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Adverse Outcomes After Hospitalization and Delirium in Persons With Alzheimer Disease

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Abstract

Background—Hospitalization, frequently complicated by delirium, can be a life-changing event for patients with Alzheimer disease (AD).

Objective—To determine risks for institutionalization, cognitive decline, or death associated with hospitalization and delirium in patients with AD.

Design—Prospective cohort enrolled between 1991 and 2006 into the Massachusetts Alzheimer's Disease Research Center (MADRC) patient registry.

Setting—Community-based.

Participants—771 persons aged 65 years or older with a clinical diagnosis of AD.

Measurements—Hospitalization, delirium, death, and institutionalization were identified through administrative databases. Cognitive decline was defined as a decrease of 4 or more points on the Blessed Information-Memory-Concentration test score. Multivariate analysis was used to calculate adjusted relative risks (RRs).

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Results—Of 771 participants with AD, 367 (48%) were hospitalized and 194 (25%) developed delirium. Hospitalized patients who did not have delirium had an increased risk for death (adjusted RR, 4.7 [95% CI, 1.9 to 11.6]) and institutionalization (adjusted RR, 6.9 [CI, 4.0 to 11.7]). With delirium, risk for death (adjusted RR, 5.4 [CI, 2.3 to 12.5]) and institutionalization (adjusted RR, 9.3 [CI, 5.5 to 15.7]) increased further. With hospitalization and delirium, the adjusted RR for cognitive decline for patients with AD was 1.6 (CI, 1.2 to 2.3). Among hospitalized patients with AD, 21% of the incidences of cognitive decline, 15% of institutionalization, and 6% of deaths were associated with delirium.

Limitations—Cognitive outcome was missing in 291 patients. Sensitivity analysis was performed to test the effect of missing data, and a composite outcome was used to decrease the effect of missing data.

Conclusion—Approximately 1 in 8 hospitalized patients with AD who develop delirium will have at least 1 adverse outcome, including death, institutionalization, or cognitive decline, associated with delirium. Delirium prevention may represent an important strategy for reducing adverse outcomes in this population.

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Hospitalization can be a major life-changing event with potentially catastrophic consequences for patients with Alzheimer disease (AD). Complications, including delirium, loss of independence, institutionalization, and death, are common outcomes (1, 2) that contribute substantially to the economic burden of AD. The risk for hospitalization is increased 3-fold for patients with AD (3–6). Each year, 20% to 40% of patients with AD are hospitalized for an average of 3.7 days per person-year.

During an average of 3 years in a cohort of community-dwelling patients with AD, we found that up to two thirds had at least 1 hospitalization, nearly one half experienced 2 or more hospitalizations (7), and an episode of delirium could increase the rate of cognitive decline (8). Although these factors distinguish patients with AD as having high risk for hospitalization and demonstrate the substantial effect of delirium on cognitive decline, the relative contributions of hospitalization and delirium to poor outcomes have not been previously examined. Our study expands on previous work documenting the effect of delirium on hospital outcomes (9) in patients with AD.

In this study, outcomes associated with hospitalization and delirium were examined by using a clinical epidemiologic cohort created by merging a clinical sample of patients followed in the Massachusetts Alzheimer's Disease Research Center (MADRC) with data from the Medicare Provider Analysis and Review (MEDPAR) database, medical records, the Social Security Death Index database, and the National Death Index (NDI). Our specific aims were to identify 1-year outcomes, including death, institutionalization, cognitive decline, and an overall composite of these outcomes, associated with hospitalization and delirium in a community-dwelling cohort of patients with AD; examine the adjusted risks for the study outcomes for the hospitalized group with and without delirium; and determine the attributable risks for hospitalization and delirium for each of the study outcomes. We hypothesized that hospitalization and delirium, independent of relevant covariates, would contribute incrementally to negative outcomes. Confirming that hospitalization and delirium play important roles in adverse outcomes may ultimately influence care and management of patients with AD.

Methods

Setting and Participants

Participants were drawn from a prospective cohort of consecutive patients enrolled between 1 January 1991 and 30 June 2006 into the MADRC patient registry. Established in 1984 as a National Institutes of Health Specialized Research Center for evaluation of persons with memory loss, the MADRC has evaluated more than 5600 patients at the Massachusetts General Hospital (MGH), a 900-bed Harvard-affiliated teaching hospital. The current study was nested within the MADRC cohort as part of a longitudinal study of hospitalization in AD described previously (7).

Patients aged 65 years or older with a diagnosis of probable or possible AD according to guidelines from the National Institute of Neurological and Communicative Diseases and Stroke and the Alzheimer's Disease and Related Disorders Association (10) who were not enrolled in a Medicare HMO, had at least 3 MADRC visits during the study interval, and gave informed consent were considered for the study (n = 825). Participants hospitalized after 1 January 2006 (n = 23) were ineligible, because 1-year follow-up would not be complete within the study time frame (through 31 December 2006).

Hospitalizations were identified by using the MEDPAR database, and corresponding medical charts were reviewed. The hospitalized group included participants hospitalized within 18 months of an MADRC visit. Participants without medical records for hospitalization were excluded (n = 5). The nonhospitalized group included participants without any hospitalizations identified by MEDPAR for up to 36 months after an MADRC visit. Participants hospitalized between 18 and 36 months after the MADRC visit were excluded from the study (n = 26) because they could not be validly assigned to either group. Thus, the final sample included 771 participants.

Written informed consent for use of MADRC and clinical data for research was obtained jointly from participants and family members, next of kin, a health care proxy, or a court-appointed guardian according to procedures approved by the MGH institutional review board. The institutional review board at MGH and Hebrew SeniorLife approved the current study using merged MADRC, Medicare, and NDI data. Local institutional review board approval at more than 40 additional Massachusetts hospitals was obtained for review of medical charts.

Data Collection

The baseline MADRC visit, defined as the visit before hospitalization, included demographic characteristics; medical history; neurologic examination; and cognitive testing, including the Information-Memory-Concentration (IMC) subtest of the Blessed Dementia Scale test (11). Dementia severity was rated across all time points by using the MGH Dementia Severity Rating (DSR) scale, an MADRC-created scale that rates general levels of functional dependence (range, 0 to 5, with 5 indicating profound impairment) and correlates highly with the widely used Clinical Dementia Rating scale (Spearman correlation coefficient, 0.87) (8). Family history of AD, symptom duration, rapid onset of symptoms, and a fluctuating or stepwise disease course were also noted.

Follow-up MADRC assessments occurred approximately every 6 months and followed a standardized protocol, including updated history, physical examination, and cognitive testing. The MEDPAR and Denominator files, which include demographic and Medicare enrollment information, were obtained for 1991 through 2006 from the Centers for Medicare & Medicaid Services. The Denominator file identified MADRC patients included in the Medicare database by matching on numerous key variables, including Social Security

number, date of birth, and sex. Information on all hospitalizations and Medicare-eligible nursing home stays, along with dates, length of stay, location, admitting diagnoses, and additional medical diagnoses, was obtained from MEDPAR.

For each index hospitalization, which was identified by Medicare or MADRC records, trained clinical chart abstractors (2 physicians and 2 nurses) reviewed the medical record. Delirium was identified by chart review (12) on the basis of recognition of key terms or presence of mental status or behavioral changes by using a method validated against the Confusion Assessment Method (13). The Confusion Assessment Method has a sensitivity of 74% (95% CI, 65% to 81%), specificity of 83% (CI, 80% to 86%), and positive likelihood ratio of 4.4 (CI, 3.6 to 5.3); however, in moderate to severe cases of delirium (representing the clinically relevant cases), sensitivity was nearly 90% (12).

Information on admitting diagnoses, comorbid conditions, and length of hospital stay was abstracted from medical records. Diagnoses from MEDPAR, chart reviews, and MADRC data were used to calculate the Charlson–Deyo comorbidity score (14, 15).

Procedures were enacted to balance the observation period for the nonhospitalized group with that of the hospitalized group. For each patient in the nonhospitalized group, a visit within that patient's interval of MADRC participation was selected at random to represent that nonhospitalized patient's index MADRC visit. The average length of time between the index MADRC visit and index hospitalization in the hospitalized group was then used to define a "pseudohospitalization date" for the nonhospitalized group (16). Multiple nonhospitalized participants were available per hospitalized patient, and the selection of the index visit was chosen to balance follow-up times between groups.

Outcomes

Adverse outcomes included institutionalization, cognitive decline, or death within 1 year of index hospitalization. Information on nursing home placement was taken from chart review or MADRC records. Deaths were confirmed by using a multistep process. First, exact matches with the NDI database for 1991 through 2006 as the reference standard were identified. If no exact match was found, then the best match with the NDI plus additional supporting data (that is, MADRC or Social Security Death Index data) were used. Finally, 33 cases underwent clinical adjudication by an expert panel of physicians (1 neurologist and 3 geriatricians). Date of death was taken from the death certificate (preferred reference standard) or other source (medical record or Medicare or Social Security database). On the basis of previous work, cognitive decline was defined as a loss of 4 or more points from baseline on the Blessed IMC test score (17–19).

A composite of any adverse outcome within 1 year, including death, institutionalization, or cognitive decline, was used for several reasons. Outcomes are not mutually exclusive and some are hierarchical. For example, if a patient died, institutionalization or cognitive decline could not be additional outcomes, although patients who were institutionalized could have death or cognitive decline as outcomes. The use of composite outcomes can increase efficiency, decrease the effect of missing data, and resolve arbitrary choices among multiple important outcomes (20).

Statistical Analysis

To compare baseline characteristics, 1-way analysis of variance was used for continuous variables and the chi-square test was used for categorical variables. Outcome rates across the study groups specified a priori (hospitalized with delirium, hospitalized without delirium, and nonhospitalized) were compared by using the chi-square test for trend. Poisson regression was performed to calculate unadjusted and adjusted relative risks (RRs). Relevant

covariates included age, race, education, family history of AD, Blessed IMC test score, DSR scale score, duration of symptoms, speed of initial symptom onset, intensive care unit admission indicating severe illness, and Charlson–Deyo comorbidity score.

The population attributable risk (PAR), measuring the potential proportion by which the incidence of the outcomes could be reduced if hospitalization or delirium were eliminated, was calculated as the product of a function of the RR of the outcome among hospitalized patients with delirium ([RR − 1]/RR) and the prevalence of delirium among those hospitalized. The risk for each adverse outcome (attributable to delirium) was calculated as the inverse of the attributable risk. An analysis stratified by baseline cognitive function was also conducted to examine the effect of delirium within strata of cognitive functioning.

Death and institutionalization outcomes were ascertained in full, without missing data. However, cognitive decline could be confirmed only for participants who returned for repeated cognitive testing. Sources of missing Blessed IMC test scores included missed MADRC follow-up within 7 months of the index hospitalization (n = 443), incomplete cognitive data (n = 321), death (n = 20), institutionalization (n = 90), or loss to follow-up (n = 372). The small amount of missing data among control variables (Table 1) was managed with multiple imputation methods by using 20 data sets, and prediction models of missing values were estimated by using all available observed data and the method of chained equations (21). To test the effect of missing data, sensitivity analyses were performed.

Role of the Funding Source

The MADRC and the National Institute on Aging funded the study. The MADRC was involved in collection of data, specifically patient demographic characteristics, medical history, neurologic examination, and cognitive testing. The funding sources were not involved in the study design, analysis, or interpretation of data or in the preparation or submission of the manuscript for publication.

Results

Table 1 shows baseline characteristics of the overall cohort (n = 771), patients hospitalized with delirium (n = 194 [25%]), patients hospitalized without delirium (n = 173 [22%]), and nonhospitalized patients (n = 404 [52%]). The mean age was 77.2 years, more than 50% were women (57%), and most patients were white (95%). The mean Blessed IMC test score was 12.5, and DSR scale scores averaged 2.4 out of 5.0, with a mean duration of symptoms of 3.1 years. Mean Charlson–Deyo comorbidity index scores of 0.8 were low. These demographic characteristics indicate that the cohort was relatively high-functioning, with few comorbid conditions and only mild stages of AD. The median length of follow-up was 2 years (interquartile range, 0.94 to 3.41 years), and the median time between MADRC visits was 0.54 years (interquartile range, 0.50 to 0.67 years). Rehospitalization occurred in hospitalized groups both with (n = 130 [67%]) and without (n = 95 [55%]) delirium during the study period (difference in proportions, 13% [CI, 3% to 23%]).

Hospitalized patients had more comorbid conditions and were older and slightly less educated than the nonhospitalized group. The hospitalized group with delirium had the most cognitive impairment at baseline and was the most impaired according to the DSR scale. These baseline differences were carefully adjusted in all subsequent analyses.

Figure 1 shows the time sequence for the development of study outcomes. Tables 2 and 3 demonstrate the overall outcomes 1 year after hospitalization. The composite outcome showed that at least 1 adverse outcome occurred in 32% of the nonhospitalized group, 55% of the hospitalized group without delirium, and 79% of the hospitalized group with delirium,

highlighting the association of hospitalization and the incremental effect of delirium with negative outcomes in this population of patients with AD.

The most common individual outcome in the hospitalized group with delirium was institutionalization, which occurred in 43%, compared with just 4% in the nonhospitalized group. Death occurred in 2% of the nonhospitalized group, 9% of the hospitalized group without delirium, and 15% of the hospitalized group with delirium. Cognitive decline was observed in all groups, as expected given the progressive nature of AD.

Table 4 shows the RRs for adverse outcomes, adjusted for race, education, family history of AD, baseline Blessed IMC test score, DSR scale score, duration of symptoms, speed of initial onset of symptoms, intensive care unit admission, and Charlson–Deyo comorbidity score. For any adverse outcome, the unadjusted RR was 1.8 (CI, 1.4 to 2.2) for hospitalized patients without delirium and 2.5 (CI, 2.0 to 3.0) for those with delirium. The unadjusted RR for death among hospitalized participants was 5.3 (CI, 2.2 to 12.8) in those without delirium but increased to 8.9 (CI, 4.0 to 20.0) in those with delirium.

For institutionalization, the unadjusted RR for hospitalization was 7.3 (CI, 4.3 to 12.5), but it was higher in hospitalized patients with delirium (RR, 10.8 [CI, 6.5 to 18.0]). Cognitive decline had an unadjusted RR of 0.9 (CI, 0.6 to 1.3) with hospitalization and no delirium and 1.6 (CI, 1.2 to 2.2) with hospitalization with delirium. After adjustment was made for confounding factors, hospitalization alone was associated with a greatly increased adjusted risk for death (4.7 [CI, 1.9 to 11.6]) and for institutionalization (6.9 [CI, 4.0 to 11.7]); if delirium also occurred, these risks increased incrementally to 5.4 (CI, 2.3 to 12.5) for hospitalization alone and 9.3 (CI, 5.5 to 15.7) for institutionalization.

In addition to adjustment for baseline cognitive scores and variables of dementia severity, stratified analyses were conducted to examine the association of delirium within strata of cognitive functioning. A Blessed IMC test score of 15 or greater (22) was used to classify patients as having major cognitive impairment, whereas those with less cognitive impairment had Blessed IMC test scores less than 15. The increased risks associated with delirium persisted within strata (data not shown).

To assess the association of delirium among hospitalized patients with adverse outcomes, both absolute attributable risks and PARs were considered. The outcome with the greatest absolute risk among hospitalized patients with delirium was institutionalization (83 out of 194, or 43%), followed by cognitive decline (38 out of 194 − 101, or 41%) (Table 2) and death (30 out of 194, or 15%) (Table 2). These risks were higher than those of hospitalized patients who did not develop delirium (Table 3).

Table 4 summarizes the PARs for the composite and individual outcomes attributable to delirium among hospitalized patients. The attributable risk estimates can be interpreted as the expected decline in occurrence of the negative outcome if delirium were eliminated, excepting the potential for residual confounding or other sufficient causes of these outcomes (23). The number needed to be exposed to hospitalization and delirium that was associated with 1 fewer occurrence of a negative outcome within 1 year (1/PAR) is also reported.

For hospitalized patients with AD, approximately 1 in 16 deaths, 1 in 7 institutionalizations, and 1 in 5 cases of cognitive decline within 1 year can be attributed to delirium. For the composite outcome, approximately 1 in 8 patients with AD who develop delirium will have a negative outcome that is attributable to the delirium, assuming no residual confounding or alternative causal mechanisms for these outcomes.

Further analyses were conducted to examine the distribution of outcomes and missing cognitive data for patients who were institutionalized (n = 66) or died (n = 20) or had both (n = 24) or neither (n = 181) of the outcomes. As a result of missing cognitive data, the sample size for each outcome differs, as shown in Figure 2. A sensitivity analysis was performed for assumptions made on missing data in the cognitive decline outcome and combined outcome.

We repeated all models, assuming first that all participants missing cognitive follow-up had cognitive decline and then that all participants had no cognitive decline. This method enabled us to examine the extremes of the effect of missing data on our results. The patterns of the results were unchanged, and the significance levels were essentially the same across all analyses. Appendix Tables 1 and 2 (available at www.annals.org) show detailed results of this sensitivity analysis.

Discussion

This study shows that, in patients with AD, hospitalization is associated with increased risks for adverse outcomes. The risk for poor outcomes is greater among patients who develop delirium, even after controlling for cogent confounders. Among hospitalized patients, a substantial proportion of risk for adverse outcomes could be attributed to delirium—specifically, 6.2% of deaths, 15.2% of institutionalization, 20.6% of cognitive decline, and 12.4% of adverse outcomes overall.

Given our previous work (7, 8) documenting the frequency of hospitalization among patients with AD, the increased risk for cognitive decline, and acceleration of cognitive decline after delirium, these results highlight an important and potentially high-yield target for future prevention strategies. Previous studies examining poor outcomes associated with hospitalization (24, 25) have been limited by the lack of measurement of delirium as a potential contributing factor. Our study builds on previous work to examine the association of both hospitalization and delirium on subsequent outcomes in patients with AD.

This study represents a unique, large-scale epidemiologic examination of the outcomes of hospitalization in a community-dwelling population of persons with AD. Although hospitalization may negatively affect patients with other types of dementia, we restricted our analyses to AD to focus on the most common form of dementia with a well-described clinical course. The MADRC data provide high-quality information in a well-characterized clinical cohort. The merging of Medicare, Social Security Death Index, and NDI data makes this clinical cohort useful as a real-world epidemiologic cohort, a major strength of this study. Use of real-world clinical populations has become increasingly important for better understanding of outcomes of care (26, 27).

The presence of delirium was assessed by using a validated method. Finally, ascertainment of death by using the NDI data and nursing home placement was complete and rigorous and verified by multiple sources of information to maximize the quality of the outcome data.

Although causality cannot be established from an observational epidemiologic investigation, this study used many approaches to maximize causal inference (28). These approaches include describing the magnitude of statistical associations, maximizing the validity of associations (that is, controlling for baseline differences in the cohorts and multiple sensitivity analyses testing different assumptions), verifying temporal precedence (that is, confirming that delirium occurs before the outcomes), and establishing biological plausibility (that is, demonstrating that delirium is well-recognized to lead to adverse outcomes).

Our estimates of attributable risk should be interpreted with caution and may not reflect causal effects of delirium on institutionalization, cognitive decline, or death. Because of the potential for residual confounding, differential measurement error, or informative censoring, our results should be interpreted with caution (23, 29). However, we carefully addressed these limitations by adjusting for known risk factors and conducting sensitivity analyses to evaluate the robustness of our findings.

Several important caveats are worth mentioning. Given the nonrandomized nature of this observational study, baseline cognitive function differed among study groups, with the group of hospitalized patients with delirium being most impaired. However, effects were carefully controlled through covariate adjustment and further examined in stratified analyses and suggest that delirium independently contributed to the poor outcomes observed.

Representation of ethnic minorities in the MADRC cohort is low (5%) and all data are obtained from 1 site (the MADRC), which limit the generalizability of the findings. Nevertheless, our sample is directly comparable to that of the National Alzheimer's Coordinating Center cohort (n = 74 169) in terms of demographic characteristics and dementia severity, except that 18% of their sample is composed of minorities.

A notable limitation of our study is missing data in this real-world clinical cohort. Thus, we used a composite measure and merged multiple databases to create a real-world cohort, which is an effective way to minimize missing data and bias (30). Further, the effect of missing data was carefully assessed, with sensitivity analyses assigning extreme values (best case or worst case) to missing data; this assessment did not affect results. Thus, we are confident about the internal validity of our findings and conclusions.

Analyses are limited to those outcomes present in our data. For example, data on functional status were available only on a limited number of patients during follow-up; thus, this factor was not further examined as a study outcome. Likewise, the occurrence of delirium in the nonhospitalized group could not be assessed. However, a large retrospective study on delirium superimposed on dementia in a community-dwelling, managed care population found that the incidence of delirium was 13% (1), and delirium in a general community setting is very low (between 1% to 2%) (31, 32). Thus, we anticipate that the number of nonhospitalized persons with delirium is relatively small. Finally, because of limitations of the Medicare data, our analysis could not separate short-term nursing home stays from long-term stays.

Hospitalization is common in patients with AD, and this study demonstrates the important and incremental associations of hospitalization and delirium with 1-year outcomes in patients with AD. Future work is greatly needed to determine whether prevention of delirium and hospitalization is possible in the high-risk population of persons with AD, and, if possible, whether this will substantially reduce the adverse outcomes of progressive cognitive impairment, institutionalization, and death observed in this study. Further investigation is greatly needed to determine whether prevention of hospitalization and delirium can decrease the attributable risk for death, institutionalization, and cognitive impairment in the vulnerable and increasing population of persons with AD.

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Appendix Table 1

Adjusted and Unadjusted Relative Risks for Cognitive Decline and Any Adverse Outcome [*]

Variable	Relative Risk (95% CI)	
	Hospitalized Patients Without Delirium [†]	Hospitalized Patients With Delirium [†]
Assuming That All Persons Missing Data on Cognitive Decline Did Not Have Decline		
Cognitive decline (*n* = 771)		
Unadjusted	0.8 (0.5–1.1)	1.1 (0.7–1.5)
Adjusted [‡]	0.8 (0.5–1.3)	1.2 (0.8–1.7)
Any adverse outcome (*n* = 771)		
Unadjusted	2.0 (1.5–2.4)	2.8 (2.2–3.4)
Adjusted [‡]	1.9 (1.5–2.4)	2.5 (2.0–3.2)
Assuming That All Persons Missing Data on Cognitive Decline Did Have Decline		
Cognitive decline (*n* = 771)		
Unadjusted	1.1 (0.9–1.2)	1.5 (1.3–1.7)
Adjusted [‡]	1.1 (0.9–1.3)	1.4 (1.2–1.6)
Any adverse outcome (*n* = 771)		
Unadjusted	1.3 (1.1–1.5)	1.6 (1.4–1.8)
Adjusted [‡]	1.3 (1.1–1.5)	1.5 (1.4–1.7)

[*] Numbers of persons with missing data are as follows: race, 7; education, 13; family history of dementia, 1; Dementia Severity Rating scale score, 33; duration of symptoms, 11; and speed of initial symptom onset, 42.

[†] Compared with nonhospitalized patients (referent).

[‡] Adjusted for age, sex, race, education, family history of dementia, Dementia Severity Rating scale score, duration of symptoms, speed of initial onset, Charlson–Deyo comorbidity score, and intensive care unit admission.

Appendix Table 2

Attributable Risk for Cognitive Decline and Any Adverse Outcome Due to Delirium Among Hospitalized Patients With Alzheimer Disease

Variable	Assuming That All Persons Missing Data on Cognitive Decline Did Not Have Decline		Assuming That All Persons Missing Data on Cognitive Decline Did Have Decline	
	Cognitive Decline	Any Adverse Outcome	Cognitive Decline	Any Adverse Outcome
Attributable risk, % [*]	17.1	13.9	10.6	8.8

Variable	Assuming That All Persons Missing Data on Cognitive Decline Did Not Have Decline		Assuming That All Persons Missing Data on Cognitive Decline Did Have Decline	
	Cognitive Decline	Any Adverse Outcome	Cognitive Decline	Any Adverse Outcome
Risk for adverse outcome (attributable to delirium)	1 in 6	1 in 7	1 in 9	1 in 11

* The attributable risk is the product of a function of the relative risk (RR) of the outcome among those hospitalized with delirium ([RR − 1]/RR) and the prevalence of delirium among those hospitalized.

Context

Hospitalization of patients with Alzheimer disease (AD) is frequent and commonly leads to serious complications. The relative role of hospitalization itself and of delirium developing during hospitalization in the occurrence of complications is important to elucidate.

Contribution

In a large prospective cohort of patients with AD, hospitalization itself was associated with a substantial increase in the risk for death and institutionalization. The occurrence of delirium during hospitalization further increased these risks. Delirium was also associated with an increased risk for further cognitive decline.

Caution

Causality cannot be inferred from this observational study.

Implication

In patients with AD, interventions to prevent hospitalization and hospital-associated delirium may be appropriate.

—*The Editors*

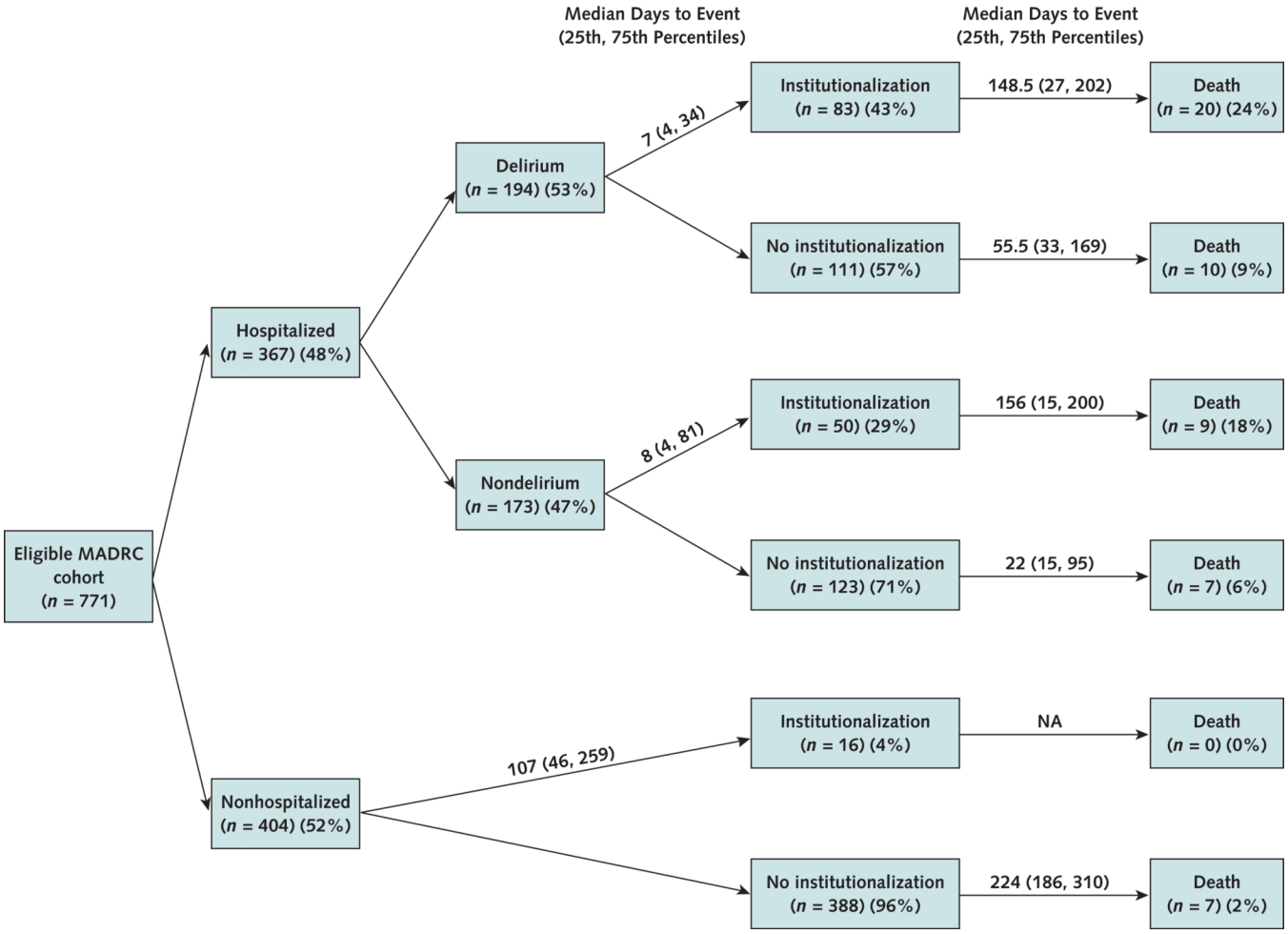

Figure 1. Temporal course of outcomes used in this study

Institutionalization and death are events that happen within 1 y of hospitalization. Median days to event refers to the median length of time from one outcome to the next. MADRC = Massachusetts Alzheimer's Disease Research Center; NA = not available.

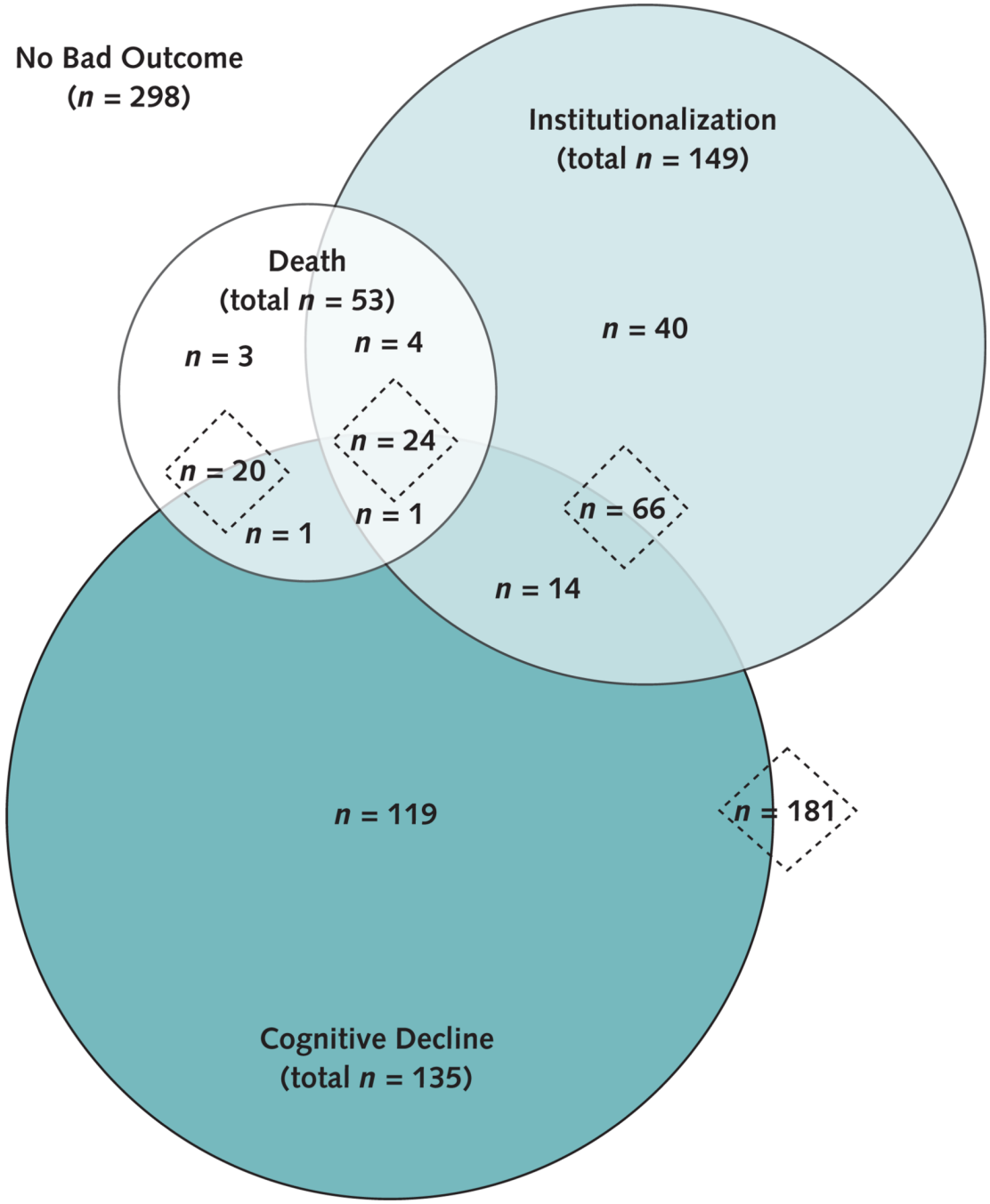

Figure 2. Overlap of outcomes of hospitalization and delirium combined to form the composite outcome

The sizes of the circles and overlaps are proportional to the total number of patients with those outcomes. The dotted diamonds indicate missing data for the outcome of cognitive decline, because classification of these participants inside (or outside) of the cognitive decline circle could not be made. Some cases where the outcome of cognitive decline was not known with certainty included persons who were known to have died ($n = 20$), who had been institutionalized and then died ($n = 24$), or who were institutionalized ($n = 66$). An additional 181 participants were known to be alive, but their outcome of cognitive decline

was not known. The total number indicated for each outcome includes those who had missing data.

Table 1

Characteristics of the Study Sample*

Variable	Total Participants (*n* = 771)	Hospitalized Patients With Delirium (*n* = 194)	Hospitalized Patients Without Delirium (*n* = 173)	Nonhospitalized Patients (*n* = 404)
Demographic characteristics				
Mean age (SD), *y*	77.2 (6.3)	78.7 (6.2)	78.8 (5.8)	75.9 (6.2)
Men, *n* (%)	330 (43)	102 (53)	63 (36)	165 (41)
Nonwhite, *n* (%)	37 (5)	12 (6)	7 (4)	18 (5)
Mean education (SD), *y*	14.0 (3.4)	13.4 (3.7)	13.9 (3.4)	14.2 (3.3)
Dementia-related factors				
Family history of AD, *n* (%)	57 (7)	15 (8)	16 (9)	26 (7)
Mean Blessed IMC test score (SD)†	12.5 (7.1)	14.6 (7.4)	10.8 (6.8)	12.2 (6.9)
Mean DSR scale score (SD)‡	2.4 (0.9)	2.7 (0.9)	2.3 (1.0)	2.4 (0.9)
Mean duration of symptoms (SD), *y*	3.1 (2.1)	2.8 (2.0)	3.1 (2.3)	3.2 (2.1)
Rapid speed of initial symptom onset, *n* (%)	46 (6)	11 (6)	9 (6)	26 (7)
Fluctuating or stepwise disease course, *n* (%)	24 (3)	5 (3)	1 (1)	18 (5)
Illness-related factors, *n* (%)				
Charlson–Deyo comorbidity score§				
0	419 (54)	86 (44)	82 (47)	251 (62)
1	196 (25)	61 (31)	51 (30)	84 (21)
≥2	156 (20)	47 (24)	40 (23)	69 (17)
Intensive care unit admission	25 (3)	15 (8)	10 (6)	0 (0)
Admission diagnosis, *n* (%)‖				
Syncope, fall, trauma	99 (27.0)	51 (26.3)	48 (27.7)	NA
Ischemic heart disease	58 (15.8)	27 (13.9)	31 (17.9)	NA
Gastrointestinal disease	34 (9.3)	16 (8.2)	18 (10.4)	NA
Pneumonia	25 (6.8)	19 (9.8)	6 (3.5)	NA
Musculoskeletal symptoms	17 (4.6)	10 (5.2)	7 (4.0)	NA
Delirium, mental status change	15 (4.1)	11 (5.7)	4 (2.3)	NA
Cerebrovascular disease	15 (4.1)	10 (5.2)	5 (2.9)	NA

Variable	Total Participants (*n* = 771)	Hospitalized Patients With Delirium (*n* = 194)	Hospitalized Patients Without Delirium (*n* = 173)	Nonhospitalized Patients (*n* = 404)
CNS or neurologic symptoms	9 (2.5)	6 (3.1)	3 (1.7)	NA
Urinary tract infection	8 (2.2)	4 (2.1)	4 (2.3)	NA
Cancer	8 (2.2)	2 (1.0)	6 (3.5)	NA
Other[¶]	79 (21.5)	38 (19.6)	41 (23.7)	NA

AD = Alzheimer disease; CNS = central nervous system; DSR = Dementia Severity Rating; IMC = Information-Memory-Concentration; NA = not available.

[*] Demographic characteristics with significant differences ($P < 0.05$) between groups include age, sex, education level, Blessed IMC test score, SR scale score, intensive care unit admission, and Charlson–Deyo comorbidity score. These variables were all controlled for in subsequent analyses. Missing data consist of race ($n = 6$), education ($n = 12$), family history of dementia ($n = 1$), Blessed IMC test score ($n = 77$), DSR scale score ($n = 34$), duration of symptoms ($n = 10$), speed of initial onset ($n = 12$), and course ($n = 14$).

[†] Blessed IMC test score ranges from 0 to 37 points, with 37 indicating the worst score.

[‡] DSR scale score ranges from 0 to 5, with 5 indicating the worst score.

[§] Charlson–Deyo comorbidity score ranges from 0 to 37 points, with 37 indicating the highest score.

[‖] Determined from principal admitting diagnosis for corresponding Medicare claim record; missing for 29 hospitalizations.

[¶] Other admission diagnoses include chronic lung disease, congestive heart failure, fever, other infections, dehydration, acute or chronic renal failure, peripheral vascular disease, psychiatric illness, and diabetes mellitus.

Table 2

One-Year Outcomes, Overall and by Study Group

Variable	Overall (*n* = 771)	Hospitalized Patients With Delirium (*n* = 194)	Hospitalized Patients Without Delirium (*n* = 173)	Nonhospitalized Patients (*n* = 404)	Trend Test	
					Chi-Square	*P* Value
Death, *n* (%)	53 (7)	30 (15)	16 (9)	7 (2)	38.8	<0.001
Institutionalization, *n* (%)	149 (20)	83 (43)	50 (29)	16 (4)	135.2	<0.001
Cognitive decline, *n* (%) *	135 (28)	38 (41)	25 (23)	72 (26)	5.4	0.020
Any adverse outcome, *n* (%) †	292 (49)	123 (77)	77 (55)	92 (32)	92.8	<0.001

* Missing values for Blessed Information-Memory-Concentration test scores on follow-up are as follows, with *n* representing the effective sample size: patients with delirium, 101 (*n* = 93); hospitalized patients without delirium, 65 (*n* = 108); and nonhospitalized patients, 125 (*n* = 279) (Figure 2).

† Missing values for composite outcome are as follows, with *n* representing the effective sample size: patients with delirium, 35 (*n* = 159); hospitalized patients without delirium, 34 (*n* = 139); and nonhospitalized patients, 112 (*n* = 292) (Figure 2).

Table 3

Adjusted and Unadjusted Relative Risks for Death, Institutionalization, Cognitive Decline, and Any Adverse Outcome [*]

Variable	Relative Risk (95% CI)	
	Hospitalized Patients Without Delirium [†]	Hospitalized Patients With Delirium [†]
Death (*n* = 771)		
Unadjusted	5.3 (2.2–12.8)	8.9 (4.0–20.0)
Adjusted [‡]	4.7 (1.9–11.6)	5.4 (2.3–12.5)
Institutionalization (*n* = 771)		
Unadjusted	7.3 (4.3–12.5)	10.8 (6.5–18.0)
Adjusted [‡]	6.9 (4.0–11.7)	9.3 (5.5–15.7)
Cognitive decline (*n* = 480)		
Unadjusted	0.9 (0.6–1.3)	1.6 (1.2–2.2)
Adjusted [‡]	0.9 (0.6–1.4)	1.6 (1.2–2.3)
Any adverse outcome (*n* = 590)		
Unadjusted	1.8 (1.4–2.2)	2.5 (2.0–3.0)
Adjusted [‡]	1.7 (1.4–2.2)	2.2 (1.8–2.7)

[*] Numbers of persons with missing data are as follows: race, 7; education, 13; family history of dementia, 1; Dementia Severity Rating scale score, 33; duration of symptoms, 11; and speed of initial symptom onset, 42.

[†] Compared with nonhospitalized patients (referent).

[‡] Adjusted for age, sex, race, education, family history of dementia, Dementia Severity Rating scale score, duration of symptoms, speed of initial onset, Charlson–Deyo comorbidity score, and intensive care unit admission.

Table 4

Attributable Risk for Death, Institutionalization, Cognitive Decline, and Any Adverse Outcome due to Delirium Among Hospitalized Patients With Alzheimer Disease

Variable	Death	Institutionalization	Cognitive Decline	Any Adverse Outcome
Attributable risk, % *	6.2	15.2	20.6	12.4
Risk for adverse outcome (attributable to delirium)	1 in 16	1 in 7	1 in 5	1 in 8

* The attributable risk is the product of a function of the relative risk (RR) of the outcome among those hospitalized with delirium ([RR − 1]/RR) and the prevalence of delirium among those hospitalized.