committees of the participating hospitals approved the study.

Consent

Because many individuals with cognitive impairment are unable to provide informed consent and because of the low-risk nature of the intervention, individuals were enrolled under a waiver of consent, which is one of several approaches to involving cognitively impaired people in research.[13] The ethics committees approved the consent process using National Health and Medical Research Council of Australia guidelines.

Study Design and Setting

This was a prospective three-phase trial that incorporated sequential introduction of screening (Phase 1, baseline, October 2013 to April 2014), diagnosis (Phase 2, August to November 2014), and prevention (Phase 3, February to May 2015) strategies conducted in EDs of two tertiary hospitals in the metropolitan region of Perth, Western Australia.

Selection of Participants

Men and women aged 65 and older presenting to the ED were recruited. Individuals aged 65 and older being admitted to an inpatient hospital bed from the ED were eligible for the study, except that those who were critically unwell and requiring immediate resuscitation, were non-English speaking, or had aphasia or other non-cognitive-related language difficulties were excluded.

Screening and Intervention

The screening tool (Figure 1) was designed to be used by the first nurse assessing the individual after triage. The tool was based on one previously published.[11] It had been planned to use the identical tool for this study, but field testing for 1 month before use in this trial revealed the need to operationalize a more-accurate way for ED nurses to identify cognitive impairment and whether it had been detected previously in their assessment, so modifications were made to the instrument. A positive screen indicated that the individual was at risk of delirium but was not considered diagnostic.

Nurse screening was introduced in Phase 1, but the screening results were not available to treating clinicians. This phase served to familiarize all nursing staff in the ED with the screening process and allowed determination of the baseline rates of delirium and outcomes in individuals who screened positive and those who screened negative without any intervention on the basis of a positive screen.

In Phase 2, results of the nurse screen were revealed to ED medical staff, and the intervention was to formalize an approach to ED diagnosis if the individual had screened positive. Senior ED physicians (specialists and advanced trainees) used the Confusion Assessment Method diagnostic algorithm,[14] and then, if delirium was diagnosed, investigated the individuals for causes of delirium.

In Phase 3, positive results of the nurse screen were communicated to all staff on a card (Appendix S1) placed on the end of the bed that served as a visual warning that this individuals was at risk for delirium and referred to preventative measures and a comprehensive preexisting clinical guideline[5] designed to minimize morbidity associated with delirium (Appendix S2). The warning card stayed with the person throughout his or her hospital stay. Thus, in Phase 3, the intervention was not directed at ED physicians acting on the positive nurse screen but used the card as a prompt to notify all staff of the risk of delirium.

Education sessions were conducted with ED nursing staff before each of the phases and with ED physicians before Phases 2 and 3 that provided general information on the importance of delirium and specific training on the intervention strategies for each phase. Each phase session lasted 1 hour and involved instructors, scenarios, and video examples. A log was kept of staff attendance. Daily reminders were provided about the study at morning handover in the ED. A weekly update on screening adherence rates was disseminated in e-mails. General hospital training regarding the warning card in Phase 3 and what it meant was one-on-one education with nurse unit managers on admitting wards but was otherwise confined to dissemination of electronic global e-mail circulars to ward staff, because it was not feasible for education sessions to be conducted with all inpatient staff.

The primary outcome measure was the percentage of participants receiving a diagnosis of delirium during that admission. *International Classification of Diseases, Tenth Revision* (ICD-10) delirium diagnostic criteria[15] were used for the formal diagnosis, and any of the ICD-10 codes F05.0, F05.1, F05.8, F05.9, R41.0, and R41.8 in any of the first 19 field codes was accepted as confirmation of the diagnosis of delirium.

Secondary outcome measures were the value of the screen in identifying those at risk of delirium, measured using likelihood ratios; in-hospital morbidity measures (falls, fractures, aspiration pneumonia); use of pharmacological sedation; discharge destination, including new discharge to assisted living; hospital length of stay; and death.

Assessors blinded to the screen results or study phase adjudicated all outcome measures. Electronic and, where necessary for some secondary outcomes, paper hospital records were used for these adjudications.

ED Delirium Screening Form: 65 years and over

POINTS

Q1. Dementia History

Is there a history of dementia or other pre-existing cognitive deficit?

If YES, **SCORE 2 POINTS** and skip Q2, go to Q3 ☐

If NO, **SCORE 0 POINTS** and go to Q2

Q2. Complete AMT4

What is your age?

What is your date of birth?

What year is it?

What is this place?

If ALL answered correctly, **SCORE 0 POINTS** ☐

If ANY incorrect, **SCORE 4 POINTS**

Q3. Acute change

Is there any history of increased confusion over the last hours/days?

Do the family state the patient's orientation/behaviour/alertness is "not normally like this"?

If YES to ANY, **SCORE 4 POINTS** ☐

If NO, **SCORE 0 POINTS**

Q4. Other risk factor scoring

SCORE 1 POINT FOR **EACH** OF THE FOLLOWING

Any HISTORY of depression? ☐

Any CURRENT abnormal heart rate or rhythm

Add total score ☐

Action:

If TOTAL SCORE is 3 or more: Delirium screen positive, alert medical staff/place warning card

If TOTAL SCORE is 2 OR less: Delirium screen negative

Figure 1. Nurse screen.

Sample Size Calculations

A previous study in the same jurisdiction found a delirium detection rate in the ED of approximately 8% of all people aged 65 and older,[11] and it was hypothesized that a 50% increase in detection to 12% would be meaningful and in keeping with international figures. To achieve this would require 1,180 participants in each of the control and intervention phases if $\alpha = 0.05$ and $1–\beta = 0.90$. A 6-month period was allowed for Phase 1 (baseline comparator phase) and two 3-month periods for the intervention phases to allow these numbers to be reached.

Analysis

All analyses were conducted using SPSS version 21 (IBM Corp., Armonk, NY) on an intention-to-treat basis. Results are presented descriptively and using relative risks and 95% confidence intervals (CIs). Proportions were compared using the Pearson chi square test. Positive (sensitivity/(1 − specificity)) and negative ((1 − sensitivity)/specificity) likelihood ratios (LR+ and LR−, respectively) were calculated for the diagnostic value of the nurse screen. Multivariate logistic regression was used to adjust for the effect of covariate (age, sex, comorbidity count, place of residence) imbalance on secondary outcomes when comparing the pre- and postintervention phases.

The Strengthening the Reporting of Observational Studies in Epidemiology checklist is provided in Appendix S3 for verification of the trial methodology.

RESULTS

Three thousand nine hundred five individuals aged 65 and older were enrolled (Appendix S3). Enrollment rates in the baseline 6 months were higher than in the intervention periods. Otherwise, the population was stable across the three phases (Table 1). In each of the periods, approximately one-quarter of all older adults being admitted to the hospital screened positive for delirium risk.

Those with a positive risk screen were significantly more likely to be diagnosed with delirium during their hospital stay (relative risk (RR) = 6.0, 95% CI = 4.9–7.3, Table 2). The standalone value of the screen itself for flagging delirium was reasonable (LR+ = 3.3, LR− = 0.4). As expected, a delirium diagnosis was more likely to be associated with numerous adverse sequelae (Table 3).

There was an absolute increase in delirium diagnosis of 2% across the study phases but this was not statistically significant (Pearson chi-square 2.49, $P = .29$), and the relative increase in participants who screened positive and therefore received the intervention was no different from that of those who screened negative (Table 4).

Whole-hospital flow changes that resulted in a higher proportion of participants being transferred to other subacute hospital facilities in Phase 3 (19%) than in Phases 1 (7%) and 2 (7%) distorted hospital length-of-stay data. It is therefore likely that the statistically significantly shorter hospital stay overall in Phase 3 (median 2 days, interquartile range (IQR) 1–5 days) than in Phase 1 (median 3 days, IQR 1–7 days) was because of greater use of transfer for frailer individuals with anticipated longer stays. Although there were favorable trends in the postintervention phase for some secondary outcomes, no differences in secondary morbidity or mortality outcomes were statistically significant on adjusted analysis (Table 3).

DISCUSSION

This large prospective study showed that a nurse screening process in the ED at initial assessment was reasonable at identifying older people at risk of delirium, but no clinically or statistically significant improvements in delirium detection or person-centered outcomes with interventions were found based on the results of this nurse screening. Faced with the overwhelming evidence that delirium is underdiagnosed and associated with poor clinical outcomes, it is widely recommended that individuals aged 65 and older being admitted to the hospital undergo cognitive screening to detect delirium, and that the underlying cause be sought and managed if delirium is found,[16–19] although the evidence base upon which these recommendations are based is not strong. This study was conducted to determine whether screening done by the ED nurse at first encounter for all people aged 65 and older being admitted to the hospital and subsequent simple actions commenced in ED in response to a positive screen would improve

Table 1. Participant Characteristics According to Phase and Results from a Delirium Screening Tool Administered in the Emergency Department

Characteristic	Phase 1, n = 2,603	Phase 2, n = 510	Phase 3, n = 778
Age, median	80	81	81
Female, %	53	55	53
From nursing home or equivalent %	12	13	10
Delirium risk screen positive, %	25	26	25

Table 2. Subsequent Delirium Diagnoses That Hospital Medical Staff Made According to Emergency Department (ED) Delirium Screening Results

	n		
ED screen	No Delirium	Delirium Diagnosed	Total
Positive	702	273	975
Negative	2,748	135	2,883
Total	3,450	408	3,858

Some of the screen results were incomplete.

Table 3. Burdensome Associations with Delirium According to Study Phase

Association	Before Intervention (Phase 1)	After Intervention (Phases 2 and 3)	Odds Ratio (95% CI)[a] After vs Before Intervention
Length of stay, days, median (interquartile range)			
No delirium	3 (1–4)	2 (1–2)	–
Delirium	7 (6–14)	6 (5–10)	
Died, %			
No delirium	2	2	0.7 (0.3–1.6)
Delirium	7	6	
Newly discharged to nursing home or equivalent %			
No delirium	3	4	0.6 (0.3–1.2)
Delirium	14	12	
Injurious falls/1,000 inpatient days			
No delirium	0.7	1.2	1.4 (0.4–5.2)
Delirium	1.9	2.8	
In-hospital aspiration pneumonia, %			
No delirium	0	1	[b]
Delirium	0	2	
New in-hospital sedation usage, %			
No delirium	2	8	0.8 (0.4–1.3)
Delirium	18	14	

[a]Adjusted for covariates and for participants with delirium.
[b]Not calculable with infinite confidence interval (CI), total events, n = 3.

delirium detection and thereby improve outcomes, but no improvement was shown with this process.

To the knowledge of the authors, this is the largest study to examine delirium screening of individuals entering the hospital through the ED. A number of studies have examined the use of different brief screening instruments in the ED setting to detect delirium and agitation, including the Delirium Triage Screen, the Richmond Agitation Sedation Scale (RASS), and the brief Confusion Assessment Method.[20–22] Each concluded that the examined instruments had good to excellent accuracy as delirium screens and that nonphysicians could administer them. A RASS score of 2 to 4 or −2 to −4 had a LR+ of 19.6 and LR− of 0.8, and a RASS score of 0 had a LR− of 0.2.[20] It has been recommended that the Delirium Triage Screen and brief Confusion Assessment Method be used stepwise because of their strong LR− (0.04) and LR+ (25.2), respectively.[22] It was decided not to compare the diagnostic accuracy of the current study instrument or strategy with any of these existing ED screening instruments, although the accuracy of any screening tool is important. Instead, it was decided to implement the screening strategy as a first step but then to use it to determine whether overall delirium detection could be improved and secondary complications of delirium minimized. There are several reasons for this. First, these are important person-centered outcomes and are more clinically relevant than reporting the accuracy or otherwise of the screening test. Second, in an era of activity-based funding, accurate detection and coding of delirium has important resource implications for hospitals.

There are several possible reasons for the findings of this study. The negative results may represent a lack of awareness of the importance of delirium of ED staff. A lack of visibility of the downstream effects of failing to detect delirium and the perception that delirium detection represents extra work without an immediate benefit to patient care may all contribute. The actions resulting from a positive screen may be inadequate, poorly timed, or incorrectly targeted to effect change in individuals at risk of delirium. Optimal methods to embed evidence-based practice into routine clinical care are the subject of scrutiny through implementation science.[23,24] In basic terms, this study used the common "diffusion of innovation" approach to implementing delirium screening and actions on the basis of a positive screen.[25] The disappointing findings in this study could represent inadequate attention to knowledge transfer. Phase 3 of the study involved a warning card system that stayed with the individual outside of the ED, where targeted education about the study could be provided only to ward managers and, other than those managers, relied on ward-based meetings and electronic bulletins to promote the intervention, with limited ability to direct or monitor behaviors. This "traditional" approach to medical education may be modestly effective and not substantively change behavior.[26]

The delirium base rate in this study of 10% was higher than expected. Although a broad range of delirium rates are described in the literature, delirium is generally poorly detected.[27] It is possible that the modest findings may be because the intervention was implemented at sites that already had superior systems for delirium detection in place, such that additional measures on top of those that were tried had less than the expected effect. It might also be that, despite efforts to avoid this, positive screen results from Phase 1 were sometimes made known to physicians, artificially inflating the baseline delirium rate.

Table 4. Delirium Diagnosis Rates According to Phase and Screen Result

Screen	Phase 1	Phase 2	Phase 3
Screen positive, %	27	29	31
Screen negative, %	4	5	6
Overall, n (%) (confidence interval)	264 (10.1) (9.0–11.4)	56 (11.0) (8.4–14.0)	94 (12.1) (10.0–14.6)

This was a large study conducted at two centers with a clearly defined hypothesis that has not previously been tested. The study had important limitations. At what point delirium was diagnosed in the hospital stay was not measured, so the precise proportion of incident delirium (not evident on ED arrival) is unknown. Because this was not a randomized experimental study, other changes in hospitals over time may have confounded the results. The exclusion of non-English-speaking people limits the generalizability of the findings. The choice of ICD-10 codes was finite, and it could be argued that ICD-10 codes for encephalopathy, for example, might also have been used to adjudicate for presence of delirium.

There are some implications for clinical practice in these results. The ED is a complex working environment, with commonly found trends worldwide of increasing numbers of visits per year, time-based targets for care, and uncontrollable surges in demand. Even within the confines of a funded trial, no significant improvement was found. It was demonstrated that ED screening is feasible and meaningful but that improving outcomes requires a different approach across the hospital. Attempting to introduce mass screening processes in the ED will succeed only if certain criteria are met: the screen is accurate, a tangible set of actions that improve outcomes results from the screen, and neither the screen nor those actions are cumbersome for ED staff.

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REFERENCES

1. Young J, Inouye SK. Delirium in older people. BMJ 2007;334:842–846.
2. Han JH, Zimmerman EE, Cutler N et al. Delirium in older emergency department patients: Recognition, risk factors, and psychomotor subtypes. Acad Emerg Med 2009;16:193–200.
3. Witlox J, Eurelings LSM, de Jonghe JFM et al. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: A meta-analysis. JAMA 2010;304:443–451.
4. Leslie DL, Inouye SK. The importance of delirium: Economic and societal costs. J Am Geriatr Soc 2011;59(Suppl 2):S241–S243.
5. Delirium: Prevention, Diagnosis and Management. London: National Institute for Health and Clinical Excellence, 2010.
6. Delirium Clinical Care Standard. Sydney: Australian Commission on Safety and Quality in Health Care, 2016.
7. Inouye SK, Bogardus ST Jr, Charpentier PA et al. A multicomponent intervention to prevent delirium in hospitalized older patients. N Engl J Med 1999;340:669–676.
8. Trabold B, Metterlein T. Postoperative delirium: Risk factors, prevention, and treatment. J Cardiothorac Vasc Anesth 2014;28:1352–13560.
9. Siddiqi N, Harrison JK, Clegg A et al. Interventions for preventing delirium in hospitalised non-ICU patients. Cochrane Database Syst Rev 2016;3: CD005563.
10. Klein Klouwenberg PMC, Zaal IJ, Spitoni C et al. The attributable mortality of delirium in critically ill patients: Prospective cohort study. BMJ 2014;349:g6652.
11. Hare M, Arendts G, Wynaden D et al. Nurse screening for delirium in older patients attending the emergency department. Psychosomatics 2014;55:235–242.
12. Carpenter CR, Shah MN, Hustey FM et al. High yield research opportunities in geriatric emergency medicine: Prehospital care, delirium, adverse drug events, and falls. J Gerontol A Biol Sci Med Sci 2011;66:775–783.
13. Prusaczyk B, Cherney SM, Carpenter CR et al. Informed consent to research with cognitively impaired adults: Transdisciplinary challenges and opportunities. Clin Gerontol 2017;40:63–73.
14. Inouye SK, van Dyck CH, Alessi CA et al. Clarifying confusion: The confusion assessment method. A new method for detection of delirium. Ann Intern Med 1990;113:941–948.
15. Thomas C, Kreisel SH, Oster P et al. Diagnosing delirium in older hospitalized adults with dementia: Adapting the confusion assessment method to international classification of diseases, tenth revision, diagnostic criteria. J Am Geriatr Soc 2012;60:1471–1477.
16. O'Mahony R, Murthy L, Akunne A et al. Synopsis of the National Institute for Health and Clinical Excellence guideline for prevention of delirium. Ann Intern Med 2011;154:746–751.
17. Rathier MO, Baker WL. A review of recent clinical trials and guidelines on the prevention and management of delirium in hospitalized older patients. Hosp Pract 2011;39:96–106.
18. Han J, Wilson A, Ely EW. Delirium in the older emergency department patient: A quiet epidemic. Emerg Med Clin North Am 2010;28:611–631.
19. Wilber ST. Altered mental status in older emergency department patients. Emerg Med Clin North Am 2006;24:299–316.
20. Han JH, Vasilevskis EE, Schnelle JF et al. The diagnostic performance of the Richmond Agitation Sedation Scale for detecting delirium in older emergency department patients. Acad Emerg Med 2015;22:878–882.
21. Han JH, Vasilevskis EE, Shintani A et al. Impaired arousal at initial presentation predicts 6-month mortality: An analysis of 1084 acutely ill older patients. J Hosp Med 2014;9:772–778.
22. Han JH, Wilson A, Vasilevskis EE et al. Diagnosing delirium in older emergency department patients: Validity and reliability of the Delirium Triage Screen and the brief Confusion Assessment Method. Ann Emerg Med 2013;62:457–465.
23. Thomas DC, Berry A, Djuricich AM et al. What is implementation science and what forces are driving a change in medical education? Am J Med Qual 2016;10:10.
24. Powell BJ, McMillen JC, Proctor EK et al. A compilation of strategies for implementing clinical innovations in health and mental health. Med Care Res Rev 2012;69:123–157.
25. Pashaeypoor S, Ashktorab T, Rassouli M et al. Predicting the adoption of evidence-based practice using "Rogers diffusion of innovation model". Contemp Nurse 2016;52:85–94.

26. Forsetlund L, Bjorndal A, Rashidian A et al. Continuing education meetings and workshops: Effects on professional practice and health care outcomes. Cochrane Database Syst Rev 2009;2:CD003030.
27. Maldonado JR. Delirium in the acute care setting: Characteristics, diagnosis and treatment. Crit Care Clin 2008;24:657–722.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Appendix S1. End-of-Bed Warning Card.

Appendix S2. Index of Comprehensive Delirium Guideline.

Appendix S3. STROBE Statement—checklist of items that should be included in reports of observational studies.

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