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Predictors of Mortality in Older Adults With Epilepsy

Implications for Learning Health Systems

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Abstract

Objective

To determine the incidence of epilepsy and subsequent 5-year mortality among older adults, as well as characteristics associated with mortality.

Methods

This was a retrospective cohort study of Medicare beneficiaries age 65 or above with at least 2 years enrollment before January 2009. Incident epilepsy cases were identified in 2009 using ICD-9-CM code-based algorithms; death was assessed through 2014. Cox regression models examined the association between 5-year mortality and incident epilepsy, and whether mortality differed by sociodemographic characteristics or comorbid disorders.

Results

Among the 99,990 of 33,615,037 beneficiaries who developed epilepsy, most were White (79.7%), female (57.3%), urban (80.5%), and without Medicaid (71.3%). The 5-year mortality rate for incident epilepsy was 62.8% (62,838 deaths). In multivariable models, lower mortality was associated with female sex (adjusted hazards ratio [AHR] 0.85, 95% confidence interval [CI] 0.84–0.87), Asian race (AHR 0.82, 95% CI 0.76–0.88), and Hispanic ethnicity (AHR 0.81, 95% CI 0.76–0.84). Hazard of death increased with comorbid disease burden (per 1-point increase: AHR 1.27, 95% CI 1.26–1.27) and Medicaid coinsurance (AHR 1.17, 95% CI 1.14–1.19). Incident epilepsy was particularly associated with higher mortality when diagnosed after another neurologic condition: Parkinson disease (AHR 1.29, 95% CI 1.21–1.38), multiple sclerosis (AHR 2.13, 95% CI 1.79–2.59), dementia (AHR 1.33, 95% CI 1.31–1.36), traumatic brain injury (AHR 1.55, 95% CI 1.45–1.66), and stroke/TIA (AHR 1.20, 95% CI 1.18–1.21).

Conclusions

Newly diagnosed epilepsy is associated with high 5-year mortality among Medicare beneficiaries. Future studies that parse the interplay of effects from underlying disease, race, sex, and poverty on mortality will be critical in the design of learning health care systems to reduce premature deaths.

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Glossary

AHR = adjusted hazards ratio; **CCI** = Charlson Comorbidity Index; **CI** = confidence interval; **CMS** = Centers for Medicare & Medicaid Services; **HR** = hazard ratio; **ICD-9-CM** = International Classification of Diseases, Ninth Revision, Clinical Modification; **MBSF** = Master Beneficiary Summary File; **RIF** = research identifiable file; **RUCC** = Rural Urban Continuum Code.

In adults, the risk of new-onset epilepsy is greatest in patients over 70, due to multiple predisposing pathologic mechanisms, including age-related vascular, degenerative, and metabolic disorders.[1,2] The older adult population is growing rapidly, and unlike all other age groups, epilepsy incidence in this group may be increasing.[3,4] Consequently, the burden of epilepsy is likely to substantially increase in the coming years, and large-scale characterizations of epilepsy in older adults, including its association with mortality, are needed.

Many chronic diseases are known to have significant racial disparities in mortality.[5–7] Such sociodemographic-based differences have been proposed for epilepsy-associated mortality in younger patients, but little is known about their existence among older adults.[8,9] Identifying high-risk populations is essential to guide clinical decisions, because epilepsy outcomes, including mortality, are known to be improved through differential treatment choices.[10–15]

As such, epilepsy could be responsive to a learning health care system research framework, in which routinely collected health care data are used to inform comparative effectiveness research, track outcomes, and evaluate treatment-related adverse events. Quantification of excess mortality and associated characteristics in older patients with new-onset epilepsy would be important initial steps for the development of such programs, particularly among individuals with neurologic comorbidities as their care requires common resources. Thus, we examined 5-year mortality after epilepsy diagnosis in adults age 65 and above and its association with sociodemographic characteristics and neurologic comorbidities. To provide additional perspective, our secondary objective was to demonstrate the difference in mortality associated with new epilepsy.

Methods

Data

Medicare is the insurer for approximately 96% of the US population over age 65,[16] and includes information regarding patient demographics, medications, measures of comorbidity, diagnoses, procedures, and geographic area. This study used data from multiple Medicare research identifiable files (RIFs) provided by the Centers for Medicare & Medicaid Services (CMS). These RIFs contain individual-level data that can be linked over time using a unique beneficiary identification code. We used the Master Beneficiary Summary File (MBSF) base segment files to obtain Medicare enrollment and eligibility, and determine baseline race, age, sex, postal code, Medicaid use, and date of death. The MBSF Chronic Conditions segment and Other Conditions segment both contain indicator variables for common chronic medical conditions, which are obtained using validated algorithms. These MBSF condition segments were used together with the Carrier file and Chronic Condition Warehouse, which contain diagnoses documented using ICD-9-CM to identify chronic conditions of interest in this study and identify each as prevalent in 2009 (as described below).

Study Design and Sample

We performed a retrospective cohort study of Medicare beneficiaries age 65 or above with enrollment for at least 2 years prior to January 2009. A 2-year lookback period allowed us to assess for Medicare eligibility (to assure completeness of data) and to identify and remove individuals with preexisting epilepsy.

Incident epilepsy cases were identified in a manner consistent with prior epilepsy incidence studies.[17,18] Epilepsy diagnosis was determined by query of the 2009 MBSF, which contains indicator and initial diagnosis date variables for 66 chronic health conditions. The MBSF epilepsy indicator variable was based on the presence of at least 1 inpatient or 2 outpatient claims with a diagnosis code of 345.x, according to the ICD-9-CM. Previous studies support the use of this algorithm.[19,20] The resulting incident epilepsy cohort formed the study sample for our primary analyses. Medicare beneficiaries meeting eligibility criteria without an incident or preexisting epilepsy diagnosis formed the comparison group for our secondary analyses.

Patient Characteristics

We extracted data on patient characteristics including age, sex, race, and dual Medicaid enrollment. Age in 2009 was extracted as a continuous variable, and also categorized as 65–69 years, 70–74 years, 75–79 years, 80–84 years, 85–89 years, or 90 + years. Race and ethnicity have only recently begun to be coded separately in Medicare data, therefore available demographic categorizations for our study were White, Black, Asian, Hispanic, Native North American, and other/unknown. Medicaid enrollment was used as a proxy for low income, as this is the most common way to qualify for Medicaid enrollment after meeting age criteria. Individual county of residence was merged with the US Department of Agriculture 2013 Rural Urban Continuum Code (RUCC) dataset. The RUCC is produced every 10 years, and using population density and proximity to metropolitan areas, assigns each US county to 1 of 9 categories, ranging from completely rural to completely urban. Older adults are generally at increased risk of death due to more than one chronic

Table 1 Conditions Used to Create Modified Charlson Comorbidity Index (CCI), Consisting of All CCI conditions Available in the Chronic Condition Warehouse and the Chronic Health Conditions File

	Reference period, number or type of claims to qualify	Codes used
Acute myocardial infarction	1 y, at least 1 inpatient claim with code	410.01, 410.11, 410.21, 410.31, 410.41, 410.51, 410.61, 410.71, 410.81, 410.91 (only first or second diagnosis on the claim)
Alzheimer disease	3 y, at least 1 inpatient, SNF, HHA, or HOP; or carrier claim with diagnosis code	331.0
Alzheimer disease, related disorders, or senile dementia	3 y, at least 1 inpatient, SNF, HHA, or HOP; or carrier claim with diagnosis codes	331.0, 331.11, 331.19, 331.2, 331.7, 290.0, 290.10, 290.11, 290.12, 290.13, 290.20, 290.21, 290.3, 290.40, 290.41, 290.42, 290.43, 294.0, 294.10, 294.11, 294.20, 294.21, 294.8, 797
Cancer, colorectal	1 y, at least 1 inpatient, SNF, or 2 HOP; or carrier claims with diagnosis codes	153.0, 153.1, 153.2, 153.3, 153.4, 153.5, 153.6, 153.7, 153.8, 153.9,154.0,154.1, 230.3, 230.4, V10.05, V10.06
Cancer, endometrial	1 y, at least 1 inpatient, SNF, or 2 HOP; or carrier claims with diagnosis codes	182.0, 233.2, V10.42
Cancer, breast	1 y, at least 1 inpatient, SNF, or 2 HOP; or carrier claims with diagnosis codes	174.0, 174.1, 174.2, 174.3, 174.4, 174.5, 174.6, 174.8, 174.9, 175.0, 175.9, 233.0, V10.3
Cancer, lung	1 y, at least 1 inpatient, SNF, or 2 HOP; or carrier claims with diagnosis codes	162.2, 162.3, 162.4, 162.5, 162.8, 162.9, 231.2, V10.11
Cancer, prostate	1 y, at least 1 inpatient, SNF, or 2 HOP; or carrier claims with diagnosis codes	185, 233.4, V10.46
Chronic kidney disease	2 y, at least 1 inpatient, SNF, or HHA, or 2 HOP; or carrier claims with diagnosis codes	016.00, 016.01, 016.02, 016.03, 016.04, 016.05, 016.06, 095.4, 189.0, 189.9, 223.0, 236.91, 249.40, 249.41, 250.40, 250.41, 250.42, 250.43, 271.4, 274.10, 283.11, 403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 440.1, 442.1, 572.4, 580.0, 580.4, 580.81, 580.89, 580.9, 581.0, 581.1, 581.2, 581.3, 581.81, 581.89, 581.9, 582.0, 582.1, 582.2, 582.4, 582.81, 582.89, 582.9, 583.0, 583.1, 583.2, 583.4, 583.6, 583.7, 583.81, 583.89, 583.9, 584.5, 584.6, 584.7, 584.8, 584.9, 585.1, 585.2, 585.3, 585.4, 585.5, 585.6, 585.9, 586, 587, 588.0, 588.1, 588.81, 588.89, 588.9, 591, 753.12, 753.13, 753.14, 753.15, 753.16, 753.17, 753.19, 753.20, 753.21, 753.22, 753.23, 753.29, 794.4
Chronic obstructive pulmonary disease	1 y, at least 1 inpatient, SNF, HHA, or 2 HOP; or carrier claims with diagnosis codes	490, 491.0, 491.1, 491.8, 491.9, 492.0, 492.8, 491.20, 491.21, 491.22, 494.0, 494.1, 496
Diabetes	2 y, at least 1 inpatient, SNF, HHA, or 2 HOP; or carrier claims with diagnosis codes	249.00, 249.01, 249.10, 249.11, 249.20, 249.21, 249.30, 249.31, 249.40, 249.41, 249.50, 249.51, 249.60, 249.61, 249.70, 249.71, 249.80, 249.81, 249.90, 249.91, 250.00, 250.01, 250.02, 250.03, 250.10, 250.11, 250.12, 250.13, 250.20, 250.21, 250.22, 250.23, 250.30, 250.31, 250.32, 250.33, 250.40, 250.41, 250.42, 250.43, 250.50, 250.51, 250.52, 250.53, 250.60, 250.61, 250.62, 250.63, 250.70, 250.71, 250.72, 250.73, 250.80, 250.81, 250.82, 250.83, 250.90, 250.91, 250.92, 250.93, 357.2, 362.01, 362.02, 362.03, 362.04, 362.05, 362.06, 366.41
Heart failure	2 y, at least 1 inpatient, or HOP; or carrier claim with diagnosis code	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.0, 428.1, 428.20, 428.21, 428.22, 428.23, 428.30, 428.31, 428.32, 428.33, 428.40, 428.41, 428.42, 428.43, 428.9
Stroke/TIA	1 y, at least 1 inpatient, or 2 HOP; or carrier claims with diagnosis codes	430, 431, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.00, 434.01, 434.10, 434.11, 434.90, 434.91, 435.0, 435.1, 435.3, 435.8, 435.9, 436, 997.02 (any diagnosis on the claim); exclusion: if any of the qualifying claims have 800 ≤ diagnosis code ≤ 804.9, 850 ≤ diagnosis code ≤ 854.1 in any diagnosis position, or diagnosis V57xx as the principal diagnosis code, then exclude
HIV or AIDS	2 y, at least 1 inpatient claim; or 2 other nondrug claims of any service type	042, 042.0, 042.1, 042.2, 042.9, 043, 043.1, 043.2, 043.3, 043.9, 044, 044.0, 044.9, 079.53, 795.71, V08 (any diagnosis on the claim); exception: 795.71 requires a second qualifying claim that is not 795.71 (a screening code); Medicare DRG codes (old codes used through 09/2007): 488, 489, 490; MS DRG codes: 969, 970, 974, 975, 976, 977; HCC code: 1 (HIV/AIDS)
TBI and nonpsychotic mental disorders due to brain damage	2 y, at least 1 inpatient; or 2 other nondrug claims of any service type with diagnosis codes	310, 310.0, 310.1, 310.2, 310.8, 310.81, 310.89, 907, 907.0, 907.1

Abbreviations: DRG = diagnosis-related groups; HHA = home health aide; HOP = hospital outpatient; MS = multiple sclerosis; SNF = skilled nursing facility; TBI = traumatic brain industry.

Table 2 Chronic Neurologic Conditions Examined as Discrete Predictors of Mortality

Comorbid condition	Reference period, number or type of claims to qualify	Codes used, from the original chronic condition warehouse and chronic health condition file and carrier files
Multiple sclerosis	2 y, at least 1 inpatient; or 2 other nondrug claims of any service type with diagnosis codes	340, 341, 341.0, 341.2, 341.20, 341.21, 341.22, 341.8, 341.9
Parkinson disease	2 y, at least 2 carrier claims	332.0
Dementia	3 y, at least 1 inpatient, SNF, HHA, or HOP; or carrier claim with diagnosis codes	331.0, 331.11, 331.19, 331.2, 331.7, 290.0, 290.10, 290.11, 290.12, 290.13, 290.20, 290.21, 290.3, 290.40, 290.41, 290.42, 290.43, 294.0, 294.10, 294.11, 294.20, 294.21, 294.8, 797
Alzheimer dementia	3 y, at least 1 inpatient, SNF, HHA, or HOP; or carrier claim with diagnosis code	331.0
Stroke/TIA	1 y, at least 1 inpatient or 2 HOP; or carrier claims with diagnosis codes	430, 431, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.00, 434.01, 434.10, 434.11, 434.90, 434.91, 435.0, 435.1, 435.3, 435.8, 435.9, 436, 997.02 (any diagnosis on the claim); exclusion: if any of the qualifying claims have 800 ≤ diagnosis code ≤ 804.9, 850 ≤ diagnosis code ≤ 854.1 in any diagnosis position; or diagnosis V57xx as the principal diagnosis code, then exclude
TBI and nonpsychotic mental disorders due to brain damage	2 y, at least 1 inpatient; or 2 other nondrug claims of any service type with diagnosis codes	310, 310.0, 310.1, 310.2, 310.8, 310.81, 310.89, 907, 907.0, 907.1

Abbreviations: HHA = home health aide; HOP = hospital outpatient; SNF = skilled nursing facility; TBI = traumatic brain industry.

illness, and the Charlson Comorbidity Index (CCI) is the most widely used index to adjust for competing mortality due to comorbid disease. An age-weighted CCI score was calculated for each beneficiary, using all available indicator variables for chronic health conditions contained in the CCI.[21] Finally, indicator variables for multiple sclerosis, dementia (defined as Alzheimer and other dementia types), Parkinson disease, traumatic brain injury, and stroke/TIA were derived from the Chronic Condition Warehouse and Carrier files. The extraction algorithms for all health conditions used to create the modified CCI and the chronic neurologic conditions examined as discrete predictors of mortality considered in the study are presented in tables 1 and 2, respectively.

Outcomes

The primary outcome was mortality, measured through December 31, 2014. CMS receives death information from a number of sources (including Medicare claims data from the Medicare Common Working File, online date of death edits submitted by family members, benefit information used to administer the Medicare program collected from the Railroad Retirement Board, and the Social Security Administration), and 99% of the death reports are validated.[22]

Five-year mortality was compared between beneficiaries with no epilepsy and those with incident epilepsy, adjusting for sociodemographic characteristics and comorbidities. We also examined whether a prior diagnosis of Parkinson disease, multiple sclerosis, dementia, traumatic brain injury, or stroke/TIA affected mortality among newly diagnosed persons with epilepsy. Among individuals with incident epilepsy, we examined whether mortality varied according to sociodemographic and residential characteristics.

Statistical Analyses

Demographic characteristics were compared using χ^2 tests for categorical variables. To examine patient characteristics associated with mortality, we built multivariable Cox regression models to estimate the risk of death for each characteristic. Time to death was measured in months from the date of epilepsy diagnosis through December 31, 2014. Surviving cases were censored at the end of the observation period. Model variables were initially selected a priori based on clinical knowledge, review of existing literature, and variable availability. Individuals with more than one preexisting neurologic disease indicator were excluded from that analysis. The statistical analyses for our study were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC).

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by the University of Pennsylvania's institutional review board and was subject to a data use agreement as per CMS policy.[22]

Data Availability

US Medicare data are publicly available for purchase through an application process overseen by the Research Data Assistance Center.[22]

Results

Demographics

We identified a total of 33,615,037 people, ages 65 and above, who had been enrolled in Medicare for at least 2 years on January 1, 2009. Of these, 99,990 (0.3%) were diagnosed with

Table 3 Characteristics of Medicare Beneficiaries With Incident Epilepsy in 2009

Characteristic	Frequency in study sample (n = 99,990), n (row %)	Deceased within 5 y, n (%)
Age, y		
65–69	15,146 (15.1)	6,818 (45.0)
70–74	21,231 (21.2)	10,630 (50.1)
75–79	20,056 (20.1)	11,851 (59.1)
80–84	19,508 (19.5)	13,532 (69.4)
85–89	15,330 (15.3)	12,141 (79.2)
90+	8,719 (8.7)	7,866 (90.2)
Age, y, mean (SD)	78.4 (7.80)	—
Sex		
Male	42,673 (42.7)	27,344 (64.1)
Female	57,317 (57.3)	35,494 (61.9)
Race		
White	79,693 (79.7)	49,538 (62.2)
Black	14,998 (15)	10,039 (66.9)
Asian	1,365 (1.4)	809 (59.3)
Hispanic	2,356 (2.4)	1,500 (63.7)
Native North American	493 (0.5)	301 (61.1)
Other	967 (1.0)	569 (58.8)
Unknown	118 (0.1)	82 (69.5)
Rural–urban continuum code		
Urban	80,533 (80.5)	50,768 (63.0)
Intermediate	13,446 (13.4)	8,420 (62.6)
Rural	5,749 (5.7)	3,487 (60.7)
Missing	262 (0.3)	163 (62.2)
Medicaid coinsurance		
No	71,282 (71.3)	9,063 (31.6)
Yes	28,708 (28.7)	19,645 (68.4)
Age-weighted Charlson Comorbidity Index score, mean (SD)	5.98 (2.13)	—

epilepsy in 2009. Table 3 displays characteristics of individuals who were newly diagnosed with epilepsy in our older adult sample. Patients with incident epilepsy were majority white (79.7%), female (57.3%), and urban residing (80.5%), and did not have Medicaid (71.3%). The mean age-weighted modified CCI score was 5.98 (95% confidence interval [CI] 5.97–5.99). The most common comorbidities were ischemic heart disease (59.9%), cataract (58.8%), stroke/TIA (53.8%), congestive heart failure (50.0%), and dementia (49.9%) (table 4).

Mortality

Nearly one third (29.2%) of the 33 million qualifying beneficiaries died during the observation period. The death rate was substantially higher in the incident epilepsy subpopulation: 62.8% (n = 62,838) died within 5 years. Cox models, built using the 98.8% of the sample that had no missing data for any covariates, demonstrated that incident epilepsy (as compared to no epilepsy) was associated with increased mortality (adjusted hazards ratio [AHR] 1.30, 95% CI 1.29–1.31) (figure 1), even after adjusting for covariates.

Table 5 and figure 2 display the results of a separate Cox model that stratified incident epilepsy according to whether one of the identifiable neurologic diagnoses was present prior to epilepsy. A preexisting diagnosis of Parkinson disease (AHR 1.29, 95% CI 1.21–1.38), multiple sclerosis (AHR 2.13, 95% CI 1.79–2.59), dementia (AHR 1.33, 95% CI 1.31–1.36), or traumatic brain injury (AHR 1.55, 95% CI 1.45–1.66) was associated with similar or greater increases in mortality. Epilepsy after stroke/TIA had the lowest measured increase in mortality (AHR 1.20, 95% CI 1.18–1.21) among Medicare-tracked neurologic conditions.

Analyses of the sample restricted to the nearly 1,000 persons with incident epilepsy found that demographic characteristics were modestly associated with mortality. In our unadjusted Cox models, female sex (hazard ratio [HR] 0.94, 95% CI 0.92–0.95) and Black race (HR 1.14, 95% CI 1.12–1.17) were associated with statistically significant differences in mortality; however, after adjustment for age, comorbid disease burden, poverty, and geographic location, only the HR for female sex (AHR 0.85, 95% CI 0.84–0.87) remained significant. Asian race (AHR 0.82, 95% CI 0.76–0.88) and Hispanic ethnicity (AHR 0.81, 95% CI 0.76–0.84) were associated with lower risk of death, but only in the adjusted model. Comorbid disease burden, on the contrary, was consistently associated with increased mortality (per 1-point increase: unadjusted HR 1.31, 95% CI 1.31–1.32, AHR 1.27, 95% CI 1.26–1.27). Medicaid coinsurance was also persistently associated with increased mortality (unadjusted HR 1.21, 95% CI 1.19–1.23, AHR 1.17, 95% CI 1.14–1.19). In unadjusted Cox models, residing in counties classified as intermediate by the RUCC was associated with significantly lower morality compared to residing in counties classified as urban (HR 0.94, 95% CI 0.91–0.97); however, after adjustment, the relationship was partially reversed, with intermediate counties being associated with increased mortality (AHR 1.06, 95% CI 1.03–1.08). There was no such difference in mortality after epilepsy diagnosis observed when comparing rural and urban counties.

Table 4 Comorbidities Among 99,990 Medicare Beneficiaries With Incident Epilepsy in 2009

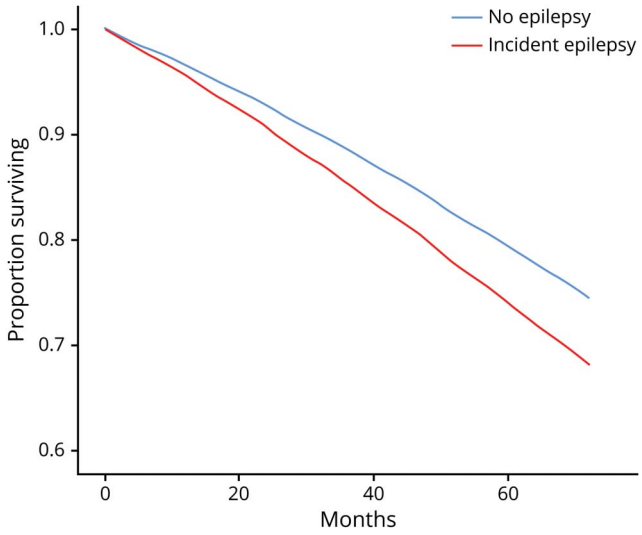
Comorbidity	Frequency in study sample (n = 99,990), n (row %)	Deceased within 5 y, n (%)
Acute myocardial infarction	9,692 (9.7)	7,451 (76.9)
Alzheimer dementia	26,355 (26.4)	21,065 (79.9)
Anxiety	25,468 (25.5)	16,642 (65.3)
Arthritis	47,514 (47.5)	30,405 (64.0)
Atrial fibrillation	24,461 (24.5)	18,337 (75.0)
Attention-deficit/hyperactivity disorder	2,518 (2.5)	1,848 (73.4)
Autism	95 (0.1)	57 (60.0)
Bipolar disorder	6,952 (7.0)	4,437 (63.8)
Breast cancer	3,921 (3.9)	2,565 (65.4)
Cataract	58,791 (58.8)	36,308 (61.8)
Cerebral palsy	610 (0.6)	334 (54.8)
Chronic kidney disease	40,167 (40.2)	30,406 (75.7)
Chronic obstructive pulmonary disease	36,725 (36.7)	26,748 (72.8)
Cirrhosis	10,066 (10.1)	7,063 (70.2)
Congenital structural abnormality of the nervous system	732 (0.7)	505 (69.0)
Congestive heart failure	49,974 (50.0)	36,818 (73.7)
Dementia (any type)	49,874 (49.9)	37,831 (75.9)
Depression	46,683 (46.7)	31,617 (67.7)
Developmental delay	229 (0.2)	136 (59.4)
Diabetes mellitus	40,349 (40.4)	26,736 (66.3)
Endometrial cancer	539 (0.5)	365 (67.7)
Glaucoma	19,885 (19.9)	12,369 (62.2)
Hearing loss	13,170 (13.2)	8,742 (66.4)
Hip fracture	9,417 (9.4)	7,447 (79.1)
HIV/AIDS	262 (0.3)	184 (70.2)
Intellectual disability	2,170 (2.2)	1,269 (58.5)
Ischemic heart disease	59,878 (59.9)	39,269 (65.6)
Learning disability	313 (0.3)	211 (67.4)
Leukemia or lymphoma	2,666 (2.7)	2,074 (77.8)
Lung cancer	3,775 (3.8)	3,352 (88.8)
Migraine	4,455 (4.5)	2,119 (47.6)
Mobility impairment	25,953 (26.0)	18,975 (73.1)
Multiple sclerosis	1,099 (1.1)	710 (64.6)
Muscular dystrophy	116 (0.1)	76 (65.5)
Obesity	13,362 (13.3)	8,315 (62.2)
Osteoporosis	38,021 (38.0)	24,144 (63.5)
Peripheral vascular disease	39,836 (39.8)	29,312 (73.6)
Personality disorders	1,857 (1.9)	1,231 (66.3)
Posttraumatic stress disorder	668 (0.7)	377 (56.4)
Pressure ulcer	22,831 (22.8)	18,518 (81.1)
Prostate cancer	5,596 (5.6)	3,765 (67.3)
Psychotic disorders	21,118 (21.1)	15,840 (75.0)
Schizophrenia	4,548 (4.6)	2,893 (63.6)
Spinal cord injury	1,276 (1.3)	929 (72.8)
Stroke or TIA	53,783 (53.8)	36,516 (67.9)
Tobacco use	13,484 (13.5)	9,086 (67.4)
Traumatic brain injury	5,090 (5.1)	3,409 (67.0)
Viral hepatitis	1,904 (1.9)	1,397 (73.4)
Vision loss	3,744 (3.7)	2,862 (76.4)

Discussion

In this study, we found a 5-year mortality rate of 62.8% in Medicare beneficiaries age 65 and above with new-onset epilepsy. The national mortality rate in older US patients with epilepsy has not been previously described. Although comparing persons with epilepsy to those without was not the primary focus of this study, the 62.8% 5-year mortality rate is notable because although it is less than the mortality associated with neurologic emergencies such as stroke or status epilepticus, it is more than double the 5-year mortality rate in the overall Medicare population from which our sample was drawn.[23] Previous studies of mortality in epilepsy have not commonly focused on older adults, and instead often highlight the excess mortality seen due to epilepsy and associated disorders in childhood.[24] Our study shows that death in older adults with incident epilepsy is common. This result, together with the changing demographics of an aging society, illustrates the need to better understand contributors to mortality in epilepsy in a mature population.

Underlining these changing demographics, we identified 99,990 incident epilepsy cases in 2009. This is notably increased from the average of around 60,000 incident epilepsy cases per year found in the 2001–2005 Medicare population (the last years this population was studied in totality).[17] There is little interval data on epilepsy incidence in the older adult

Figure 1 Effect of New Epilepsy Diagnosis on Survival of Medicare Beneficiaries, 2009–2014



Models included sex, race, age, age-adjusted Charlson Comorbidity Index, Rural Urban Continuum Code category, and Medicaid enrollment category. MS = multiple sclerosis; PD = Parkinson disease; TBI = traumatic brain injury.

population, but, in agreement with our findings, 2 recent studies of the Medicare population in Arizona also showed an increase in epilepsy incidence within the past decade.[25,26] There are multiple likely reasons for this ostensible difference in 1-year incident sample size, including (1) changes to epilepsy diagnosis coding due to evolving clinical recognition or alterations in billing practices; (2) growth in the aging adult population, as suggested by census data[27]; or (3) increasing numbers of individuals surviving with conditions known to increase the risk of secondary epilepsy, including cardiovascular and cerebrovascular disease, metabolic derangement, and neurodegeneration.[28–30]

Defining the variance in the outcomes and burden of epilepsy in the Medicare population is critical because of the known association between outpatient epilepsy care quality and health outcomes across epilepsy subtypes.[10,11] Importantly, unlike what has been found in other chronic diseases, we found little evidence of health inequity in terms of increased mortality among minorities or women.[31,32] Rather, after correcting for lower income (via Medicaid coenrollment) and comorbidity burden, female sex, Hispanic ethnicity, and Asian race appear to be inversely associated with death. One possible explanation relates to the underlying mechanisms for epilepsy: it is possible that women and some minorities develop epilepsy through less malignant pathologic mechanisms or have a more benign epilepsy. Although seemingly reassuring at first consideration, this potential explanation calls into question whether such benign epilepsy syndromes are more easily preventable. If so, our data provide early evidence of a preponderance of preventable, nonlethal epilepsy syndromes among older women and minorities.

There appears to be geographic variation in mortality—after accounting for race, sex, age, and Medicaid enrollment, patients living in urban counties appear to have lower mortality than those living in intermediately rural/suburban counties, but not completely rural areas. Possible reasons for this urban-associated decrease in mortality are not clear from these data, but could relate to specialist availability and other health care resources that would be predicted to be more plentiful in urban locations, or differential health-seeking behaviors of suburban-dwelling individuals.[33,34] This study provides the baseline data for future interventional studies of health care delivery, quality, and survival after an epilepsy diagnosis, which we hope will identify scalable process improvements that achieve better outcomes for persons with epilepsy, regardless of where they reside.

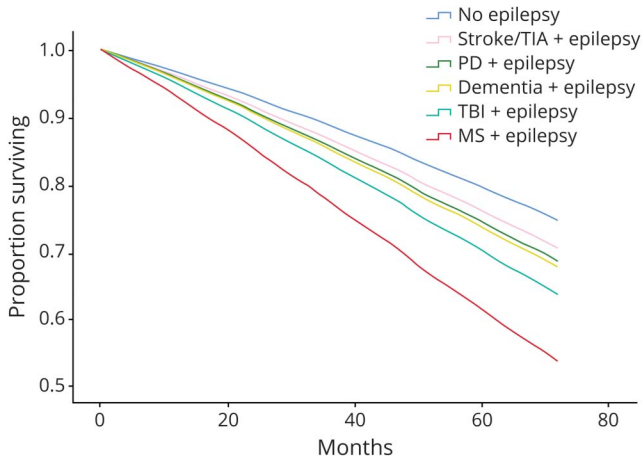
Incident epilepsy was associated with higher mortality when compared to mortality in a general Medicare population, as can

Table 5 Hazard of Death in Medicare Beneficiaries With a History of a Major Neurologic Condition and Incident Epilepsy in 2009–2014

Condition	Crude 5-y death rate	Unadjusted 5-y hazard of death (95% CI)	Adjusted[a] 5-y hazard of death AHR (95% CI)
No epilepsy	29.6	Ref	Ref
Incident epilepsy			
+ Dementia	73.2	4.15 (4.07–4.22)	1.33 (1.31–1.36)
+ Stroke/TIA	67.3	3.56 (3.52–3.59)	1.20 (1.18–1.21)
+ Traumatic brain injury	65.8	3.37 (3.15–3.61)	1.55 (1.45–1.66)
+ Multiple sclerosis	63.5	2.04 (1.71–2.43)	2.13 (1.79–2.59)
+ Parkinson disease	69.4	1.94 (1.81–2.07)	1.29 (1.21–1.38)
+ None of the above neurologic diagnosis	44.9	1.91 (1.88–1.94)	1.62 (1.59–1.65)

Abbreviations: AHR = adjusted hazards ratio; CI = confidence interval.
[a] Adjusted for age, race, sex, rural/urban continuum category, and age-weighted modified Charlson Comorbidity Index.

Figure 2 Underlying Neurologic Disease is Associated With Increased Mortality Among Older US Adults With Incident Epilepsy, 2009–2014



Models included neurologic disease category, sex, race, age, age-adjusted Charlson Comorbidity Index, Rural Urban Continuum Code category, and Medicaid enrollment category.

be reasonably expected. Having a second, prior neurologic diagnosis was uniformly associated with increased mortality in the 5 years following epilepsy diagnosis. Stroke, an episodic disorder associated with the development of seizures or epilepsy, had lower HRs than neurodegenerative disorders (Parkinson disease and dementia). This observation most likely reflects the higher risk of death conferred by neurodegenerative disease. Whereas the focus of this study was on developing the population-level data to inform policy, epidemiologic surveillance, and health care system design, the high mortality in the dementia subgroup reaffirms clinical knowledge that seizures are typically a late manifestation of neurodegenerative disease and a marker of poor prognosis.

This study is unique in that it uses a national sample of US adults age 65 and above to describe 5-year mortality in incident epilepsy and provide evidence that poverty and comorbid disease drives death in this population. This study, however, has several possible limitations. First, our study assessed the Medicare population during 2009–2014, and may not reflect the current experience. Administrative claims data contain codes produced for billing and documentation purposes, and so do not allow for a detailed examination of socioeconomic background, health care attitudes, medication adherence, functional status, or disease severity. This is a significant consideration as all these factors would be expected to affect mortality and are important in developing effective interventions to improve clinical outcomes. We used validated ICD-9-CM codes for epilepsy, but despite being widely used in Medicare analyses, these codes have not been specifically validated in this population. There is a known lag-time between epilepsy onset and diagnosis[35,36]; our results, therefore, likely represent mortality further into the disease state than 5 years.

A learning health care system is one in which research (science, informatics) and care (delivery, incentives, and culture) are aligned for continuous improvement.[37] Initial knowledge to fuel these health systems requires careful epidemiologic studies that can then be effectively translated prospectively into appropriate real-time tools at a patient, clinician, health system, or policy level. We assessed a large cohort of Medicare beneficiaries and present national data on mortality in older patients with new-onset epilepsy in the United States. Our data represent the afferent limb of a learning health system approach to epilepsy in the older adult population, as an initial step toward structural improvements in the delivery of epilepsy care. Future studies will use Medicare claims linked to electronic medical records to parse the interplay between race, sex, poverty, and comorbid disease on mortality and to determine the comparative effectiveness of newer epilepsy treatments in elderly patients with epilepsy. Together with these initial data, these epidemiologic studies will inform the development of interdisciplinary real-time, practice-changing interventions to reduce premature deaths and improve outcomes in older adults with epilepsy.

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Disclosure

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Leah J. Blank, MD, MPH	Icahn School of Medicine at Mount Sinai, New York, NY	Study conceptualization and design, data interpretation, writing the manuscript, developing the tables/figures
Emily K. Acton, BS	University of Pennsylvania Perelman School of Medicine, Philadelphia	Study conceptualization and design, data interpretation, writing the manuscript, developing the tables/figures
Allison W. Willis, MD, MS	University of Pennsylvania Perelman School of Medicine, Philadelphia	Study conceptualization and design, data and statistical analyses, data interpretation, writing the manuscript, developing the tables/figures

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