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Persistent Delirium Predicts Increased Mortality

Dan K. Kiely, MPH, MA, **Edward R. Marcantonio, MD, SM**, **Sharon K. Inouye, MD, MPH**, **Michele L. Shaffer, PhD**, **Margaret A. Bergmann, MS, GNP**, **Frances M. Yang, PhD**, **Michael A. Fearing, PhD**, and **Richard N. Jones, ScD**
Institute for Aging Research, Hebrew SeniorLife, Boston, Massachusetts (Drs. Inouye, Yang, Fearing, Jones and Mr. Kiely); Division of General Medicine and Primary Care, Beth Israel Deaconess Medical Center, Boston, Massachusetts (Dr. Marcantonio, Ms Bergmann); Harvard Medical School/Beth Israel Deaconess Medical Center Department of Medicine, Boston, Massachusetts (Drs. Inouye, Marcantonio); Harvard Medical School/Brigham and Women's Hospital, Department of Psychiatry, Boston, Massachusetts (Dr. Yang); Division of Biostatistics, Department of Public Health Sciences, Penn State College of Medicine, Hershey, PA (Dr Shaffer).

Abstract

OBJECTIVES—To examine the association between persistent delirium and one-year mortality in newly admitted delirious post-acute care (PAC) facility patients, who were followed regardless of residence.

DESIGN—Observational cohort study.

SETTING—Eight greater-Boston skilled nursing facilities specializing in PAC.

PARTICIPANTS—Four hundred and twelve PAC patients with delirium at the time of admission after an acute hospitalization.

MEASUREMENTS—Assessments were done at baseline and four follow-up times: 2-week, 4-week, 12-week and 26-week. "Confusion Assessment Method"-defined delirium was assessed, as were factors used as covariates in analyses including: age, gender, comorbidity, functional status and dementia. The outcome was one-year mortality determined by the National Death Index and corroborated by medical record, and proxy telephone interview.

RESULTS—Nearly one-third remained delirious at 6 months. The cumulative one-year mortality was 39%. Independent of age, gender, comorbidity, functional status and dementia, subjects with persistent delirium were 2.9 (95% confidence interval, 1.9, 4.4) times more likely to die during the one-year follow-up compared to subjects who resolved their delirium. This association remained strong and significant in groups with and without dementia. Additionally, when delirium resolved, the risk of death diminished thereafter.

Address correspondence to: Dan K. Kiely, MPH, MA, Institute for Aging Research, Hebrew SeniorLife, 1200 Centre Street, Boston, MA 02131-1097, Telephone: 617 363 8655, Fax: 617 363 8964, Email: kiely@hrca.harvard.edu.

Author Contributions:
DK Kiely - study concept and design, analysis and interpretation of data, and preparation of manuscript.
ER Marcantonio - study concept and design, acquisition of subjects and/or data, interpretation of data, and preparation of manuscript.
SK Inouye - study concept and design, interpretation of data, and preparation of manuscript.
ML Shaffer - study concept and design, analysis and interpretation of data, and preparation of manuscript.
MA Bergmann - study concept and design, acquisition of subjects and/or data, and preparation of manuscript.
FM Yang - study concept and design, and preparation of manuscript.
MA Fearing – study concept and design, and preparation of manuscript.
RN Jones - study concept and design, analysis and interpretation of data, and preparation of manuscript.

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CONCLUSION—Among patients who were delirious at the time of PAC admission and followed regardless of residence, persistent delirium was a significant independent predictor of one-year mortality.

Keywords

delirium; mortality; survival; post-acute care

INTRODUCTION

Delirium is a clinical syndrome characterized by an acute decline in attention and cognition. It is common among hospitalized and post-acute care (PAC) 1–3 patients, and associated with an increased risk of morbidity, mortality, and loss of independence.4–10 Costs attributable to delirium are estimated at over $100 billion (2005 US dollars) per year when including Medicare expenditures for hospitalization, and additional direct health care costs accrued after hospital discharge such as PAC, institutionalization, emergency room visits, rehospitalization, physician or clinic visits, rehabilitation services, and formal home health care. 10, 11

Previous studies reported associations between delirium and mortality in the hospital setting, although findings have been inconsistent. 12–21 Most studies found an association between delirium and mortality in unadjusted analyses, but for many of these studies, the association did not remain after adjusting for confounding factors. 12–14, 20 However, many of these studies may not have been adequately powered to detect a significant association between delirium and mortality.

We previously reported that patients admitted to PACs with delirium have higher mortality than those without delirium.22 An important limitation of that study was that delirium status was determined at a single time – admission to PAC. It did not longitudinally examine the association between delirium and mortality. Our current study is the first to examine whether persistent delirium is associated with greater mortality.

The objective of this study was to follow a cohort of patients with delirium at the time of PAC admission over one year, regardless of their residence at follow-up, and examine the association between persistent delirium and mortality at four follow-up time points. We hypothesized that persistent delirium is independently associated with increased mortality, and that earlier resolution (defined as delirium resolving during an earlier assessment interval) will be associated with lower mortality.

METHODS

Study Sample

Subjects were drawn from a previous cluster-randomized clinical trial of a Delirium Abatement Program (DAP) involving eight greater-Boston skilled nursing facilities specializing in PAC. Usual care or the DAP intervention was implemented depending upon facility randomization. The DAP was an intervention directed at the facility and formal caregivers rather than the patient. The facilities ranged in size from 81 to 224 beds, and 40 to 80 of the beds were Medicare-certified. Methodological details of the DAP have been previously published. 23 A previous study has documented that the DAP intervention was not influential on the course of delirium24. However, to ensure that the intervention did not influence our analyses, we performed our analyses on: 1) all subjects and 2) “usual care” subjects only. Moreover, the analysis involving all subjects was adjusted for intervention status.

Patients and their caregivers were recruited between October 1, 2000 and December 31, 2003. Eligibility requirements included: delirium at PAC admission, 65 years or older, admitted directly from an acute-care medical or surgical hospitalization, spoke English, no significant hearing impairment, communicative prior to acute illness, not admitted for terminal care, no end-stage dementia, not completely ADL dependent prior to hospitalization and lived within 25-miles of our research site. Intake interviews were conducted by trained research assistants and ideally completed within 72 hours (average time to interview = 2.5 days), but not longer than 5 days after admission. A research assistant completed a standardized mental status assessment (details below). Because all subjects were delirious at initial assessment, only persons who survived long enough to be eligible for a follow-up visit and had the opportunity to resolve their delirium were analyzed. Thus, subjects were required to have survived 14 days and have at least one follow-up assessment to allow for longitudinal analyses. Due to the impaired cognitive ability of the patients, family caregivers provided informed consent using a protocol approved by the Hebrew SeniorLife Institutional Review Board.

Mortality Sources

Mortality information was obtained from three sources. First, information was obtained from the National Death Index (NDI)25 for the study's one-year follow-up. The NDI is a National Center for Health Statistics database that compiles mortality data submitted by state vital statistics offices and facilitates studies in health research by reducing the time, expense, effort, and pragmatic limitations involved in ascertaining death in a study cohort. Second, trained research nurses obtained medical record information for subjects who had died within the first 30 days of being admitted to a PAC facility. Third, information was obtained from a telephone interview with the proxy for subjects who died after 30 days, or who died following PAC discharge to another setting (e.g., home or during a subsequent hospitalization).

The NDI was the main source of mortality information. If NDI information was not available for a subject, the other sources were used, which only was true for 10 subjects (2%). The three sources were corroborated and were found to be consistent in 95% of the cases. Exact matches or near exact matches were achieved in greater than 99% of cases, and the remainder were resolved through adjudication. The NDI was used to determine death in the period between the final six-month assessment and one-year follow-up, and also in those 5% of cases where there was disagreement. We ran an analysis where the 5% of disagreement cases were dropped and the results were nearly identical.

Delirium Assessments

Assessments were done at baseline and four follow-up times: 2-week, 4-week, 12-week, and 26-week. Multiple assessors were employed, and interrater reliability of the assessment team was excellent for delirium (kappa = 0.95). 26

A trained research assistant administered a standardized, structured mental status examination and a series of diagnostic instruments for delirium. The Mini-Mental State Examination (MMSE) 27, the Digit Span28 (up to 5 forwards, 4 backwards), and the Delirium Symptom Interview (DSI)29 were used to determine the presence of specific critical symptoms of delirium. Subsequently, interviewers used the MMSE, Digit Span and DSI to complete the Memorial Delirium Assessment Scale30, a measure of delirium severity.

The assessor used patient findings from the previously mentioned instruments to complete the Confusion Assessment Method (CAM); 31 a diagnostic algorithm used to determine the

presence of delirium. It involves four key features: 1) acute change in mental status with a fluctuating course, 2) inattention, 3) disorganized thinking, and 4) altered level of consciousness.31 CAM-defined delirium was considered positive if criteria 1 and 2 were present, and either criteria 3 or 4 were present. The validity of the CAM algorithm has been demonstrated previously to have greater than 95% sensitivity and specificity when compared with a psychiatrist's diagnosis, even in populations with a high prevalence of dementia.31 Results of a recent review study support the finding that the CAM has a high sensitivity and specificity when used in various studies.32 Everyone in this study was required to have delirium at baseline. Delirium was considered persistent if delirium was present at every follow-up assessment or if it resolved and reoccurred.

Covariates

Several baseline patient factors including age, gender, comorbidity, functional status and dementia were used as covariates in adjusted analyses. A brief validated interview was administered to the caregiver at study intake to assess current comorbidity, and this information was used to complete the Charlson Comorbidity Index (CCI).33, 34 If the CCI "Alzheimer's disease or another form of dementia" item was positive or an ICD-9-CM code from the hospital discharge summary indicated the presence of Alzheimer's disease or dementia, then the dementia variable was coded as positive. Due to concern for collinearity arising from inclusion of dementia and CCI simultaneously as covariates in the multivariable model, we calculated the CCI score omitting the "Alzheimer's disease or another form of dementia" item.

A total of 14 primary diagnoses for hospital admission (table 1) were obtained and considered as possible covariates in multivariate analyses. Each diagnosis was examined individually. Similarly, each item of the CCI (except the dementia item, for reasons mentioned above) was also considered individually. If any of these variables were significantly associated with mortality in our bivariate analyses (i.e., each analysis included only one of these variables at a time), they were included in a composite comorbidity score that was included in a multivariate analysis that did not include the CCI (due to collinearity). This was done to confirm that significant primary diagnoses for hospital admission and CCI items were not confounding the association between persistent delirium and 1-year mortality. Though this composite variable was a significant factor in the multivariate analysis, as was the CCI, it did not alter the effect estimate of persistent delirium on 1-year mortality when used in place of the CCI, and consequently the CCI was used instead in our final analyses.

Information on the patient's functional status was obtained using the modified Katz Activities of Daily Living (ADL) scale.35 Katz's scale was modified to include walking and grooming in addition to the 6 original activities (bathing, dressing, toileting, continence, transferring and feeding). The caregiver's report of the patient's functional ability prior to the acute illness that resulted in hospitalization was obtained. Functional data derived from proxies have been shown to be comparable to self-report or performance-based measures. 36 ADLs were rated at three levels ranging from 0 (total dependence) to 2 (independence), and when summed yielded a total scale values ranging from 0 (complete dependence) to 16 (complete independence).

Other Patient Characteristics

Table 1 includes additional measures to describe baseline characteristics of the study sample. The Mini-Mental State Examination 37, a valid and reliable brief examination of generalized cognitive function, assesses memory, concentration, attention, and language yielding a maximum (best) score of 30. In this case, it reflects the effects of both chronic

cognitive impairment (if present) and of delirium. The Blessed Dementia Rating Scale (BDRS)38 is a proxy-based instrument used to assess cognitive impairment prior to hospitalization and was completed by the patient's primary caregiver. Higher scores indicate greater levels of impairment (range 0–28).

Statistical Analyses

Means and standard deviations for continuous variables, and frequencies and percentages for categorical variables were computed to describe the sample. The association between delirium and one-year mortality was examined using survival models. The effect of delirium persistence or resolution on the risk of death was evaluated using an extension of the Cox proportional hazards model with delirium status as a time dependent variable. 39, 40 Using the delirium status from the most recent assessment, this model allows delirium status to be updated for all patients at the time of each death. Baseline covariates were included in the multivariable analyses, as was intervention status (DAP vs. usual care) when all subjects were included in analyses. Unadjusted and adjusted hazard ratios (HR) and corresponding 95% confidence intervals were calculated.

Model assumptions were further evaluated and survival function plots were generated using discrete time survival analysis models.41 Delirium was entered as a time-varying covariate, but the effect was held constant in all discrete time intervals, similar to Cox proportional hazards analyses. The model uses a general baseline hazard over all assessment periods. The trajectories for the five possible monotone delirium resolution patterns are illustrated.

Finally, the adjusted (without dementia) proportional hazards model was stratified by dementia status to determine if the association between persistent delirium and one-year mortality differed by dementia status. An alpha level of 0.05 was used in all analyses to determine statistical significance and guide inference. SAS, Version 9.1 for Windows (SAS Institute, Inc., Cary, NC) and STATA version 9/SE for Windows (College Station, Texas) were used for statistical analyses.

RESULTS

Among 7794 patient admissions in the enrollment period, 6352 (81%) met screening criteria for the study. A total of 4744 (75%) were screened and 667 (14%) were classified as delirious. For 210 of the 667, we were unable to obtain consent from the proxy (138 proxies refused, 56 proxies did not respond within the enrollment period, 14 patients died before the proxies were reached, and two proxies could not provide consent). Thus, 457 subjects were initially available. Among the 457 subjects, 412 subjects (>90%) had at least one follow-up assessment and were included in the analyses.

Of the 412 subjects, 162 subjects died during the one-year follow-up yielding a one-year cumulative mortality of 39%. Approximately 3.6% died between 2 and 4 weeks, 11.2% died between 4 weeks and 12 weeks, 12.9% died between 12 weeks and 26 weeks, and 11.6% died between 26 weeks and 52 weeks. Delirium prevalence among survivors decreased over time: 100% at baseline (n=412), 67% at 2 weeks (n=370), 56% at 4 weeks (n=350), 40% at 12 weeks (n=292) and 32% at 26 weeks (n=257). Notably, at 6 months, delirium persisted in nearly one-third of the cohort.

The average age of the study sample was 84 years and 65% were women (table 1). The average MMSE score was 12.5, two-thirds of subject's functional ability, prior to the acute illness that resulted in hospitalization, were less than independent, 54% had a comorbidity score greater than 1 and more than a third (38%) were classified as having dementia. Thus,

this sample represents an old and frail population, with substantial comorbidity, and levels of cognitive and functional impairment.

Table 2 presents hazard ratios and 95% confidence intervals (CI) estimating the association between persistent delirium and mortality. In the adjusted analysis (age, gender, comorbidity, functional status, dementia and intervention status), subjects who failed to resolve their delirium were 2.9 (95% CI 1.9, 4.4) times more likely to die during the one-year follow-up compared to subjects whose delirium resolved. The mean cumulative hazard (over all persons, all follow-up) of death within one year of admission (at a mean follow-up of 115 days) in the absence of persistent or recurrent delirium was 9%, and in the presence of a persistent or recurrent delirium was 27%. In the dementia stratified adjusted analyses (table 3), the strong and significant association of persistent delirium with mortality was present across both groups (dementia HR=2.6, 95%CI=1.2–5.5; no dementia HR=3.0, 95%CI=1.8–5.0).

Figure 1 illustrates the survival functions derived from discrete time survival models. The increase in mortality risk is estimated including both cases of persistent and recurrent delirium. As Figure 1 indicates, subjects who fail to resolve their delirium have the highest risk of mortality, and subjects who resolve their delirium the earliest have the lowest mortality risk. The remaining trajectories show that earlier resolution of delirium is associated with a lower mortality risk; thus, when delirium resolves, the risk of death diminishes thereafter.

The adjusted analyses that included intervention status revealed that the effect of the intervention did not impact on the risk of death (p=.65) and supported our previous conclusion that the intervention did not influence delirium resolution.24 To further verify that the intervention status of the subjects was not influencing the association between persistent delirium and mortality, we repeated the analyses restricting the sample to only those subjects who did not receive the intervention (i.e., “usual care” only). The results (not shown) were similar such that all conclusions drawn from these analyses did not differ from the analyses including all subjects.

Discussion

The results of this study indicate that delirium persists and is associated with a high one-year mortality rate. Patients whose delirium persisted were nearly three times more likely to die during the one-year follow-up compared to patients who resolved their delirium, even after adjusting for the confounding effects of age, gender, comorbidity, functional status and dementia. Notably, the contribution of persistent delirium to increased mortality is significant and substantial among individuals with and without dementia.

Compared to the one-year (2004) mortality rates of acute conditions such as heart disease (27%) and influenza/pneumonia (3%), the mortality rate for persistent delirium is substantially higher.42 Furthermore, for survivors, failure to recover function often leads to long-term nursing home placement, 43 decreased quality of life and increased healthcare expenditures since the resolution of delirium in the PAC setting is a prerequisite for functional recovery.44

The vast majority of previous research on the association between delirium and mortality has been done in the hospital setting and the findings are inconsistent. Although most studies reported an association between delirium and mortality in unadjusted analyses, not all associations persisted after adjusting for confounding factors. Dolan et al. 12, Francis et al. 45, Inouye et al. 14, and Pompei et al. 20 reported that delirium was not significantly associated with mortality after adjusting for confounding factors, but many of these studies

may have been under-powered for examination of mortality. Kakuma et al. 15, Kelly et al. 16, Metitieri et al. 19, McCusker et al. 17 and Rockwood et al. 21 reported that delirium was associated with an increased risk of death even after adjusting for confounding factors.

Marcantonio et al.22 compared six-month mortality rates for 504 subjects with either delirium (n=188), subsyndromal delirium (n=246) or no delirium (n=70). Subjects with delirium were 5.2 [95%CI 1.8–14.5] times more likely to die compared to subjects without delirium, independent of age, preexisting dementia and medical comorbidity. The current study differs from the Marcantonio et al.22 study in that all subjects were delirious at admission and were followed prospectively, regardless of setting, to see if delirium persisted. In all previous studies, delirium was defined as present or absent at a single time point. Results from our current analyses support and extend previous studies by examining changes in delirium over time at four follow-up time-points.

The focus of this study was to examine the association between persistent delirium and mortality while controlling for factors that could potentially confound this association. Our focus was not to examine the direct association of these confounding factors with delirium or mortality, or the potential role these factors might play in the causal chain between persistent delirium and mortality.

One unique aspect distinguishing this study from previous studies is that it focused on persistent delirium. Traditionally, delirium has been viewed as a transient event. This study adds to the accumulating body of evidence [1–3, 8, 44, 46, 47] that delirium may not be a transient, short-lived phenomenon.

Our results have substantial clinical relevance. Notably, we found an increased risk of mortality with the presence of delirium over time. When delirium resolves, the risk of death diminishes thereafter (Figure 1). This temporal association provides stronger evidence of an etiologic link between delirium and mortality than previous studies.

Our results suggest that delirium may not merely be a marker for sicker individuals who are going to die of their underlying disease, but rather that delirium may confer its own independent mortality risk.48 The delirious individual is unable to effectively interact with the environment, leading to a vicious cycle of worsening debility and adverse events that may result in death. Resolution of delirium at any time is a worthy clinical goal and efforts should continue throughout the continuum of care.

The strengths of this study deserve comment. First, trained research personnel, using an established and validated diagnostic algorithm (CAM), performed the delirium assessments. Second, our study used repeated time assessments of delirium thus allowing the examination of delirium and its association with mortality over time. Third, our study involved detailed interviews with family and facility caregivers to assess baseline characteristics and important covariates. Fourth, mortality data was obtained from 3 sources: the National Death Index, medical record reviews, and proxy informants and corroborated across the sources. Fifth, although the cohort was initially enrolled in the PAC setting, patients were interviewed at follow-up regardless of residence. Finally, we screened nearly 5000 new PAC admissions with detailed mental status assessments, and the final sample represents the largest cohort of delirious patients ever enrolled in a research study.

This study has several limitations. Our data were collected on patients with delirium admitted to PAC facilities in a single metropolitan region and our findings may not generalize to patients with delirium recruited in other settings or locations. This study did not have information on other potential confounding factors such as drug use (e.g., antipsychotics) or nutritional status. Dementia status was identified in the discharge

summary or in a discussion with the family and this could lead to an under-reporting. Also, a small percent of patients without follow-up assessment were excluded and it was not possible to determine if their delirium resolved. Finally, despite the adjustment for confounders, it is possible that failure to resolve delirium is an exceptionally good marker of frailty or comorbidity. Thus, rather than conferring direct mortality risk, delirium may serve as a marker for impaired homeostasis in the elderly and may have prognostic value independent of the usual markers of illness severity.13

In conclusion, delirium is persistent and associated with a nearly three-fold increase in one-year mortality, independent of age, gender, morbidity, functional status and dementia. This association is present independent of dementia status. Future studies should examine the association of persistence of subsyndromal delirium and one year mortality. 22 Future research is needed to develop effective interventions designed to resolve delirium in a timely manner. Before interventions can be targeted at delirious patients, we need to better understand what is different about residents who remain delirious and what factors contribute to their death. Such factors include chronic health conditions, medications and aggressiveness of medical care. These interventions may reduce the high one-year mortality associated with unresolved delirium in the PAC, community and other settings.

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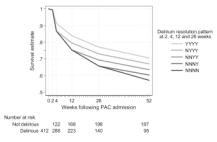

Figure 1.

Estimated survival curves of the time to death for five delirium resolution patterns. Estimated survival obtained from discrete time survival models fitted with general baseline hazard and a constant risk of death due to delirium. Parameters were estimated with logistic regression. Y = Delirium Present; N = Delirium Not Present. PAC = post-acute care.

Table 1

Subject characteristics (demographics, comorbidity, functional status, mental status and primary diagnoses) assessed at post-acute facility admission (n = 412).

Demographics	
Age (mean ± SD)	84.0 ± 7.4
Female, n (%)	267 (65)
White, not Hispanic, n (%)	375 (91)
Married, n (%)*	105 (26)
Education > high school, n (%)*	90 (24)
Home residence before acute hospital admission, n (%)	384 (93)
Comorbidity, Functional and Mental Status	
Charlson comorbidity index†, (mean ± SD)	2.3 ± 2.4
Activities of Daily Living‡, (mean ± SD)	13.3 ± 3.3
Mini-Mental State Examination score§, (mean ± SD)	12.5 ± 6.9
Blessed Dementia Rating Scale score//, (mean + SD)	7.3 ± 4.7
Dementia¶, n (%)	156 (38)
Primary Diagnoses for Hospital Admission*	
Injury/Fracture, n (%)	81 (21)
Neurological/CVA, n (%)	57 (14)
Cardiovascular, n (%)	50 (13)
Respiratory, n (%)	47 (12)
Infection, n (%)	28 (7)
Arthritis n (%)	27 (7)
Delirium/Mental Status, n (%)	24 (6)
Fluid/Electrolytes problem, n (%)	17 (4)
Gastrointestinal, n (%)	15 (4)
Failure to thrive and related symptoms, n (%)	14 (4)
Cancer, n (%)	10 (3)
Bleeding, n (%)	10 (2)
Renal, n (%)	8 (2)
Peripheral Vascular Disease, n (%)	5 (1)

Abbreviation: SD = standard deviation.

*Married (18 missing values); Education > high school (35 missing values); Primary diagnoses for hospital admission (19 missing values).

†Based on the Charlson comorbidity index administered to the patient's next of kin. Note that the “Alzheimer’s disease and dementia” item was not included.

‡ADL function was measured using the modified Katz Activities of Living Scale, with 8 items, each scored 0 = dependent, 1 = requires assistance, 2 = independent; range 0–16, 16 = fully independent.

§Valid and reliable neuropsychological test that assesses memory, concentration, attention, and language; range 0–30, 30 = best.

//Assessed cognitive impairment prior to hospitalization; range 0–28, 28=worst.

¶Dementia based on report of proxy from the intake Charlson comorbidity index or ICD-9-CM code consistent with dementia in the hospital discharge summary.

Table 2

Hazard Ratios and 95% confidence intervals estimating the association between delirium and one-year mortality (n = 412).

	1-Year Mortality	
	Hazard Ratio	**95% CI**
Unadjusted Model	3.0	2.0 – 4.5
Adjusted Model 1*	2.9	1.9 – 4.4
Adjusted Model 2†	2.9	1.9 – 4.4

Abbreviation: CI = confidence interval.

*Model 1 for age, gender, comorbidity (without dementia item), function, and dementia.

†Model 2 for age, gender, comorbidity (without dementia item), function, dementia and intervention status. Note that 249 subjects received the intervention and 163 subjects received the usual care.

*†Note: the adjusted analyses involved 393 subjects as 19 (<5%) had missing covariate values.

Table 3

Hazard Ratios and 95% confidence intervals estimating the association between delirium and one-year mortality, stratified by dementia* (n = 412).

	1-Year Mortality			
	Dementia (n = 156)		No Dementia (n = 256)	
	Hazard Ratio	95% CI	Hazard Ratio	95% CI
Unadjusted	3.1	1.5 – 6.4	3.1	1.9 – 5.0
Adjusted†	2.6	1.2 – 5.4	3.0	1.8 – 5.0

Abbreviation: CI = confidence interval.

*Defined using information from the interview and chart review (see text for details).

†Adjusted for age, gender, comorbidity (without dementia item) and function.

Note: the adjusted analyses involved 393 subjects as 19 (<5%) had missing covariate values.