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Economic Burden, Mortality, and Institutionalization in Patients Newly Diagnosed with Alzheimer's Disease

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Handling Associate Editor: Helen Wu

Accepted 31 August 2017

Abstract.

Background: Current information is scarce regarding comorbid conditions, treatment, survival, institutionalization, and health care utilization for Alzheimer's disease (AD) patients.

Objectives: Compare all-cause mortality, rate of institutionalization, and economic burden between treated and untreated newly-diagnosed AD patients.

Methods: Patients aged 65–100 years with ≥ 1 primary or ≥ 2 secondary AD diagnoses (ICD-9-CM:331.0) with continuous medical and pharmacy benefits for ≥ 12 months pre-index and ≥ 6 months post-index date (first AD diagnosis date) were identified from Medicare fee-for-service claims 01JAN2011–30JUN2014. Patients with AD treatment claims or AD/AD-related dementia diagnosis during the pre-index period were excluded. Patients were assigned to treated and untreated cohorts based on AD treatment received post-index date. Total 8,995 newly-diagnosed AD patients were identified; 4,037 (44.8%) were assigned to the treated cohort. Time-to-death and institutionalization were assessed using Cox regression. To compare health care costs and utilizations, 1 : 1 propensity score matching (PSM) was used.

Results: Untreated patients were older (83.85 versus 81.44 years; $p < 0.0001$), with more severe comorbidities (mean Charlson comorbidity index: 3.54 versus 3.22; $p < 0.0001$). After covariate adjustment, treated patients were less likely to die (hazard ratio[HR] = 0.69; $p < 0.0001$) and were associated with 20% lower risk of institutionalization (HR = 0.801; $p = 0.0003$). After PSM, treated AD patients were less likely to have hospice visits (3.25% versus 9.45%; $p < 0.0001$), and incurred lower annual all-cause costs (\$25,828 versus \$30,110; $p = 0.0162$).

Conclusion: After controlling for comorbidities, treated AD patients have better survival, lower institutionalization, and sometimes fewer resource utilizations, suggesting that treatment and improved care management could be beneficial for newly-diagnosed AD patients from economic and clinical perspectives.

Keywords: Alzheimer's disease, institutionalization, Medicare, mortality

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INTRODUCTION

Alzheimer's disease (AD) is characterized by a gradual decline in memory and cognitive skills that limit a patient's ability to perform daily activities [1, 2]. An estimated 5.4 million US patients are currently diagnosed with AD, with about 5 million patients over age 65 [2, 3]. Age, genetics, physical inactivity, unhealthy diet, and some cardiovascular diseases have been reported as significant risk factors of AD [1]. With the aging US population, AD prevalence is expected to increase to approximately 13 million by 2050 [2]. Currently, no cure for AD exists. Existing treatments focus on relieving symptoms and slowing symptom progression, maintaining cognitive and daily function, and managing behavioral symptoms [4]. So far, four medications (donepezil, rivastigmine, galantamine, and memantine) have been approved for AD management [2].

AD is also known to be one of the main causes of disability and institutionalization among the elderly population leading to significant economic burden [5, 6]. The 2016 direct costs for all individuals diagnosed with AD were estimated at \$221 billion, including \$150 billion to Medicare and Medicaid [1]. Other studies examining the economic burden of AD have only assessed prevalent cases and have not compared the current economic burden among treated and untreated AD patients [7, 8]. Due to a scarcity of information on specific AD-related outcomes, this study evaluated all-cause mortality, rate of institutionalization, and economic burden of treated versus untreated patients newly diagnosed with AD in the United States.

METHODS

Data source

A retrospective analysis was performed using a 5% random national sample of the Medicare administrative database and Minimum Data Set (MDS) from January 2010 through December 2014. The MDS data was linked to Medicare data to assess the overall health care utilization of AD patients. MDS data includes severity proxy measurements, such as the Cognitive Performance Scale (CPS), and the Activities of Daily Living (ADL) Dependency Scale, captured for patients with available MDS data.

Patient identification

Primary analysis population

Patients aged 65–100 years and with at least 1 primary or at least 2 secondary diagnoses for AD (International Classification of Disease 9th Edition Clinical Modification [ICD-9-CM] code: 331.0) during the identification period from January 2011 to June 2014 were included in the primary analysis cohort (Fig. 1). The first AD diagnosis date observed during the identification period was designated as the index date. Patients were also required to have continuous health plan enrollment with medical and pharmacy benefits for at least 12 months pre-index date (baseline period) and at least 6 months post-index date (follow-up period). Patient data were assessed until the earliest of death, health plan disenrollment, or the end of the study period.

Patients with diagnosis claims for AD, AD-related dementia (ICD-9-CM: 290.xx, 294.xx, 331.1, 331.2, 331.7, 331.82, 331.89, 331.9, 797), or pharmacy claims for an AD treatment (donepezil, rivastigmine, galantamine, and memantine) during the baseline period were excluded.

Patients were assigned to treated and untreated cohorts based on AD treatment prescriptions within 6 months of index AD diagnosis during the follow-up period.

Economic analysis population

Time-to-treatment analysis indicated that 10% of the primary analysis population did not receive their first AD treatment until 1 year or longer after their diagnosis. Therefore, a subset of patients from the primary analysis population was selected to analyze economic outcomes, excluding the 10% who received their first AD treatment 1 year or more after AD diagnosis. This subset of patients was required to 1) have continuous health plan enrollment with medical and pharmacy benefits for at least 12 months pre-index date and at least 12 months post-index date; and 2) have received their first AD treatment within 6 months of their index AD diagnosis.

Study variables

Outcomes variables for primary analysis population

Overall survival and rate of institutionalization were the main end points of the primary analysis. Overall survival was defined as patients who did not die during the study period. Using the MDS data,

patients who resided in a post-acute skilled nursing home (SNF) or nursing home for at least 120 consecutive days were considered institutionalized [9]. Mortality and institutionalization rates during the overall follow-up period were captured and estimated in 100 person-years.

Outcomes variables for economic analysis

All-cause and AD-related dementia health care resource use and costs were the main outcomes for economic analysis. Claims were attributed to AD-related dementia if they were associated with a primary or non-primary diagnosis of AD or AD-related dementia.

Baseline variables

Baseline socio-demographic characteristics included age, race, sex, and US geographical region. Clinical characteristics included Charlson Comorbidity Index (CCI) score [10] and individual comorbid conditions during the 12 months prior to the index date.

All-cause health care utilization and costs as well as a number of diagnostic tests (magnetic resonance imaging [MRI], positron emission tomography [PET], and computed tomography [CT] scans) were evaluated for the 12-month baseline period.

The CPS and ADL Dependency Scale were available for patients with linked MDS data. The CPS has five components that address cognitive and communication domains (memory, decision making, and making self-understood), presence of coma, and eating dependency [11]. CPS scores range from 0 (intact) to 6 (very severe impairment). The ADL-Short Form (SF) includes four items (eating, personal hygiene, toileting, and locomotion) [12]. The ADL-SF sums the individual ADL items (rating of 0 to 4) into a scale running from 0 to 16.

Statistical analysis

All study variables, including baseline and outcome measures, were examined descriptively. Numbers and percentages were provided for dichotomous and polychotomous variables. Means and standard deviations were provided for continuous variables. For dichotomous and polychotomous variables, *p*-values were calculated according to the chi-square test, and for continuous variables, *t*-tests were used to calculate *p*-values.

In the primary analysis, a multivariable Cox proportional hazard model with time dependent and

independent covariates was applied to estimate hazard ratio (HR) and 95% confidence interval (CI) of overall survival and rate of institutionalization between treated and untreated AD patients. Time independent covariates included patients' socio-demographic and clinical characteristics. AD treatment was included in the Cox model as a time-dependent covariate.

In the economic analysis, possible confounders of health care utilization and costs were controlled using 1 : 1 propensity score matching (PSM) between patients who received treatment within 6 months of AD diagnosis and untreated AD patients.

RESULTS

Primary analysis

Patient characteristics

A total of 59,921 Medicare beneficiaries aged between 65–100 years had an index diagnosis of AD between January 2011 and June 2014. From this sample, 50,926 patients were excluded because they had an AD or AD-related dementia diagnosis or were prescribed AD treatment during the baseline period. A total of 8,995 treatment naïve and newly-diagnosed AD patients were selected for the primary analysis of mortality and institutionalization (treated: *n* = 4,037; untreated: *n* = 4,958; Fig. 1).

Approximately 44.8% of patients initiated treatment (average 122 days post-AD diagnosis); mean follow-up days for treated and untreated patients was 681 versus 794 days, *p* < 0.0001. Treated patients were prescribed donepezil (68.8%), memantine (18.0%), rivastigmine (12.1%), and galantamine (1.2%) as their first treatment. Of newly-diagnosed AD patients, 74% were diagnosed in a physician's office or outpatient hospital, and 18.2% were diagnosed in an inpatient setting.

The untreated cohort included older patients (84.1 versus 81.6 years, *p* < 0.0001), with a greater proportion of Caucasian (81.4% versus 80.4%, *p* = 0.2384) and female patients (75.7% versus 72.5%, *p* = 0.0007) compared to the treated cohort (Supplementary Table 1). Supplementary Table 2 shows the baseline clinical characteristics of newly-diagnosed AD patients. At baseline, comorbid conditions such as congestive heart failure (23.6% versus 14.6%, *p* < 0.0001), peripheral vascular disease (16.9% versus 13.1%, *p* < 0.0001) and pneumonia (9.9% versus 6.0%, *p* < 0.0001) were generally more prevalent

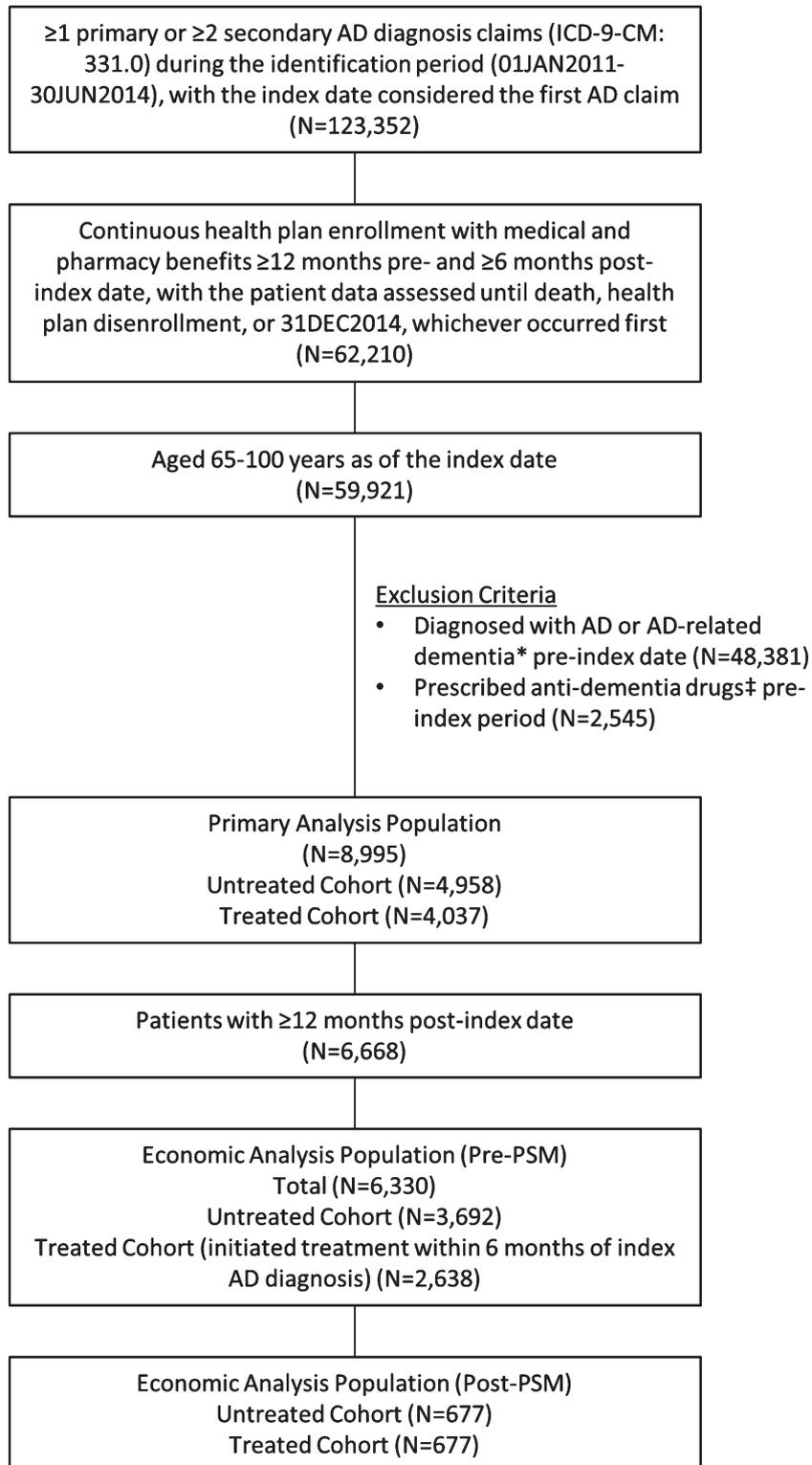


Fig. 1. Patient selection flow chart. AD, Alzheimer's disease; PSM, propensity score matching. *ICD-9-CM diagnosis claim for AD: 331.0; ICD-9-CM diagnosis claim for AD-related dementia: 290.xx, 294.xx, 331.1, 331.2, 331.7, 331.82, 331.89, 331.9, 797. ‡ donepezil, rivastigmine, galantamine, or memantine.

Table 1
Cox model for time-to-death and time-to-institutionalization among newly-diagnosed AD patients (primary analysis population)

Covariates	Time-to-Death			Time-to-Institutionalization		
	HR	(95% CI)	<i>p</i> -value	HR	(95% CI)	<i>p</i> -value
Index Treatment (Time-Dependent covariate)						
Untreated (Reference)						
Treated	0.69	(0.63, 0.75)	<0.0001	0.801	(0.71, 0.903)	0.0003
Time invariant covariate						
Age Group						
65–74 (Reference)						
75–84	1.76	(1.51, 2.06)	<0.0001	1.154	(0.972, 1.37)	0.102
85–94	3.14	(2.71, 3.65)	<0.0001	1.829	(1.549, 2.159)	<0.0001
95–100	5.04	(4.20, 6.06)	<0.0001	1.983	(1.558, 2.525)	<0.0001
Race						
White (Reference)						
Black	0.78	(0.68, 0.90)	0.0005	1.021	(0.861, 1.21)	0.815
Hispanic	0.69	(0.56, 0.85)	0.0004	0.571	(0.417, 0.781)	0.0005
Other (Asian/Native American)	0.66	(0.53, 0.83)	0.0003	0.999	(0.767, 1.302)	0.9961
Gender						
Male (Reference)						
Female	0.85	(0.77, 0.93)	0.0003	1.122	(0.989, 1.272)	0.0748
US Geographic Region						
Northeast (Reference)						
North Central	1.15	(1.02, 1.30)	0.0257	1.031	(0.886, 1.201)	0.692
South	1.15	(1.03, 1.28)	0.0134	0.902	(0.786, 1.034)	0.1392
West or Other	1.14	(1.00, 1.30)	0.0431	0.595	(0.495, 0.715)	<0.0001
Baseline Comorbid Conditions						
CCI Score	1.05	(1.03, 1.06)	<0.0001	1.018	(0.999, 1.038)	0.0701
Individual Comorbidities						
Parkinson's Disease	1.01	(0.84, 1.22)	0.8964	0.956	(0.743, 1.229)	0.7238
Epilepsy	1.08	(0.89, 1.30)	0.4323	1.097	(0.852, 1.413)	0.4732
Mood Disorder	0.84	(0.76, 0.93)	0.0006	1.264	(1.115, 1.434)	0.0003
Pneumonia	1.32	(1.16, 1.50)	<0.0001	1.1	(0.908, 1.334)	0.3305
Mild Cognitive Impairment	0.64	(0.48, 0.86)	0.0029	0.581	(0.404, 0.834)	0.0033

Cox model with time-dependent covariates was performed among Untreated $n=4,958$ and Treated $n=4,037$ cohorts. HR, hazard ratio; CI, confidence interval; CCI, Charlson Comorbidity Index.

in the untreated cohort. In addition, the untreated cohort had higher mean CCI scores (3.54 versus 3.22, $p<0.0001$) and lower utilization of baseline tests including computed tomography (CT) scan (19.1% versus 22.6%, $p<0.0001$) and magnetic resonance imaging (MRI) (6.0% versus 12%, $p<0.0001$) compared to the treated cohort.

Approximately 1,915 AD patients resided in a SNF facility or nursing home during the baseline period. Untreated patients had higher baseline ADL scores of 8.8 versus 7.4 ($p<0.0001$) and CPS scores of 3.2 versus 2.0 ($p<0.0001$) indicating more significant impairment of daily function and cognition in comparison to treated patients. A lower proportion of patients in the untreated cohort had a diagnostic test such as a CT scan or MRI during the baseline period.

Outcome: Mortality

Untreated patients had a higher unadjusted incidence rate of death (18.9 versus 9.9 per 100

person-years, $p<0.0001$). After covariate adjustment using Cox regression, patients were less likely to die if they had ever received an AD treatment (adjusted HR = 0.69, $p<0.0001$, Table 1).

Outcome: Institutionalization

A larger proportion of untreated patients were institutionalized at the time of diagnosis (10.5% versus 4.3%, $p<0.0001$). After their index AD diagnosis, the untreated cohort had, on average, a shorter time-to-institutionalization period (188.5 versus 283.1 days, $p<0.0001$), and a higher rate of institutionalization compared to the treated cohort (11.0 versus 9.5 per 100 person-years, $p=0.0044$). After adjusting for baseline differences using Cox regression, patients who received AD treatment at any point were associated with a 20% lower risk of being institutionalized (adjusted HR = 0.80, $p=0.0003$, Table 1). Older age and prior mood disorder diagnosis were risk factors associated with institutionalization.

Economic analysis

Patient characteristics

A total of 6,668 patients were further selected from the primary analysis population if they had at least 12 months of follow-up. For the treatment cohort, the first AD treatment claim was required to have occurred within 6 months of the index AD diagnosis. A total of 6,330 patients were included in the final economic analysis population (treated cohort: $n=2,638$; untreated cohort: $n=3,692$; Fig. 1).

For patients in the treated cohort ($n=2,638$), the average number of days to initiate the first AD treatment was 33 days (median: 10 days). Treated patients were prescribed donepezil (70.9%), memantine (15.9%), rivastigmine (11.9%), and galantamine (1.3%) as their first treatment.

Untreated patients were older (83.6 versus 81.1 years, $p<0.0001$) and had a higher proportion of women (75.8% versus 72.6%, $p=0.0049$) than treated patients. Patients in the untreated cohort also had a higher prevalence of key individual comorbidities as well as higher CCI scores (3.5 versus 3.1, $p<0.0001$) compared to the treated cohort. The results were similar to those observed within the primary analysis population (Supplementary Tables 3 and 4).

During the 12-month baseline period, the untreated cohort had higher utilization for inpatient (25.0% versus 18.4%, $p<0.0001$), post-acute SNF (14.1% versus 6.8%, $p<0.0001$), home health agency ([HHA]; 19.3% versus 16.3%, $p=0.0022$), and hospice visits (3.1% versus 0.5%, $p<0.0001$), but lower utilization for outpatient office (86.1% versus 92.7%, $p<0.0001$) and outpatient hospital visits (66.6% versus 73.3%, $p<0.0001$), compared to the treated cohort. The same trend was observed for health care costs.

Economic outcomes

A 1:1 PSM was used to adjust for baseline demographic and clinical characteristics between the treated and the untreated patients. A total of 677 patients were matched from each cohort with well-balanced baseline characteristics.

Monthly trends in total Medicare expenditures spiked at the time of AD diagnosis (Fig. 2). The cost differences between treated and untreated patients were determined for the months leading up to the diagnosis and continued to increase throughout the span of the disease, especially in the first few months immediately after the diagnosis. In fact, during the

month of diagnosis, untreated and treated AD patients incurred significantly elevated health care costs, more so in the untreated cohort, although not statistically significant (mean \$7,306 versus \$6,308; $p=0.1059$). Inpatient and post-acute SNF care were the main cost drivers of the Medicare expenditures incurred around the time of diagnosis. Inpatient spending increased significantly from the month leading up to diagnosis to the month of AD diagnosis (untreated: from \$334 to \$3,039; treated: from \$86 to \$2,599; both $p<0.0001$); spending also increased for post-acute SNF expenditure (untreated: \$197 to \$1,774; treated: \$93 to \$1,774; all $p<0.0001$).

The average annual total Medicare expenditures (Fig. 3) were significantly higher among untreated patients (\$30,110 versus \$25,828; $p=0.0162$), driven mostly by hospice care (cost difference=\$2,658; $p<0.0001$). Inpatient and post-acute SNF costs were important cost drivers; however, the cost differences in inpatient (\$658; $p=0.4252$), and post-acute SNF (\$1,124; $p=0.161$) were not statistically significant between untreated and treated patients. AD-related health care costs accounted for 43% (untreated) and 48% (treated) of the total Medicare expenditures. Treated patients compared to untreated patients had significantly higher AD-related office costs (\$457 versus \$274; $p<0.0001$). However, AD-related hospice care and associated costs (\$2,452 versus \$322; $p<0.0001$) were significantly higher in the untreated cohort.

A similar trend was observed in terms of health care utilizations. Compared to treated patients, untreated patients had significantly more hospice visits (0.76 versus 0.17; $p<0.0001$). On the other hand, there were more outpatient office (14.88 versus 13.19; $p=0.0148$) and pharmacy (31.79 versus 29.44; $p=0.0493$) visits in treated patients compared to untreated patients (Supplementary Table 5). AD-related health care utilizations (Supplementary Table 5) were substantially higher in treated patients compared to untreated patients; except for hospice care visits (0.57 versus 0.10; $p<0.0001$) which were higher in the untreated cohort.

DISCUSSION

This retrospective analysis was conducted to evaluate overall survival, rate of institutionalization, and economic burden of treated versus untreated patients newly diagnosed with AD. After controlling for patient characteristics including comorbidities, we

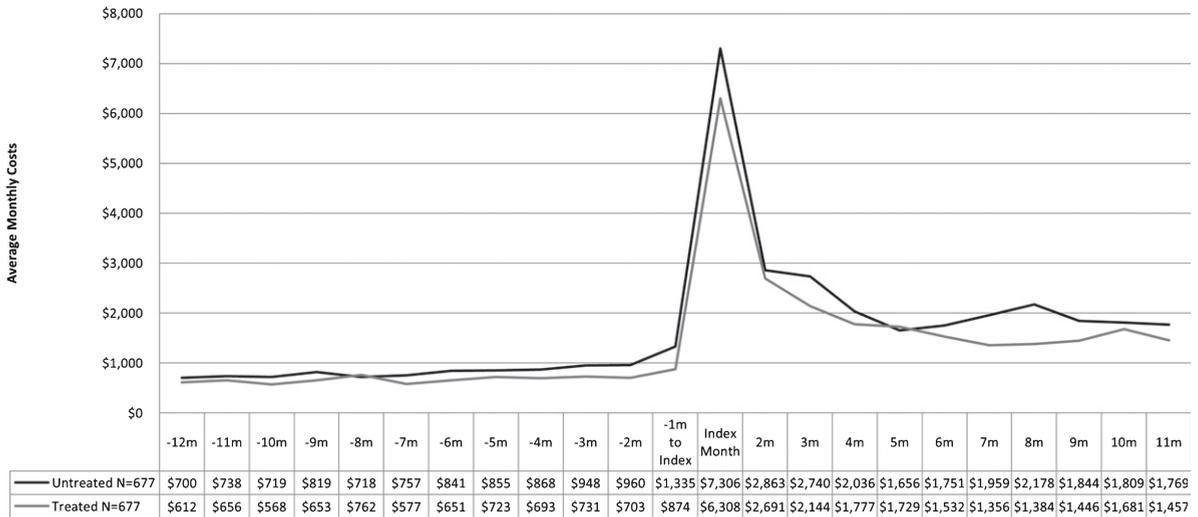


Fig. 2. PSM-adjusted all-cause average monthly cost among newly-diagnosed AD patients (economic analysis population). PSM, propensity score matching model adjusting for age, race, gender, geographic region, Charlson Comorbidity Index score, baseline all-cause health care utilization, baseline diagnostic tests (CT and MRI), and prevalence of individual comorbidities including Parkinson’s disease, epilepsy, mood disorder, pneumonia, and mild cognitive impairment.

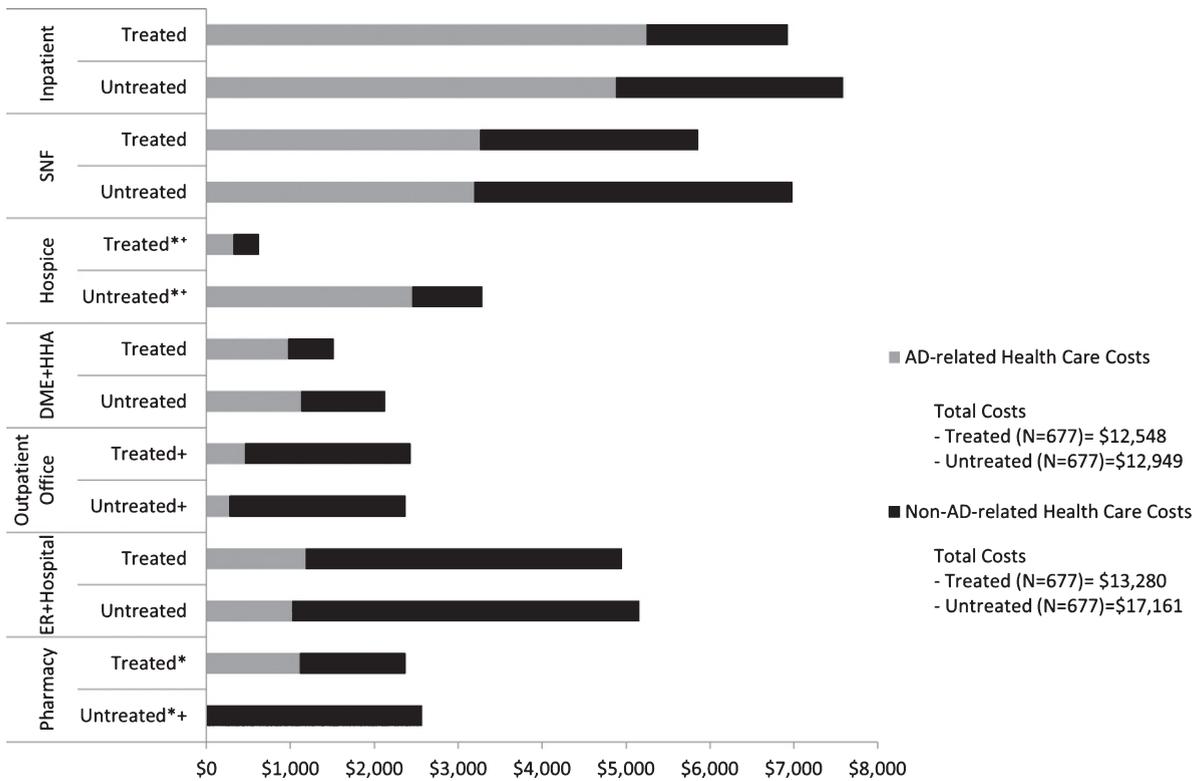


Fig. 3. Post-index PSM-adjusted annual all-cause and AD-related health care costs among newly-diagnosed AD patients (economic analysis population). AD, Alzheimer’s disease; DME, durable medical equipment; ER, emergency room; HHA, home health agency; PSM, propensity score matching model adjusting for age, race, gender, geographic region, Charlson Comorbidity Index score, baseline all-cause health care utilization, baseline diagnostic tests (CT and MRI), and prevalence of individual comorbidities including Parkinson’s disease, epilepsy, mood disorder, pneumonia, and mild cognitive impairment. * $p < 0.05$ treated versus untreated for all-cause health care costs; + $p < 0.05$ treated versus untreated for AD-related cause health care costs.

observed that newly-diagnosed AD patients who received treatment had a lower risk of dying and being institutionalized compared to untreated counterparts. In addition, they incurred lower overall expenditures of approximately \$4,282 in total Medicare spending for the 12 months post-AD diagnosis compared to untreated patients. However, total AD-related costs were only slightly lower for the treated cohort, and the difference was not statistically significant. In addition, a large portion of the AD-related costs incurred by the untreated AD patients was due to their AD-related hospice care. Previous studies showed that chronically ill patients with the ability and willingness to manage their health and care are more likely to adhere to or initiate treatment and, as a result, incur lower health care costs [13, 14]. It is difficult to infer that the improved survival and lower institutionalization rates were solely due to AD treatment administration. However, the observed benefit from the study findings suggests that receiving AD treatment could be considered as a proxy for better quality of care, access to care, and improved health because patients who received AD therapy also most likely received consistent medical attention for other severe comorbidities. In general, AD patients get sicker faster due to their condition, and the cost of treating multiple complicated comorbidities results in overall higher spending [15, 16].

Early detection of dementia is beneficial to provide timely care and offer direct benefits to patients with dementia [17]. However, our study showed that close to 11% of untreated patients and approximately 4.3% of treated patients were institutionalized at time of the AD diagnosis. In addition, 67.8% of untreated AD patients were diagnosed in ambulatory settings compared to 81.2% of treated AD patients. This finding is consistent with previous reports [18], implying that many patients may receive their first AD diagnosis when they meet a health care professional as a result of another more serious health event. Furthermore, untreated patients had lower numbers of physician office and pharmacy visits, indicating a possible failure of ambulatory care management, which echoed prior study findings [19, 20].

The current study found that Medicare total costs in newly-diagnosed AD patients peaked significantly during the month of diagnosis, and AD-related costs accounted for 43–48% of the total Medicare expenditures. This finding is similar to those of other studies that examined the diagnostic pathways to AD10 and Medicare expenditures for patients with AD and AD-related dementia or MCI [21]. The

major cost components of Medicare expenditures were found to be the use of inpatient and post-acute SNF services post-AD diagnosis in our analysis. Studies on hospital data have suggested that early and timely detection of AD can be cost-saving [6, 10, 22].

There were several limitations in this study. By using retrospective claims data to identify newly-diagnosed AD patients, these patients may represent individuals across the spectrum of AD severity and may not reflect results for patients with new onset of AD. In addition, measures such as AD duration, disease severity and progression, cause of death, patient health behaviors, and caregiver information were not available in the Medicare data. Furthermore, non-pharmacological treatment information including computer cognitive training, diet, and regular moderate exercise were unavailable in the claims. Therefore, these estimates were not measured in our analysis. The lack of disease severity data can lead to potential underestimation of the severity of the disease of interest. However, we controlled for the differences between the treated and untreated cohorts using PSM, which created similar cohorts with well-balanced baseline demographic and clinical characteristics.

Services reimbursed by Medicaid, such as custodial care for patients who resided in a nursing facility for more than 100 days, are not reflected in this analysis. Moreover, this study included fee-for-service patients who had continuous enrollment in Medicare Parts A and B, which may limit the generalizability of the study results since patients enrolled in Medicare Part C were not included.

A strict and robust inclusion criterion was applied to capture newly-diagnosed AD patients by excluding patients who had an AD or dementia-related diagnosis as well as patients who were prescribed AD medications prior to the first index AD diagnosis. Although many patients receive AD treatment without a diagnosis, this analysis assessed newly-diagnosed AD patients. Prior AD or AD-related diagnosis was the cause for most patient exclusions (80%). The exclusion criterion was applied in order to omit patients whose AD diagnosis may have manifested from other comorbid diagnoses.

Since Medicare is the primary payer for elderly patients in the United States, the results from our analysis are expected to reflect the health care resource utilization and cost patterns of the elderly patient population with newly-diagnosed AD.

Conclusion

For patients who were newly diagnosed with AD, initiation of treatment as close to diagnosis as possible may translate to improved survival, lower institutionalization rates, fewer resource utilizations, and lower health care expenditures. Patients with newly diagnosed AD experience elevated health care costs, mostly driven by hospital and post-acute skilled nursing home visits during the period following diagnosis. This analysis suggests that early diagnosis, better treatment and care management, especially in an ambulatory setting, could be beneficial for AD patients, caregivers, and the health care system from both economic and clinical perspectives.

ACKNOWLEDGMENTS

This study was funded by Merck & Co., Inc. Christopher M. Black, Rezaul K. Khandker and Baishali M. Ambegaonkar are employees of Merck & Co., Inc., and Xiaohan Hu was an employee of Merck & Co., Inc. at the time of the analysis. Lin Xie, M. Furaha Kariburyo, and Onur Baser are employees of STATinMED Research, which is a paid consultant to Merck & Co., Inc. Howard Fillit, was a consultant for Merck & Co., Inc.

Authors' disclosures available online (<http://j-alz.com/manuscript-disclosures/17-0518r1>).

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: <http://dx.doi.org/10.3233/JAD-170518>.

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