Receipt of Electroconvulsive Therapy and Subsequent Development of Amyotrophic Lateral Sclerosis: A Cohort Study

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We investigated the potential relationship between receipt of electroconvulsive therapy (ECT) and development of amyotrophic lateral sclerosis (ALS). We conducted a cohort study using a sample of more than one million beneficiaries enrolled in the U.S. Medicare health insurance program from 1997 to 2017. Using time-varying proportional hazard modeling, we compared ALS occurrence among patients diagnosed with psychiatric conditions who received ECT to ALS occurrence among patients diagnosed with psychiatric conditions but who did not receive ECT. We observed moderately increased, but imprecise, hazard ratios (HR) for ALS following ECT (HR = 1.39, 95% confidence interval [CI]: 0.69–2.80). A statistically significant increase in the HR of ALS was observed among those who received more than 10 ECT treatments (>10 treatments, HR = 2.24, 95% CI: 1.00–5.01), compared to those receiving no ECT, with an even stronger association observed among subjects older than 65 years (HR = 3.03, 95% CI: 1.13–8.10). No monotonic exposure-response relationship was detected in categorical analyses. Our results provide weak support for the hypothesis that receipt of ECT increases the risk of developing ALS. Additional studies in larger populations, or in populations where ECT is more common, will be needed to refute or confirm an association between receipt of ECT and subsequent development of ALS. Bioelectromagnetics. 43:81–89, 2022. © 2021 Bioelectromagnetics Society.

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INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a rapidly progressive and mostly fatal motor neuron disease [Kiernan et al., 2011; Chuquilin et al., 2017]. The underlying pathology of the disease involves the selective degeneration and death of both upper motor neurons (UMN) in the cerebral cortex and lower motor neurons (LMN) in the spinal cord. Clinical manifestation may be initially dominated by either UMN or LMN symptoms. The generally accepted diagnostic clinical criteria, however, include the presence of both UMN and LMN symptoms [Brooks, 1994; Gordon 2013]. The annual incidence of ALS is estimated around 1–2.5 per 100,000 people in Europe and North America [Nelson and McGuire, 2006; Al-Chalabi and Hardiman, 2013]. Since patients diagnosed with ALS have a fairly short survival (20–48 months), the annual mortality rate closely follows the incidence rate of the disease [Chiò et al., 2009]. The incidence of the disease, which is slightly higher among men than women, sharply increases with age, reaching its peak in the 60s with an annual incidence rate of approximately 8 to 12 per 100,000 [Nelson and McGuire, 2006]. Generally, ALS cases are classified into three major types—familial, sporadic, and endemic cases of the Western Pacific. Familial cases comprise about 5%–10% of ALS cases

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worldwide [Filippini et al., 2020]. Despite advances in our understanding of the role of genetic changes in the development of ALS, the etiology of the most common type, sporadic ALS, remains largely unknown [Martin et al., 2017]. While a number of lifestyle-related environmental (e.g., smoking, diet, exercise) and occupational exposures (e.g., the Gulf War, military service, metals, solvents) have been hypothesized and investigated, the etiologic role of these factors remains uncertain [Al-Chalabi and Hardiman, 2013].

Exposure to extremely low frequency (ELF) magnetic fields (MF) and electric shocks and working in "electrical occupations" have been studied since the 1980s as potential occupational risk factors for ALS development. ALS has been associated with electrical environments and electrical occupations in some occupational epidemiologic studies [WHO, 2007; Huss et al., 2018; Gunnarsson and Bodin, 2019]. A meta-analysis of occupational exposure to ELF-MF and neurodegenerative diseases reported a weak association between job titles indicating electrical occupations and ALS; the authors concluded that occupational exposure to ELF-MF did not appear to explain this association [Vergara et al., 2013]. It has been suggested that exposure to electric shocks, that is electric currents through the body, in these electrical occupations and environments, rather than exposure to ELF-MF, may be the causal factor and explain the observed association for electrical occupations [Kheifets et al, 2009]. Although no clear mechanism has been identified for the potential etiologic role of electric shocks in the development of ALS, it has been suggested that electric shocks, as a form of trauma, may lead to demyelinisation, reactive gliosis, and neuronal death [e.g. Deapen and Henderson, 1986].

A study based on death certificate data that specifically investigated the potential role of electric shocks and ELF-MF in the development of ALS did not support the hypothesis [Vergara et al., 2015]. Another study found some evidence of an association with magnetic fields, but not with electric shocks or electrical occupations [Huss et al., 2015]. A large study from Sweden did not observe an association for occupational exposure to magnetic fields or electric shocks, but reported a weak, statistically significant association for electric shocks among individuals younger than age 65 [Fischer et al., 2015; Peters et al., 2019]. A Dutch study reported an association between occupational ELF-MF exposure and ALS; however, the findings were based on small numbers, and the association diminished after adjusting for the effects of other occupational exposures [Koeman et al., 2017]. A recent study from New Zealand reported an association between occupational exposure to electric shocks and ALS but did not show associations with exposure to work-related ELF-MF [Chen et al., 2021]. A more recent meta-analysis reported a weak association between occupational exposure to ELF-MF and the risk of ALS and reported no association between occupational exposure to electric shocks and risk of ALS; however, there was substantial heterogeneity in the results of the included studies [Jalilian et al., 2020].

More research is needed to refute or confirm the role of electric shocks in the etiology of ALS. In occupational settings, it is difficult to separate exposure scenarios for electric shocks and ELF-MF because they often occur together, making an independent assessment of the effects of the two exposures challenging [Vergara et al., 2013]. While several occupational epidemiologic studies attempted to use separate job-exposure matrices for ELF-MF and electric shocks occurring during work [Fischer et al., 2015; Huss et al., 2015; Vergara et al., 2015], the possibility of confounding of one exposure by the other remains in the individual studies and may explain the inconsistencies in the observed results. Thus, identification of scenarios where electric shocks occur without the potential for ELF-MF exposure is essential for investigating the independent effect of electric shocks on the development of ALS.

Electroconvulsive therapy (ECT), a relatively common treatment for some psychiatric conditions, presents a setting where a well-documented exposure to electric shocks occurs in a medical setting without substantial exposure to ELF-MF. ECT is a treatment of choice for some psychiatric conditions and mood and thought disorders, such as severe depression and schizophrenia [Mankad et al., 2010]. ECT applies electric currents across the brain to depolarize cerebral neurons and thereby produce a generalized seizure. The treatment is not associated with sustained exposure to ELF-MF. Approximately 1%–5% of psychiatric inpatients undergo ECT [Chanpattan, 2007; Gazdag et al., 2013; Loh et al., 2013]. This provides a unique opportunity to examine the potential role of electric shocks in ALS development in a controlled and well-documented clinical environment without the confounding effect of ELF-MF. The purpose of our analyses was to assess whether the incidence of ALS differs among ECT recipients compared to those who did not receive ECT.

METHODS

We conducted a cohort analysis using a 5% systematic sample of U.S. Medicare health insurance program beneficiaries enrolled in the traditional fee-for-service program from 1997 to 2017, who represent

approximately 80% of all Medicare enrollees during our study period [Kaiser Family Foundation, 2019]. The Medicare program has a nationwide and practically universal coverage for both inpatient and outpatient services for elderly U.S. residents over age 65. People under 65 with certain disabilities and medical conditions may also be eligible for Medicare. Enrollment in Medicare increased during our study period from less than 40 million in the 1990s to 56.8 million in 2017. For each year, the Medicare 5% systematic sample data files include de-identified information on both inpatient and outpatient claims from hospitals and nursing facilities, as well as professional service claims from physicians regardless of the setting where service was rendered. The 5% sample is selected based on the last two digits of the beneficiaries' Social Security Number (SSN). The last four digits of the SSN are essentially random numbers. Since the same digits were used from year to year to select the 5% sample, the same beneficiaries are sampled each year, which allows tracking of the same individuals across years. This sampling method is "systematic," as opposed to "random," because the same digits were used as the selection criteria each year. But because the last two digits are randomly assigned, the sample is also a representative "random" sample. Because ECT is primarily used as a treatment modality for certain psychiatric conditions, our cohort was restricted to patients who were diagnosed with schizophrenic disorders, episodic mood disorders, or other depressive disorders. Patients with the following diagnoses were included in the cohort: International Classification of Diseases (ICD), Ninth Revision, codes 295, 296, and 311; and ICD, Tenth Revision, codes F200 through F209, F250 through F259, and F301 through F339. Each subject entered the cohort at the first mention of any of these psychiatric diagnoses, and were followed until diagnosis of ALS, death from any reason, end of enrollment, or end of 2017, whichever occurred first. ALS diagnosed within the first 6 months of follow up were excluded from our analyses to ensure that identified ALS cases were newly diagnosed incident cases and not prevalent cases at cohort entry.

Cumulative incidence of ALS was calculated and plotted as the complement of the Kaplan–Meier survival probability. The standard error and corresponding pointwise confidence intervals (CIs) for the Kaplan–Meier survival probabilities were estimated using Greenwood's formula [Greenwood, 1926]. The log-rank test was used to test cumulative incidence differences across strata (male vs. female; race/ethnicity). We used time-varying Cox proportional hazard modeling with yearly intervals to assess covariate-adjusted ALS risk in association with ECT. In addition to including covariates in the model to control for potential confounding, our study model also included the Fine and Gray adaptation of the traditional proportional hazard model to account for competing risk associated with death prior to development of ALS [Fine and Gray, 1999]. We treated age as the primary time axis in our proportional hazard models. At a given interval, the cumulative number of ECT treatments was used as the measure of exposure to electric shocks. Members of the cohort were considered unexposed prior to and within the first 6 months after the receipt of their first ECT treatment and were considered exposed thereafter. We performed unadjusted and adjusted analyses. We report corresponding hazard ratios (HRs) and 95% CIs for the association of ECT with incident ALS. In our final models, we adjusted for sex, race, year of birth, year of entry into the cohort, Medicare-Medicaid dual eligibility, and three main U.S. regions grouped by magnitude of ALS mortality [Noonan et al., 2005]. Variables in the adjusted model were selected a priori based upon subject matter knowledge.

For an evaluation of a potential exposure-response relationship, the number of ECT treatments were categorized into three categories: no exposure (no ECT treatment), low exposure (1–10 ECT treatments), and high exposure (11 or more ECT treatments). Each ECT treatment is credited 6 months after the actual treatment date. The exposure categories were chosen based on the median number of ECT treatments (10) among ECT recipients. In addition, we also conducted analyses using the number of ECT treatments as a continuous variable. For our analyses, we used de-identified data files released and approved for research purposes by the Centers for Medicare and Medicaid Services; no additional ethics or institutional review board approval was required.

Our initial analyses included all subjects that qualified for cohort membership based on their psychiatric diagnoses. In subsequent analyses, however, we implemented two exclusions to our study population: (1) subjects who entered the Medicare 5% sample in 1997 and (2) subjects who were under age 65 when they entered the Medicare 5% sample. We excluded those who entered the Medicare 5% sample in 1997 since they represented a combination of new enrollees and those who enrolled in Medicare in previous years, and we had no information on their medical history prior to 1997. Subjects who entered the Medicare 5% sample in 1998 and later only included new enrollees. We excluded enrollees under age 65 since they must have had some medical

conditions that qualified them for Medicare prior to the regular enrollment age of 65. ALS is one of the medical conditions that qualify for Medicare eligibility; however, in our dataset, we did not have information on the qualifying medical condition for enrollees under age 65, with the exception of end-stage renal disease.

In our main analyses, the underlying cohort included all patients with the above-specified psychiatric conditions, regardless of whether the psychiatric diagnosis was listed as a primary or secondary diagnosis. As part of our sensitivity analyses, we repeated all analyses including only those patients who had any of the specified psychiatric conditions as a primary diagnosis, and conducted sensitivity analyses with the inclusion of ALS cases that occurred within the first 6 months after the psychiatric diagnosis, and without employing a 6-month lag after ECT treatment. We also evaluated the relationship between severity of the psychiatric conditions, as measured by psychiatric diagnosis-related number of office visits, hospital admission, emergency room visits, and total Medicare claim payment and ALS development. Data processing and statistical analyses were carried out using SAS statistical software, version 9.4 (SAS Institute, Cary, NC).

RESULTS

Our cohort included 1,226,151 subjects with psychiatric conditions representing approximately 22% of the approximately five million beneficiaries ever included in the Medicare 5% sample. A larger fraction of the study subjects (9.2%) entered the cohort in 1997, the first year of the study, than in any subsequent years (range from 4.1% to 5.5%). About 84% of the subjects were white, 64% of the subjects were women, and 66% of the subjects were age 65 or older. Of the cohort members, 6% were diagnosed with schizophrenic disorders, 31% were diagnosed with episodic mood disorders, and 63% were diagnosed with other depressive disorders. Of the cohort members, 7936 subjects (0.6%) received ECT treatment, and 1246 subjects (0.1%) were diagnosed with ALS. Characteristics of cohort members are shown in Table 1.

As anticipated, ALS incidence increased with age, and ALS occurred more frequently among men: adjusted HR for women versus men ranged between 0.61 (95% CI: 0.54–0.68) and 0.68 (95% CI: 0.60–0.77), depending on specific models (with and without adjustment) and population inclusion criteria. ALS incidence also increased for whites: HR for blacks versus whites ranged between 0.66 (95% CI: 0.50–0.86) and 0.77 (95% CI: 0.58–1.03), while HR for others versus whites ranged between 0.67 (95% CI: 0.48–0.94) and 0.76 (95% CI: 0.56–1.02). Among the cohort members who received ECT, 15 patients were subsequently diagnosed with ALS (0.2%). ALS was not associated with severity of the psychiatric conditions, as measured by number of office visits, hospital admission, emergency room visits, and total Medicare claim payments.

Figures 1 and 2 present the cumulative incidence of ALS by age and by ECT treatment among the elderly (age 65 and older); the 95% CIs for the incidence curves overlap across the treatment groups. Tables 2 and 3 present unadjusted and adjusted ECT-specific HRs. We observed moderately increased, but imprecise HRs for ALS following ECT treatment. Among all members of the cohort enrolled in 1998 or later, receipt of any ECT treatment compared to no ECT treatment was associated with an adjusted HR of 1.39 (95% CI: 0.69–2.80), and in the continuous analyses, the adjusted HR was 1.03 (95% CI: 1.01–1.06) per treatment. Receipt of more than 10 ECT treatments was associated with an approximate two-fold increase in the adjusted HRs, compared to patients receiving no ECT treatment. Among all members of the cohort enrolled in 1998 or later, receipt of more than 10 ECT treatments compared to no ECT treatment was associated with an adjusted HR of 2.24 (95% CI: 1.00–5.01). Among the elderly (age 65 and older) enrolled in 1998 or later, receipt of more than 10 ECT treatments compared to no ECT treatment was associated with an even greater increase of adjusted HR (HR = 3.03; 95% CI: 1.13–8.10). No monotonic exposure-response pattern was observed in any of our categorical analyses. In fact, the results display a slight, although not statistically significant, deficit of ALS cases in the intermediate exposure category (1–10 ECT treatments) as compared to no ECT treatment.

DISCUSSION/CONCLUSION

To our knowledge, this is the first study to explore the potential relationship between ECT, a source of electric currents in the brain without significant exposure to ELF-MF, and subsequent development of ALS. Within the limitations of our data, we observed moderately increased, but imprecise HRs for ALS development following ECT treatment. The association between receipt of 11 or more ECT treatments and the subsequent development of ALS was somewhat stronger; at the same time, however, we observed a slight deficit of ALS risk in the intermediate exposure category (1–10 ECT treatments). Despite our large

TABLE 1. Characteristics of All Cohort Members (All Ages, $n = 1{,}226{,}151$) and Elderly Cohort Members (Ages 65+, $n = 808{,}362$) by ECT Treatment, Years 1997–2017[a,b]

	Full cohort				Elderly cohort			
	Use of ECT				Use of ECT			
	No		Yes		No		Yes	
	n	%	*n*	%	*n*	%	*n*	%
Total (N)	1,218,215	100.0	7936	100.0	804,745	100.0	3617	100.0
Disability								
Disabled	348,411	28.6	3785	47.7	--	--	--	--
No Disability	869,804	71.4	4151	52.3	804,745	100.0	3617	100.0
Regions by motor neuron disease mortality (per 100,000)[c]								
Low (<1.7)	581,072	47.7	3364	42.4	383,293	47.6	1550	42.9
Medium (1.7–2.0)	485,575	39.9	3541	44.6	322,718	40.1	1612	44.6
High (2.0+)	151,568	12.4	1031	13.0	98,734	12.3	455	12.6
ALS								
No	1,216,984	99.9	7921	99.8	803,929	99.9	<3617	>99
Yes	1,231	0.1	15	0.2	816	0.1	<10	<1
Sex								
Male	438,102	36.0	2760	34.8	263,246	32.7	1145	31.7
Female	780,113	64.0	5176	65.2	541,499	67.3	2472	68.3
Birth year								
<1930	388,268	31.9	2247	28.3	388,268	48.2	2247	62.1
1930s	251,972	20.7	1389	17.5	226,385	28.1	943	26.1
1940s	258,227	21.2	1304	16.4	166,925	20.7	411	11.4
1950s	161,459	13.3	1206	15.2	23,167	2.9	16	0.4
1960+	158,289	13.0	1790	22.6	--	--	--	--
Age								
01–64	413,470	33.9	4319	54.4	--	--	--	.--
65–69	229,170	18.8	1247	15.7	229,170	28.5	1247	34.5
70–74	155,858	12.8	895	11.3	155,858	19.4	895	24.7
75–79	144,106	11.8	765	9.6	144,106	17.9	765	21.2
80–84	128,535	10.6	473	6.0	128,535	16.0	473	13.1
85+	147,076	12.1	237	3.0	147,076	18.3	237	6.6
Year of entry								
1990s	214,299	17.6	3777	47.6	146,183	18.2	2030	56.1
2000s	524,103	43.0	2991	37.7	354,278	44.0	1180	32.6
2010s	479,813	39.4	1168	14.7	304,284	37.8	407	11.3
Race								
Other	76,823	6.3	335	4.2	42,210	5.2	81	2.2
White	1,025,547	84.2	7232	91.1	709,194	88.1	3438	95.1
Black	115,845	9.5	369	4.6	53,341	6.6	98	2.7
Residence								
Midwest	296,732	24.4	2362	29.8	197,445	24.5	1078	29.8
Northeast	238,177	19.6	2172	27.4	161,431	20.1	1054	29.1
South	483,511	39.7	2572	32.4	313,782	39.0	1133	31.3
West	199,795	16.4	830	10.5	132,087	16.4	352	9.7
Medicaid								
No Buy-In	850,262	69.8	5710	72.0	637,656	79.2	3200	88.5
State Buy-In	367,953	30.2	2226	28.0	167,089	20.8	417	11.5

Abbreviations: ECT = electroconvulsive therapy.

[a]To protect patient confidentiality, case counts below 10 are not reported.

[b]Percentages shown for each category may not sum to one hundred percent due to rounding.

[c]Categorized based on results in [Noonan et al., 2005].

cohort size, we had a relatively small number of exposed ALS cases in our cohort ($n = 15$), which resulted in imprecise ECT-specific HR estimates, with 95% CIs including 1.0 in most analyses. Exclusion of subjects who entered the Medicare 5% sample in 1997 and subjects under age 65 resulted in considerable changes in our ECT-specific HR estimates, which may indicate the presence of bias in our HR estimates before

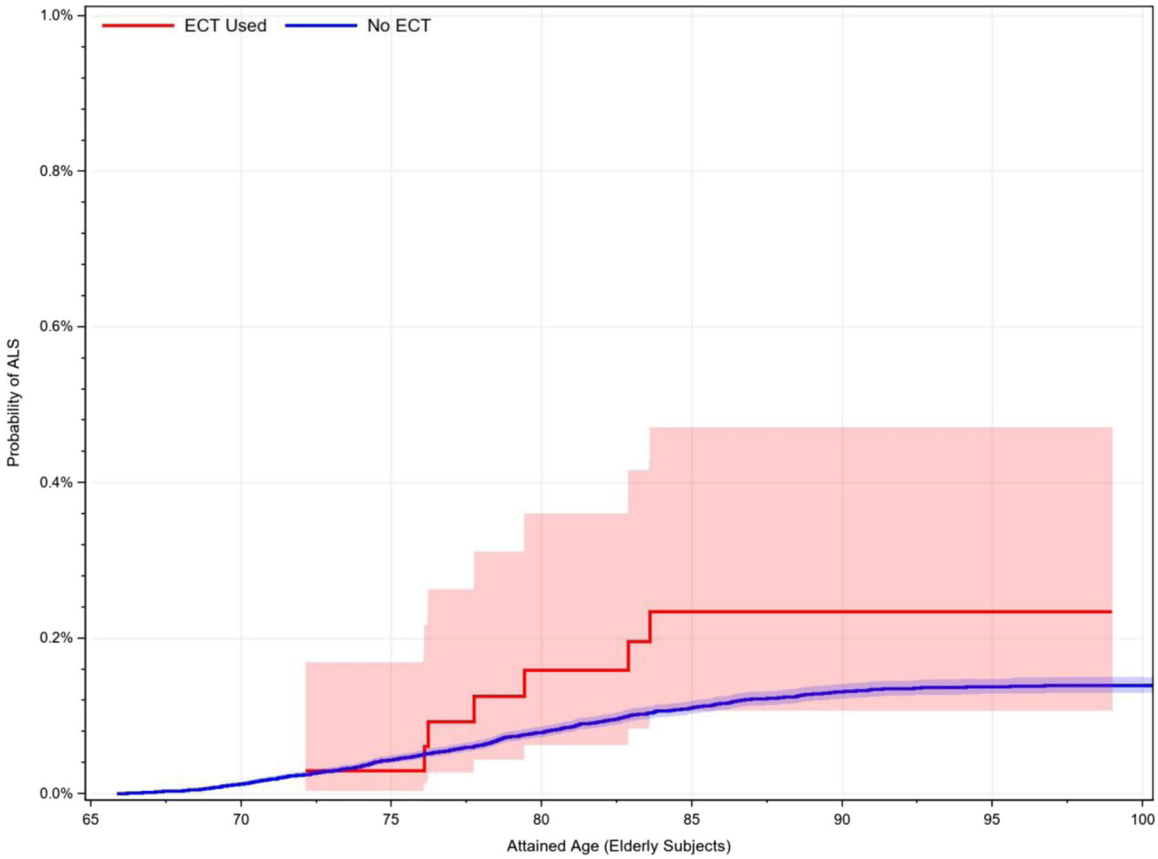

Fig. 1. Cumulative incidence of ALS by age and ECT (Treatment vs. No Treatment) in the elderly cohort (years 1997–2017). Shaded areas represent 95% CIs of the point estimates in the corresponding incidence curves. ALS = amyotrophic lateral sclerosis; CI = confidence interval; ECT = electroconvulsive therapy.

or after these exclusions, or in both sets of estimates. Restricting our analyses to the elderly population (age 65 and older) and to those who entered the Medicare 5% sample after 1997 likely provided, in principle, the most unbiased sample but resulted in a substantial decrease in total sample size and the number of exposed cases (~43% reduction). This reduction in sample size, particularly in the number of exposed cases, which were less than 10 in several analyses, may have also resulted in small number bias, potentially inflating our effect estimates [Greenland et al., 2000, 2016]. We considered the possibility that confounding by severity of the psychiatric disorders contributed to our results. While severity of the psychiatric conditions is associated with ECT, severity measures were not related to ALS in our dataset; thus, there is no evidence for confounding by severity in our analyses.

The strengths of our study include its cohort design, the large sample size (well over one million study subjects), the nationwide coverage of the study, the length of follow up (21 years), the well-documented nature of a specific form of electric shock treatment without substantial exposure to ELF-MF in a medical setting, and the virtually complete ascertainment of ALS diagnoses among the cohort members. Limitations of our study include the relatively small fraction of subjects with ECT treatments (0.6%) and the rarity of ALS diagnoses, which limited the power of our study to detect an association. We had no information on other types of electric shocks, including occupational exposure to electric shocks experienced by the study subjects, or treatment, including ECT, received prior to Medicare enrollment by subjects with pre-existing psychiatric conditions at enrollment, which may result in potential exposure misclassification. The lack of information on medical conditions qualifying patients under 65 for Medicare eligibility, the lack of information on Medicare enrollees that do not participate in the traditional Medicare program, and that ECT is employed in a highly selective population of psychiatric patients may limit the generalizability of our findings.

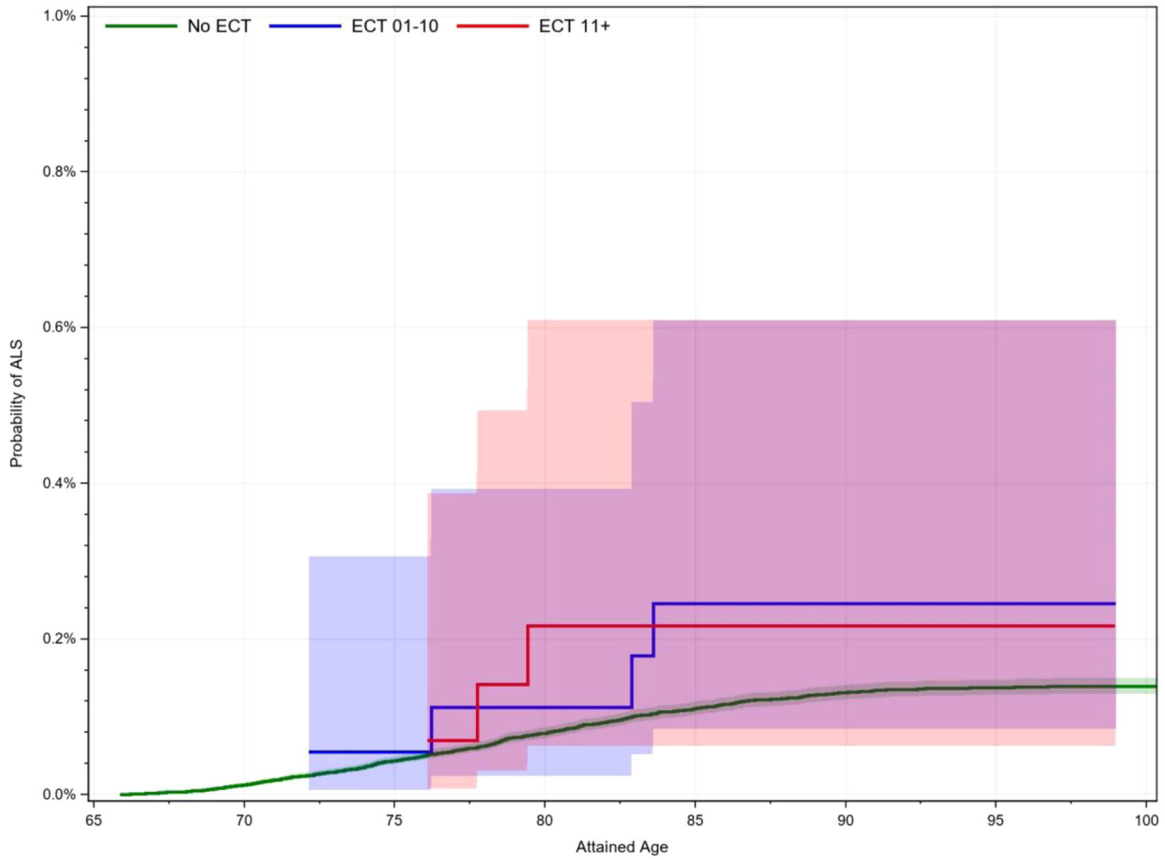

Fig. 2. Cumulative incidence of ALS by age and ECT (No Treatment, 1–10 Treatments, and 11 or More Treatments) in the elderly cohort (Years 1997–2017). Shaded areas represent 95% CIs of the point estimates in the corresponding incidence curves. ALS = amyotrophic lateral sclerosis; CI = confidence interval; ECT = electroconvulsive therapy.

TABLE 2. Unadjusted and Adjusted HR and 95% CI for Diagnosis of ALS and Use ECT, Treatment Versus No Treatment, and Number of ECT Treatments as a Continuous Variable (Per Treatment)

Cohort definition	ECT treatment	ALS cases (*n*)[a]	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[b]
Full cohort (1997–2017)	No	1231	1.00 (reference)	1.00 (reference)
	Yes	15	1.33 (0.77–2.29)	1.30 (0.75–2.25)
	Continuous variable		**1.02 (1.01–1.04)**	**1.03 (1.01–1.04)**
Elderly cohort (1997–2017)	No	816	1.00 (reference)	1.00 (reference)
	Yes	<10	1.20 (0.54–2.67)	1.17 (0.52–2.61)
	Continuous variable		1.02 (0.99–1.05)	1.02 (0.99–1.05)
Full cohort (1998–2017)	No	1045	1.00 (reference)	1.00 (reference)
	Yes	<10	1.43 (0.71–2.86)	1.39 (0.69–2.80)
	Continuous variable		**1.03 (1.00–1.06)**	**1.03 (1.01–1.06)**
Elderly cohort (1998–2017)	No	711	1.00 (reference)	1.00 (reference)
	Yes	<10	1.82 (0.76–4.39)	1.75 (0.72–4.22)
	Continuous variable		**1.04 (1.00–1.07)**	**1.04 (1.00–1.07)**

Abbreviations: ALS = amyotrophic lateral sclerosis; CI = confidence interval; ECT = electroconvulsive therapy.
[a]To protect patient confidentiality, case counts below 10 are not reported.
[b]Adjusted for sex, race, year of birth, year of entry into cohort, Medicare-Medicaid dual eligibility, and region.

TABLE 3. Unadjusted and Adjusted HR and 95% CI for Diagnosis of ALS and Use of ECT: No Treatment; 1–10 ECT Treatments; 11 or More ECT Treatments

Cohort definition	Number of ECT treatments	ALS cases (n)[a]	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[b]
Full cohort (1997–2017)	No	1231	1.00 (reference)	1.00 (reference)
	1–10	<10	0.95 (0.40–2.30)	0.94 (0.39–2.26)
	11+	<10	1.75 (0.87–3.51)	1.72 (0.85–3.44)
Elderly cohort (1997–2017)	No	816	1.00 (reference)	1.00 (reference)
	1–10	<10	0.75 (0.19–3.00)	0.73 (0.18–2.93)
	11+	<10	1.71 (0.64–4.58)	1.67 (0.62–4.46)
Full cohort (1998–2017)	No	1045	1.00 (reference)	1.00 (reference)
	1–10	<10	0.66 (0.17–2.66)	0.65 (0.16–2.61)
	11+	<10	**2.32 (1.04–5.17)**	**2.24 (1.00–5.01)**
Elderly cohort (1998–2017)	No	711	1.00 (reference)	1.00 (reference)
	1–10	<10	0.67 (0.09–4.78)	0.65 (0.09–4.63)
	11+	<10	**3.18 (1.19–8.51)**	**3.03 (1.13–8.10)**

Abbreviations: ALS = amyotrophic lateral sclerosis; CI = confidence interval; ECT = electroconvulsive therapy.
[a]To protect patient confidentiality, case counts below 10 are not reported.
[b]Adjusted for sex, race, year of birth, year of entry into cohort, Medicare-Medicaid dual eligibility, and region.

In summary, we observed moderately increased, but imprecise HRs for ALS following ECT treatment. The highest HRs for ALS were observed among elderly patients who received more than 10 ECT treatments, though no monotonic exposure-response pattern was detected. Additional studies in larger populations, or in populations where ECT treatment is more common, will be needed to refute or confirm an association between ECT and subsequent development of ALS.

ETHICS STATEMENT

For our analyses, we used de-identified data files released and approved for research purposes by the Centers for Medicare and Medicaid Services; no additional ethics or institutional review board approval was required. The underlying data are publicly available for research purposes.

AUTHOR CONTRIBUTIONS

GM, EL, and LK contributed to the conception of design; EL contributed to data acquisition and statistical analysis; and all authors contributed to interpretation of results, drafting the manuscript, and approving the final version.

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