Published in final edited form as:
J Am Geriatr Soc. 2010 August ; 58(8): 1542–1548. doi:10.1111/j.1532-5415.2010.02924.x.

Hospitalization in Community-Dwelling Persons with Alzheimer's Disease: Frequency and Causes

James L. Rudolph, M.D., S.M[#,†,*,††], **Nicole M. Zanin, B.A**[#,*,‡], **Richard N. Jones, Sc.D.**[*,‖,††], **Edward R. Marcantonio, M.D., S.M.**[§,*,‖,††], **Tamara G. Fong, M.D., Ph.D.**[*,¶,††], **Frances M. Yang, Ph.D.**[*,¶,††], **Liang Yap, Ph.D.**[**,††], and **Sharon K. Inouye, M.D., M.P.H.**[*,‖,††]

[*]Aging Brain Center, Institute for Aging Research, Hebrew SeniorLife, Boston, MA

[†]VA Boston Healthcare System, Geriatric Research Education and Clinical Center, Boston, MA

[‡]Boonshoft School of Medicine, Wright State University, Dayton, OH

[§]Division of General Medicine and Primary Care, Boston, MA

[¶]Department of Neurology, Beth Israel Deaconess Medical Center, Boston, MA

[‖]Division of Gerontology, Beth Israel Deaconess Medical Center, Boston, MA

[**]Massachusetts Alzheimer's Disease Research Center, Massachusetts General Hospital, Boston, MA

[††]Harvard Medical School, Boston, MA

Abstract

Objectives—To examine the rates of and risk factors for acute hospitalization in a prospective cohort of older community-dwelling Alzheimer's disease (AD) patients

Design—Longitudinal patient registry

Setting—AD Research Center

Participants—827 older persons with AD

Measurements—Acute hospitalization after AD research center visit was determined from Medicare database. Risk factor variables included demographics, dementia-related, comorbidity and diagnoses were measured by interviews and Medicare data.

Results—Of 827 patients during 1991–2006 (median follow-up 3.0 years), 542 (66%) were hospitalized at least once, and 389 (47%) were hospitalized ≥ 2 times, with a median of 3 days

Corresponding Author: James L. Rudolph, MD, SM, VABHS GRECC, 150 South Huntington Ave, Boston MA 02130; Ph 857-364-6812; Fax 857-364-4544; jrudolph@partners.org.
[#]Both authors have contributed equally and have agreed to share first authorship

Conflict of Interest: The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this paper.

Author Contributions:
Study concept and design: SK Inouye
Acquisition of data: L Yap, SK Inouye
Analysis and interpretation of data: J Rudolph, NM Zanin, RN Jones, ER Marcantonio, T Fong, FM Yang
Drafting of the manuscript: J. Rudolph, NM Zanin, SK Inouye
Critical revision of the manuscript for important intellectual content: J Rudolph, NM Zanin, RN Jones, ER Marcantonio, T Fong, FM Yang, L Yap
Statistical expertise: RN Jones, SK Inouye
Obtained funding: N Zanin, J Rudolph, SK Inouye
Administrative, technical, or material support: RN Jones, L Yap, SK Inouye

spent in the hospital per person-year. Leading reasons for admission included syncope or falls (26%), ischemic heart disease (17%), gastrointestinal disease (9%), pneumonia (6%), and delirium (5%). Five significant independent risk factors for hospitalization included higher comorbidity (hazard ratio (HR), 1.87; 95% confidence interval (95%CI) 1.57, 2.23), previous acute hospitalization (HR, 1.65; 95%CI 1.37, 1.99), older age (HR, 1.51; 95%CI 1.26, 1.81), male sex (HR, 1.27; 95%CI 1.04, 1.54) and shorter duration of dementia symptoms (HR, 1.26; 95%CI 1.02, 1.56). Cumulative risk of hospitalization increases with the number of risk factors present at baseline: 38% with 0 factors; 57% with 1 factor; 70% with 2–3 factors; and 85% with 4–5 factors ($P_{trend}<0.001$).

Conclusion—In community-dwelling population with generally mild AD, hospitalization is frequent, occurring in two-thirds of participants over a median follow-up time of 3 years. With these results, clinicians may be able to identify dementia patients at high risk for hospitalization.

Keywords

Hospitalization; geriatrics; dementia; Alzheimer's disease; delirium

INTRODUCTION

Alzheimer's disease (AD) is a devastating, relentlessly progressive neurodegenerative disease for which no curative treatments are currently available. Currently, AD affects 5.1 million Americans over age 65,1 and the prevalence is steadily increasing. In 2010, the incidence of AD is estimated to be 454,000 per year and will be 615,000 per year by 2029 without effective preventive strategies.2 Healthcare costs for AD are estimated at $100 billion per year in the United States, making it the third most costly disease, exceeded only by heart disease and cancer.1, 3, 4

The high prevalence of AD exerts a strong influence on overall healthcare expenditures.5 Patients with AD have 2–5 times higher healthcare costs and utilization, even after adjusting for comorbidity.4, 5 Hospitalization costs are 2.8 times higher in AD patients than age-matched Medicare beneficiaries, and represent the major driver of Medicare expenditures for AD patients.6

Hospitalization often represents a pivotal event for persons with AD, with loss of independence and institutionalization representing frequent and unfortunate outcomes.7 Previous studies have documented that hospital outcomes for patients with AD are significantly worse than for those without AD, with respect to delirium, functional losses, prolonged length of stay, institutionalization and death.8–10 Despite its clinical and economic impact, relatively few studies11–15 have examined hospitalization in AD patients. In particular, previous studies have not explored risk factors that predispose patients to hospitalization in the earlier stages of AD, which is more common.

The specific aims of the proposed study were: 1) to examine the frequency of hospitalization in a community-dwelling cohort of AD patients followed in the Massachusetts Alzheimer's Disease Research Center (MADRC); 2) to ascertain the principal admitting diagnoses associated with hospitalization; and 3) to evaluate baseline risk factors for hospitalization—including demographic, AD-related, and illness-related factors. Our overall goal was to clinically identify AD patients at high risk for hospitalization based on baseline risk factors.

METHODS

Setting and Subjects

Study participants were drawn from the prospective cohort of consecutive patients assembled by the Massachusetts Alzheimer's Disease Research Center (MADRC) Patient Registry, and enrolled from January 1, 1991 to June 30, 2006. The MADRC was established in 1984 as a National Institutes of Health Specialized Research Center for evaluation of persons with memory loss. Since 1984, the MADRC has evaluated over 5,600 patients at the Massachusetts General Hospital (MGH), a 900-bed Harvard-affiliated teaching hospital with 1.5 million outpatient visits per year.

Eligible patients were aged 65 years and older and had a clinical diagnosis of probable or possible AD, established by the examining neurologist based on National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) guidelines (n=1837).16 This study was nested within the MADRC cohort as part of a longitudinal study of cognitive trajectory in Alzheimer's Disease.17 As a result, patients were excluded if they had less than 3 visits with the MADRC (n=920) to ensure complete baseline data collection and approximately one year of follow-up. Patients with <3 visits were older, less likely to be married, and had more severe dementia compared to the study cohort. Additionally patients were excluded if they were enrolled in a Medicare Health Maintenance Organization (HMO) (n=68) which precluded complete collection of hospitalization data in the Medicare database, or if they refused consent for use of their clinical data for research purposes (n=22). The final sample included 827 participants.

The informed consent policy of the MADRC includes obtaining joint consent of patients and their next of kin, health care proxy, or guardian. The current study, conducted using secondary data from the MADRC and medical record review, merged with Medicare data, was approved by the institutional review boards of the MGH and the Hebrew SeniorLife.

Data Collection

The initial assessment in the MADRC included a medical history, neurological examination, and cognitive testing with dementia severity rating. Follow-up assessments were completed every 6 months, and included an updated history, physical examination, and cognitive testing.

Medicare Provider Analysis and Review (MedPAR) and Denominator files were obtained for years 1991–2006 from the Center for Medicare and Medicaid Services (CMS). The Denominator file enabled identification of patients enrolled in a Medicare HMO, who were ineligible for our study. We obtained information on all hospitalizations, along with dates, length of stay, location, admitting diagnoses, and additional medical diagnoses from MedPAR.

Study Outcome

The outcome was the first acute hospitalization (index hospitalization) after the index visit at the MADRC. Psychiatric, long-term care, and rehabilitation admissions were not included as hospitalizations. The index MADRC visit was defined as the first MADRC visit after the patient reached Medicare eligibility at age 65 years.

Potential Risk Factor Variables

Three major categories of potential risk factors were examined: socio-demographic, dementia-related, and acute illness-related. Socio-demographic variables included age,

gender, race, education, and marital status. Dementia-related variables included family history of dementia, cognitive function assessed by the Blessed Information-Memory-Concentration (IMC) score, 18 MADRC Dementia Severity Rating scale, duration of symptoms before diagnosis, speed of initial onset, and course of deterioration. Illness-related variables included the Deyo-Charlson comorbidity index19, 20 and previous acute hospitalization. Continuous variables (e.g., Blessed scores, duration of symptoms, and dementia severity), were examined continuously and by quintiles for a significant association, a U-shaped relationship, and a non-linear relationship with hospital risk.

To facilitate development of a clinical risk stratification system for clinicians, we dichotomized the variables. We chose cut-points for continuous variables based on previous studies, data distributions, and clinical sensibility. Patients were categorized as having either <12 years of education or ≥12 years of education. The Blessed IMC score is a global cognitive test ranging from 0 to 37, with higher scores indicating impairment.18 A cutpoint of ≥ 15 correlates with major cognitive decline and associated functional deterioration.21 Severity of AD was staged with the MADRC Dementia Severity Rating scale, which rates general levels of functional dependence (range 0–5, with 5 indicating profound impairment) and correlates strongly (Spearman correlation coefficient = 0.87, P<0.0001)17 with the Clinical Dementia Rating Scale in our sample.22 After collecting the relevant history, cognitive exam, and physical exam, MADRC neurologists rated the speed and course of AD symptoms. Speed of initial onset of AD symptoms was categorized as “rapid onset”, defined as a decline over weeks to a few months or “slow onset”, defined as a decline over several months to years. Course of symptoms was categorized as fluctuating or stepwise, contrasted with stable or improving.

Previous hospitalizations were defined as any acute hospitalization during the year before the index MADRC visit. The Deyo-Charlson index is a widely used comorbidity index, created using International Classification of Diseases Ninth Revision (ICD-9) codes for the index hospitalization from Medicare and medical record data. A score of ≥1 is commonly used to indicate high comorbidity.19, 20 For the 48 subjects (5.8%) who were missing diagnosis information, we used equipercentile equating23 to calculate an equivalent score based on medical diagnoses collected by the MADRC.

Admitting Diagnoses

For hospitalized patients, the admitting diagnosis from Medicare was examined, because it reflected most closely the reason for hospitalization. For analysis, these were rank-ordered by frequency.

Statistical Analysis

Descriptive statistics, including proportions, means, standard deviations, medians, and interquartile ranges (25–75 percentile) were calculated. To examine potential risk factor variables, bivariable analyses were first conducted using unadjusted Cox proportional hazards models, with time to index hospitalization as the dependent variable. The time to hospitalization was defined as the years from index MADRC visit through index hospitalization visit for subjects who were hospitalized, or through the entire study period for those who were not hospitalized (censored either at death or end of the study period). Subsequently, multivariable proportional hazards models were conducted, adjusting for age, gender, race, education, marital status, family history of dementia, Blessed IMC score, MADRC Dementia Severity Rating, duration of symptoms, speed of onset, disease course, Deyo-Charlson Comorbidity Index and previous acute hospitalization. Schoenfeld’s global test24 was conducted to test the proportionality assumption, which was not violated in any of our models. The Gompertz model25 was used to confirm the results from the Cox

models. Regression coefficients were estimated using the maximum likelihood method, and estimated hazards ratio (HR) and their associated 95% confidence intervals (CI) were presented. A C-statistic was calculated as an estimate of the model calibration. The small number of missing values (see Results) were imputed using multiple imputation methods. Analyses were performed using the SAS statistical analysis program (Version 9.1, SAS Institute, Cary, NC) and STATA (Version 10.1, Stata Corporation, College Station, Texas). All statistical tests were two-tailed, and an alpha level of less than 0.05 was used to indicate statistical significance.

Risk Stratification System—To develop a risk stratification system, we utilized the clinical characteristics which were significantly associated with hospitalization after adjustment. The points for the risk stratification system were assigned by adding one point for each risk factor present. We then examined the incidence of index hospitalization with increasing point totals and collapsed points with similar incidence. This risk stratification system is shown for descriptive purposes only, to show that the risk of hospitalization increases with the number of risk factors present. A Chi-square test for trend was used to examine the incidence of hospitalization across strata.

RESULTS

Baseline patient characteristics of the 827 AD patients are summarized in Table 1. The mean (± standard deviation) follow-up was 4.0 ± 3.5 years (median = 3.0 years). The mean age of the cohort was 75.8 ± 6.2 years. Over half of the cohort was female (58%), and the majority were white (94%). The mean Blessed IMC score was 10.1 points and MADRC Dementia Severity Rating scale scores averaged less than 2 points, consistent with a relatively high-functioning, community-dwelling population with mild Alzheimer's disease. The mean duration of symptoms for the cohort was 3.1 years, indicating that the cohort was generally in the early stages of AD. The cohort had relatively low Deyo-Charlson comorbidity index scores (0.8 ± 1.3 points), signifying relatively low medical comorbidity with a low anticipated one-year mortality. During the one-year period prior to the index hospitalization, one- third of patients had a previous acute hospitalization.

Table 2 demonstrates that 542 patients (66%) were hospitalized at least once during their follow-up period, after a median of 2.2 years. Hospitalization occurred in 111 hospitals across 15 states. The annual rate of hospitalization was 16.3 per 100 person-years (95% confidence interval, 15.0–17.7). During the entire study period, 389 (47%) were rehospitalized after their initial hospitalization for a median of 2 hospitalizations per person. Among the hospitalized group, patients spent a median of 3.0 days in the hospital per year.

Primary diagnoses associated with hospitalization are presented in Table 3. Patients were most commonly admitted for syncope, fall, or trauma (26%); ischemic heart disease (17%), gastrointestinal disease (9%), pneumonia (6%), and delirium or mental status change (5%). Diagnoses occurring in <5% of admissions included cerebrovascular disease, musculoskeletal disorders, urinary tract infection, fever or other infections, chronic lung disease, congestive heart failure, cancer, dehydration, neurological disease, renal failure, psychiatric disorders, diabetes mellitus, and peripheral vascular disease.

A small number of missing values were present for potential risk factor variables, including education (n=13, 1.6%), family history of dementia (n=1, 0.1%), MADRC Dementia Severity Rating (n=12, 1.5%), duration of symptoms before diagnosis (n=11, 1.3%), speed of initial onset (n=13,1.6%), course of AD (n=15, 1.8%), Deyo-Charlson score (n=48, 6%), and previous hospitalization (n=57, 7%) patients. Multiple imputation methods were used for the multivariable analyses.

Five significant risk factors for hospitalization were identified in both unadjusted and adjusted analyses (Table 4), including demographic (age and male sex), dementia-related (rapid onset of disease with shorter duration of symptoms), and illness-related variables (high Deyo-Charlson comorbidity score and previous acute hospitalization). The C-statistic was 0.66 (95% confidence interval, 0.63–0.68). The strongest risk factor was high comorbidity, associated with an 87% increased adjusted risk of hospitalization. Other important risk factors included acute hospitalization in the past year (65% increased adjusted risk); older age (51% increased adjusted risk); male sex (27% increased adjusted risk); and shorter duration of symptoms (26% increased adjusted risk). Interestingly, other dementia-related predictors, including Blessed IMC score, MADRC Dementia Severity Rating, family history of dementia, speed of initial onset, and course of disease were not significant predictors of hospitalization and there was no U-shaped or non-linear relationship with hospitalization. Moreover, race, education level and marital status were not significant predictors.

Table 5 shows that a higher number of risk factors increases the risk for hospitalization with a significant trend. Those with one risk factor were 1.8 times as likely to be hospitalized as those with no risk factors. Those with 2–3 risk factors were 3.0 times as likely; and those with 4–5 risk factors were 6.1 times as likely to be hospitalized as those with no risk factors. Thus, the number of risk factors present at baseline directly impacts the risk of subsequent hospitalization.

DISCUSSION

This study demonstrates that hospitalization is a frequent outcome in persons with Alzheimer's disease, even at relatively early stages of disease. In our sample of community-dwelling persons with (on average) mild AD and low comorbidity, two-thirds were hospitalized at least once during the follow-up period, and nearly half were hospitalized 2 or more times. Due to longer duration of follow-up (3.0 years on average), these cumulative risks are higher than those described in previous studies of community-dwelling samples.11 Our results reinforce previous studies reporting on the high rates of hospitalization in AD patients more generally, which are at least 3 times higher than non-affected, age-matched persons.13, 26, 27

This study has face validity in that three of our independent risk factors for hospitalization (age, comorbidity, and prior hospitalization) have been identified in other studies of the Alzheimer's and older primary care populations.15, 26. Our study expands the literature by identifying two additional risk factors for hospitalization which are routinely assessed in Alzheimer's Disease patients (male sex and short duration of symptoms) The short duration of symptoms before diagnosis indicates that patients on a rapid or accelerated trajectory of decline before presenting for dementia evaluation may be more likely to be hospitalized. Interestingly, in this community-dwelling population severity of dementia and other dementia-related variables including cognitive score, dementia severity rating, and clinical course were not significant risk factors for hospitalization. While some studies have found that more severe dementia was predictive of hospitalization, the severity index is not always collected systematically.11–13 For example, dementia severity measured at the time of hospitalization will be higher because of the physiologic decompensation and possibly superimposed delirium28 which brought the patient to the hospital. By measuring severity at ADRC visits prior to hospitalization, we are capturing a picture of the baseline dementia severity, rather than acute dementia severity.

Taken together, the risk factors identified help to identify a high risk group. For instance, patients with 2 or more risk factors have a >70% cumulative risk of hospitalization over

approximately three years, and would be an important group to target for future intervention strategies. While validation in other samples would be needed, our results describing the risk factors for hospitalization yield important and clinically relevant information. While speculative, it is possible that early stage AD patients are more likely to be hospitalized than their age-matched peers because of increasing problems related to their cognitive deficits, even at the early stages, such as judgment errors resulting in falls, medication errors or noncompliance, decreases in thirst or appetite resulting in dehydration or malnutrition, and the like. Even in the early stages, it is likely that subtle cognitive problems may have adverse impacts on health and medical care.

Understanding potential factors leading to hospitalization in the AD population are important for quality of life, cost-savings, and development of interventions to prevent hospitalization. Many of the identified conditions are potentially preventable with simple interventions in the home and hospital, and with discharge teaching/homecare follow-up. The five leading reasons for hospitalization in this cohort included falls, ischemic heart disease, gastrointestinal disease, pneumonia, and delirium which are consistent with recent work.[15, 29] Falls may be effectively prevented in community-dwelling elderly through strategies such as exercise programs, balance training, reduction of high-risk medications, vision adaptations, and home safety enhancements.[30] Prevention strategies for ischemic heart disease include blood pressure control, cholesterol reduction, smoking cessation, diet modification, and increased physical activity.[31–33] These interventions would also reduce cerebrovascular events, the sixth most common reason for hospitalization. For gastrointestinal bleeding and peptic ulcer disease, leading gastrointestinal diagnoses in our sample, avoidance of non-steroidal drugs, use of antacids or gastroprotective drugs, and eradication of *H pylori*, may be effective preventive strategies.[34] Strategies for prevention of pneumonia, including improved swallowing techniques, aspiration precautions, avoidance of sedative medications, consistent use of influenza and pneumococcal vaccination, and prompt use of appropriate anti-viral treatment during flu season, may help to reduce these admissions.[35] Finally, well-established strategies for delirium prevention, including avoidance of psychoactive medications, enhancing nutrition and hydration, preventing infection, addressing electrolyte or metabolic derangements, and ensuring oxygenation, would be effective approaches to reduce hospitalization.[36] It is important to note that many of these evidence-based strategies have not been tested specifically for their preventive efficacy in persons with Alzheimer's disease.

This study has noteworthy strengths. It represents a unique large-scale epidemiologic study examining the frequency and risk factors for hospitalization in a community-dwelling AD population. High quality data from the MADRC provided a large, well-characterized clinical cohort of 827 patients, with prospective gold-standard neurologist diagnoses of AD according to clinical criteria and longitudinal follow-up for a median of 3 years. Furthermore, the careful combination of MADRC and MedPAR data allowed near-complete examination of all hospitalization data across several hospitals and states.

The results of this study are limited because we were unable to fully assess acute indications for hospitalization such as delirium, medication, and social factors including caregiver support from the MADRC assessments and Medicare data. Additionally, for the initial year of the study (1991), we did not have prior hospitalization records. A sensitivity analysis using multiple imputation of these records did not significantly change the results. Finally, this study would have benefited from further assessment at the index MADRC visit of the relationship between speed of cognitive decline and recent delirium.

The generalizability of these results are limited by several factors listed below. First, the exclusion of patients with <3 MADRC visits may have limited our generalizability to

patients earlier in the disease and those who were more likely to follow-up. Second, the minority representation in this sample is relatively low (6%). While we have verified that the MADRC sample is comparable to the National Institute on Aging/National Alzheimer's Coordinating Center (NACC) sample of 85,460 AD patients in terms of age, gender, educational level, and dementia onset, the minority representation is lower in the MADRC than in the overall NACC sample (6% vs.18%). Third, the data were drawn from a single site which may limit generalizability to patients who have access to an academic medical center or ADRC. However, the primary care and thus, most of the decisions regarding hospitalization of the AD patients were made by the primary care physicians. Finally, it is important to stress that all of these factors influence only external validity (generalizability), and the internal validity of our study findings remains uncompromised.

There are important implications of our work. First, the study allows us to identify AD patients at high risk for hospitalization, who would be important to target for future preventative efforts. Second, the study lays the groundwork for future intervention studies to prevent hospitalization in this vulnerable group. Finally, the outcomes of hospitalization in AD patients warrant further examination in future studies. Documenting the prevalence and etiologies of hospitalization in AD patients represents a crucial first step in this future research imperative. Given the frequency of hospitalization in the currently 5 million patients with AD, an intervention to prevent or shorten hospitalization would potentially save Medicare billions of dollars per year.[5, 37]

Acknowledgments

The authors thank Mr. Douglas C. Tommet for statistical analysis, Mr. Daniel Habtemariam for data management, and Drs. John Growdon and Bradley T. Hyman for access and use of the MADRC data. This work is dedicated to the memory of Joshua Helfand and Mitsuo Inouye, M.D.

Dr. Inouye holds the Milton and Shirley F. Levy Family Chair in Alzheimer's disease. Dr Rudolph is funded by a VA Research Career Development Award.

This study is supported in part by the American Federation for Aging Research Medical Student Training in Aging Research program, #T35AG026781 (NMZ, JLR), and Grants #K24AG000949 (SKI) and #R03AG029861 (JLR) from the National Institute on Aging, #IIRG-08-88737 (SKI) from the Alzheimer's Association, and the Aging Brain Center, Institute for Aging Research, Hebrew SeniorLife. The MADRC database is funded by NIH/NIA P50AG005134.

Sponsor's Role: The funding sources had no involvement in the design, analysis, manuscript preparation, or decision to publish the manuscript.

REFERENCES

1. 2009 Alzheimer's disease facts and figures. Alzheimers Dement. 2009; 5:234–270. [PubMed: 19426951]
2. Hebert LE, Scherr PA, Bienias JL, et al. Alzheimer disease in the US population: prevalence estimates using the 2000 census. Arch Neurol. 2003; 60:1119–1122. [PubMed: 12925369]
3. Zhu CW, Scarmeas N, Torgan R, et al. Longitudinal study of effects of patient characteristics on direct costs in Alzheimer disease. Neurology. 2006; 67:998–1005. [PubMed: 16914696]
4. Zhao Y, Kuo TC, Weir S, et al. Healthcare costs and utilization for Medicare beneficiaries with Alzheimer's. BMC Health Serv Res. 2008; 8:108. [PubMed: 18498638]
5. Rice DP, Fillit HM, Max W, et al. Prevalence, costs, and treatment of Alzheimer's disease and related dementia: a managed care perspective. Am J Manag Care. 2001; 7:809–818. [PubMed: 11519239]
6. Bynum JP, Rabins PV, Weller W, et al. The relationship between a dementia diagnosis, chronic illness, medicare expenditures, and hospital use. J Am Geriatr Soc. 2004; 52:187–194. [PubMed: 14728626]

7. Gill TM, Allore HG, Holford TR, et al. Hospitalization, restricted activity, and the development of disability among older persons. JAMA. 2004; 292:2115–2124. [PubMed: 15523072]
8. Pedone C, Ercolani S, Catani M, et al. Elderly patients with cognitive impairment have a high risk for functional decline during hospitalization: The GIFA Study. J Gerontol A Biol Sci Med Sci. 2005; 60:1576–1580. [PubMed: 16424291]
9. Fick DM, Agostini JV, Inouye SK. Delirium superimposed on dementia: a systematic review. J Am Geriatr Soc. 2002; 50:1723–1732. [PubMed: 12366629]
10. Zilkens RR, Spilsbury K, Bruce DG, et al. Clinical epidemiology and in-patient hospital use in the last year of life (1990–2005) of 29,884 Western Australians with dementia. J Alzheimers Dis. 2009; 17:399–407. [PubMed: 19363266]
11. Albert SM, Costa R, Merchant C, et al. Hospitalization and Alzheimer's disease: results from a community-based study. J Gerontol A Biol Sci Med Sci. 1999; 54:M267–M271. [PubMed: 10362011]
12. Andrieu S, Reynish E, Nourhashemi F, et al. Predictive factors of acute hospitalization in 134 patients with Alzheimer's disease: A one year prospective study. Int J Geriatr Psychiatry. 2002; 17:422–426. [PubMed: 11994930]
13. Nourhashemi F, Andrieu S, Sastres N, et al. Descriptive analysis of emergency hospital admissions of patients with Alzheimer disease. Alzheimer Dis Assoc Disord. 2001; 15:21–25. [PubMed: 11236821]
14. Natalwala A, Potluri R, Uppal H, et al. Reasons for hospital admissions in dementia patients in Birmingham, UK, during 2002–2007. Dement Geriatr Cogn Disord. 2008; 26:499–505. [PubMed: 19005254]
15. Malone DC, McLaughlin TP, Wahl PM, et al. Burden of Alzheimer's disease and association with negative health outcomes. Am J Manag Care. 2009; 15:481–488. [PubMed: 19670951]
16. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology. 1984; 34:939–944. [PubMed: 6610841]
17. Fong TG, Jones RN, Shi P, et al. Delirium accelerates cognitive decline in Alzheimer disease. Neurology. 2009; 72:1570–1575. [PubMed: 19414723]
18. 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. [PubMed: 5662937]
19. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol. 1992; 45:613–619. [PubMed: 1607900]
20. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987; 40:373–383. [PubMed: 3558716]
21. Stern Y, Mayeux R, Sano M, et al. Predictors of disease course in patients with probable Alzheimer's disease. Neurology. 1987; 37:1649–1653. [PubMed: 3658173]
22. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology. 1993; 43:2412–2414. [PubMed: 8232972]
23. Kolen, MJ.; Brennan, RL. Test Equating, Scaling, and Linking: Methods and Practices. 2nd ed.. New York: Springer-Verlag; 2004.
24. Abeysekera WWM, Sooriyarachchi MR. Use of Schoenfeld’s global test to test the proportional hazards assumption in the Cox proportional hazards model: An application to a clinical study. J Natn Sci Foundation Sri Lanka. 2009; 37:41–45.
25. Cleves, MA.; Gould, WW.; Gutierrez, RG. An introduction to survival Analysis using STATA. College Station, TX: Stata Press; 2002.
26. Inouye SK, Zhang Y, Jones RN, et al. Risk factors for hospitalization among community-dwelling primary care older patients: Development and validation of a predictive model. Med Care. 2008; 46:726–731. [PubMed: 18580392]
27. Fick DM, Kolanowski AM, Waller JL, et al. Delirium superimposed on dementia in a community-dwelling managed care population: A 3-year retrospective study of occurrence, costs, and utilization. J Gerontol A Biol Sci Med Sci. 2005; 60:748–753. [PubMed: 15983178]

28. Fick DM, Hodo DM, Lawrence F, et al. Recognizing delirium superimposed on dementia: assessing nurses' knowledge using case vignettes. J Gerontol Nurs. 2007; 33:40–47. quiz 48–49. [PubMed: 17310662]

29. Mitchell SL, Teno JM, Kiely DK, et al. The clinical course of advanced dementia. N Engl J Med. 2009; 361:1529–1538. [PubMed: 19828530]

30. Gillespie LD, Robertson MC, Gillespie WJ, et al. Interventions for preventing falls in older people living in the community. Cochrane Database Syst Rev. 2009:CD007146. [PubMed: 19370674]

31. Smith SC Jr, Allen J, Blair SN, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute. Circulation. 2006; 113:2363–2372. [PubMed: 16702489]

32. Hooper L. Primary prevention of CVD: diet and weight loss. Clin Evid (Online). 2007; 2007

33. Stensel D. Primary prevention of CVD: physical activity. Clin Evid (Online). 2007; 2007

34. Bhatt DL, Scheiman J, Abraham NS, et al. ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use. Am J Gastroenterol. 2008; 103:2890–2907. [PubMed: 18853965]

35. Loeb M. Community-acquired pneumonia. Clin Evid (Online). 2008; 2008

36. Inouye SK. Delirium in older persons. N Engl J Med. 2006; 354:1157–1165. [PubMed: 16540616]

37. Geithner TF, Solis HL, Sebelius K, et al. 2009 Annual report of the boards of trustees of the federal hospital insurance and federal supplementary medical insurance trust funds. Center for Medicare & Medicaid Services. 2009

Table 1

Baseline Characteristics of the Alzheimer's Disease Cohort (N = 827)

Characteristic*	Mean ± SD or n (%)
Demographics	
Age, years	75.8 ± 6.2
Female	480 (58%)
Non-White	49 (6%)
Education, years	14.0 ± 3.5
Unmarried	284 (34%)
Dementia-related	
Family history of dementia	60 (7%)
Blessed IMC score (0–37 points, 37 worst)	10.1 ± 5.8
Dementia Severity Rating (0–5 points, 5 worst)	1.9 ± 0.7
Duration of symptoms, years	3.1 ± 2.1
Speed of initial onset, rapid (vs. slow)	48 (6%)
Course, fluctuating or stepwise (vs. stable or improving)	28 (4%)
Illness-related	
Deyo-Charlson score† (0–33 points, 33 highest)	0.8 ± 1.3
Previous acute hospitalization	269 (33%)

SD=Standard deviation; IMC=Information-Memory-Concentration

*Missing data were present as follows: education (n=13); family history of dementia (n=1); Dementia Severity Rating (n=12); duration of symptoms (n=11); speed of initial onset (n=13); course (n=15); Charlso-Deyo (n=48); previous acute hospitalization (n=57)

†Equipercentile equating used for imputation of missing values in 48 subjects. See text for details.

Table 2

Frequency of Hospitalization in Alzheimer's Disease Patients

Outcome	n (%)	Median (q1, q3)	Mean ± SD
Study Cohort: N = 827			
Index hospitalization	542 (66%)		
Number hospitalized after initial MADRC visit*			
Year 0 (n=827 remaining)	135 (16%)		
Year 1 (n=692 remaining)	110 (16%)		
Year 2 (n=573 remaining)	105 (18%)		
Year 3 (n=422 remaining)	64 (15%)		
After Year 3 (n=314 remaining)	128 (41%)		
Length of follow-up, years		3.0 (1.6, 5.3)	4.0 ± 3.5
Years to index hospitalization		2.2 (1.0, 3.9)	2.7 ± 2.1
Hospitalization Cohort: N = 542			
Length of stay, index hospitalization, days		5 (3, 7)	5.8 ± 4.9
Total number of hospitalizations, per person		2 (1, 4)	3.2 ± 2.8
Number of hospitalizations, per-person year		0.6 (0.3, 1.0)	0.8 ± 0.8
Number of hospital days, per-person year		3 (1.7, 6.4)	5.5 ± 7.5

SD=standard deviation; q1=the first quartile (25^{th} percentile); q3=the third quartile (75^{th} percentile)

*The number of available patients declines each year after the initial, because of cohort losses (e.g. death, drop out of MADRC, etc)

Table 3

Reasons for Hospitalization in the Alzheimer's Disease Cohort (N=542)

Principal Admitting Diagnoses	n	%
Syncope, Fall, Trauma	141	26%
Ischemic Heart Disease	93	17%
Gastrointestinal Disease	48	9%
Pneumonia	34	6%
Delirium, Mental Status Change	25	5%
Cerebrovascular Disease	23	4%
Musculoskeletal Disorder	21	4%
Urinary Tract Infection	15	3%
Fever, Other Infections	14	2%
Chronic Lung disease	10	2%
Congestive Heart Failure	10	2%
Cancer	10	2%
Neurological Disease	10	2%
Dehydration	8	1%
Acute or Chronic Renal Failure	4	1%
Psychiatric Disorder	4	1%
Diabetes Mellitus	2	1%
Peripheral Vascular Disease	2	1%
Other	70	13%

Table 4

Variables Considered as Risk Factors for Hospitalization (N = 827)

Variables *	Hospitalization in the Presence of Factor	Hospitalization in the Absence of Factor	Unadjusted Hazards Ratio, 95% CI	Adjusted Hazards Ratio, 95% CI
	n/N (%)			
Demographics				
Age, ≥ 75 years	340/478 (71)	202/349 (58)	1.60 (1.34 – 1.91)‡	1.51 (1.26 – 1.81)‡
Male	244/347 (70)	298/480 (62)	1.41 (1.19 – 1.67)‡	1.27 (1.04 – 1.54)‡
Non-White	31/49 (63)	511/778 (66)	0.81 (0.57 – 1.17)	0.84 (0.58 – 1.22)
Education < 12 years	78/106 (74)	454/708 (64)	1.22 (0.96 – 1.55)	1.18 (0.92 – 1.52)
Unmarried	182/284 (64)	360/543 (66)	0.90 (0.76 – 1.08)	0.92 (0.75 – 1.13)
Dementia-related				
Family history of dementia	42/60 (70)	500/766 (65)	0.98 (0.72 – 1.34)	1.15 (0.83 – 1.58)
Blessed IMC score20≥ 15 points	111/171 (65)	431/656 (66)	0.98 (0.80 – 1.21)	0.99 (0.79 – 1.24)
Dementia Severity Rating ≥ 2 points	381/579 (66)	151/236 (64)	1.11 (0.92 – 1.34)	1.20 (0.98 – 1.47)
Duration of symptoms ≤ 1.5 years	130/191 (68)	404/625 (65)	1.26 (1.03 – 1.53)‡	1.26 (1.02 – 1.56)‡
Rapid speed of initial onset	29/48 (60)	502/766 (66)	1.05 (0.72 – 1.53)	0.83 (0.56 – 1.22)
Course, fluctuating or stepwise	15/28 (54)	514/784 (66)	0.78 (0.47 – 1.29)	0.92 (0.55 – 1.54)
Illness-related				
Deyo-Charlson score ≥ 1†	303/381 (80)	239/446 (54)	1.99 (1.68 – 2.36)‡	1.87 (1.57 – 2.23)‡
Previous acute hospitalization	198/269 (74)	318/501 (64)	1.92 (1.60 – 2.30)‡	1.65 (1.37 – 1.99)‡

CI=Confidence Interval; IMC=Information-Memory-Concentration

*Missing data were present as follows: education (n=13); family history of dementia (n=1); Dementia Severity Rating (n=12); duration of symptoms (n=11); speed of initial onset (n=13); course (n=15); Deyo-Charlson (n=48); previous acute hospitalization (n=57). Multiple imputation methods used for missing values in multivariable Cox model (see text for details).

†Equipercentile equating used for imputation of missing values in 48 subjects. See text for details.

‡P<0.05. C-statistic for the final model (5 significant variables) was 0.66, 95% confidence interval 0.63–0.68.

Table 5

Risk Gradient by Number of Risk Factors at Baseline

Number of Risk Factors	Rate of Hospitalization n/N (%)*	Hazard Ratio, 95%CI†
0	31/83 (38%)	Referent
1	117/205 (57%)	1.8 (1.2 – 2.6)
2–3	307/437 (70%)	3.0 (2.0 – 4.3)
4–5	88/103 (85%)	6.1 (4.1 – 9.3)

CI=Confidence interval

* Test for linear trend: x2 = 108.95 p-value <0.001

† Multiple imputation methods used for missing values (see text for details).