Original Paper

Neuro
epidemiology

Neuroepidemiology 2015;44:6–15
DOI: 10.1159/000369813

Received: April 23, 2014
Accepted: November 2, 2014
Published online: January 7, 2015

Epidemiology of Amyotrophic Lateral Sclerosis and Effect of Riluzole on Disease Course

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Key Words
Epidemiology · Amyotrophic lateral sclerosis · Riluzole · Austria

Abstract
Objectives: To assess the epidemiology of ALS in Austria and to evaluate the long-term effect of riluzole treatment on survival. ***Methods:*** Hospital discharge and riluzole prescription databases were used to identify ALS cases from January 2008 to June 2012. Using the capture-recapture method we evaluated the incidence and prevalence of ALS and patients' survival in dependence of age, gender and riluzole treatment. ***Results:*** The corrected incidence and prevalence of ALS were 3.13/100,000 person-years (95% CI, 2.77 to 3.50) and 9.14/100,000 persons (95% CI, 8.53 to 9.79), respectively. Median survival from diagnosis was 676 days (95% CI, 591 to 761). A younger age at diagnosis was associated with a longer survival. Gender did not appear to affect survival time. Riluzole therapy was associated with a survival advantage only for the initial treatment period. The adjusted hazard ratio of mortality for using riluzole increased continually over time resulting in an apparent reversal of its beneficial effect after 6 months of therapy. ***Conclusions:*** We report incidence and prevalence estimates that are on the upper end of the wide range discussed in literature. Riluzole seems to exert a beneficial effect only in the first 6 months of therapy.

Introduction

Large population-based databases and disease registries can be helpful in many different ways. They provide data on epidemiological aspects and can thus guide the rational allocation of health resources. In addition, epidemiological studies comprise patients with the full clinical spectrum of a disease and are therefore a better 'real-world' representation of a disease in comparison to clinical studies where phenotypes are often narrowly defined.

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In clinical studies on ALS a significant proportion of patients is excluded due to strict research criteria and the time horizon of patient follow-up is usually limited [1, 2]. Another advantage of large databases is that their analysis can sometimes reveal clues to underlying pathophysiological mechanisms, which might otherwise not be detectable [3, 4].

Drawing on figures from a large Austrian hospital discharge and prescription database we performed the first epidemiological study on ALS in Austria for the period from January 1, 2008 to June 30, 2012. We evaluated the incidence and prevalence of the disease, and to address the above-mentioned points we assessed the influence of several prognostic factors on the survival of ALS patients.

Methods

Data Sources

The data of this study are based on registries with invoice data of the nine regional sickness funds of Austria (Gebietskrankenkassen, GKK), which together capture 77.7% of the total Austrian population aged 20 years or older (i.e., 5,194,837 out of 6,685,432 residents; according to the register-based census held on October 31, 2011, the total population of Austria was 8,401,940 as downloaded from http://www.statistik.at). Individuals younger than 20 years were excluded from the study population to avoid misclassification with juvenile onset motor neuron diseases.

The registries comprise each insurant's demographic details, all hospital discharge diagnoses and all prescription data. To identify patients with ALS during the study period (January 1, 2008 to June 30, 2012) we searched the registries for (i) all patients who were discharged from a hospital with a main diagnosis of ALS (code G12.2 according to the International Classification of Disease, 10th revision) or (ii) who were prescribed riluzole during the study period. This included privately insured patients. However, outpatients with ALS who had never been hospitalised or prescribed riluzole during the study period would have not been captured. Since ALS is the only diagnosis for which riluzole is approved and for which the costs are covered by the sickness funds, the diagnoses of ALS could reliably be deduced from riluzole prescriptions.

After identifying ALS patients by this method several demographic parameters were extracted from the GKK database: gender, date of birth, time of death, date and number of riluzole prescriptions, dates of inpatient stays. Any information about disease severity including (non-invasive) ventilation and gastrostomy were not included by the database. Individual patients were pseudonymised with a thirty-two digit number before being analysed further. The study was approved by the ethical committees of Burgenland and of the Medical University of Vienna.

Incidence and Prevalence of ALS

The time point of ALS diagnosis was assumed to be either (i) the day of the first hospital discharge during the study period (provided the main discharge diagnosis was ICD-10 G12.2), or (ii) the day of the first riluzole prescription, whichever was earlier.

The incidence rates (IR) and prevalence ratios (PR) for the years 2009, 2010 and 2011 were determined and age-standardised to the total Austrian population, and for comparison with other studies, also to the US 1990 and US 2010 Census populations. We did not determine the IR and PR for the year 2008 because without knowledge of previous years any hospitalisation or riluzole prescription would have wrongly been attributed as first-ever occurrences to the year 2008. Thus, any hospitalisation or riluzole prescription was accepted as a first-ever occurrence just after the exclusion of any such event for the same individual in at least one preceding year.

Prognostic Parameters and Riluzole Effect

To evaluate potential prognostic factors we performed survival analyses, for which patients were stratified by gender, age at diagnosis (dichotomised with the median age at diagnosis as a cut off) and riluzole use. To evaluate a possible time-dependent effect of riluzole therapy we classified patients into five groups according to their therapy ratio, which was defined as the duration of riluzole therapy in days divided by the survival time from diagnosis in days. The duration of riluzole therapy was calculated as the total dosage of prescribed pills divided by the defined daily dose for riluzole (i.e., 100 mg). Survival analyses were then performed for each of the five groups. An evaluation of survival times solely in dependence of the duration of riluzole treatment (without considering therapy ratio) would have biased the results since patients with longer therapy durations will have lived necessarily longer.

Regarding the analysis of riluzole's effect on survival we further accounted for a possible bias due to a delay in the start of riluzole treatment after diagnosis by adjusting for the immortal time bias. Immortal time refers to a span of time in the observation period of a cohort during which the outcome under study could not have occurred. In our study a patient, eventually receiving riluzole, was inevitably immortal before the start of riluzole treatment. Not accounting for this factor would have introduced a survival benefit for exposed patients. To correct for this bias we used a time-varying covariate for riluzole exposure in order to avoid misclassification of exposed patients' survival time before the first prescription as the exposed follow-up time [5]. Other potential confounding factors we adjusted for were gender, age at diagnosis, the total duration of all inpatient stays during the study period and comorbidities. To adjust for comorbidities we applied the Chronic Disease Score (CDS), a validated statistical tool which serves as a proxy for the existence of chronic diseases [6]. A summary weight is calculated representing an individual's burden of chronic disease and predicting mortality [7, 8].

Correcting for Misclassified and Unobserved Cases

The capture-recapture method is commonly used in wildlife surveys but has also become an important tool in human epidemiological studies. Individuals of interest are captured in at least two data sources and the degree of overlap between the data sources is noted. Then, the ratio of individuals recaptured in the second data source to those uniquely captured in the first data source approximates the ratio of those in the second data source to the total population of interest. Such an analysis requires source independence, which means that capturing one individual in the first data source will not affect its capture in the second data source. Any positive interdependence of sources will lead to an underestima-

tion and any negative interdependence of sources to an overestimation of not captured individuals and, thus, the total population of interest.

To account for unobserved cases neither being detected by the hospital discharge database (HDD) or the prescription database (PD) the two-source capture-recapture method was performed [9, 10]. This refers to outpatients never having been hospitalised or prescribed riluzole during the study period. To overcome any possible difference in case ascertainment it was applied separately for different age and gender groups. IR and PR were consequently corrected for this factor.

To estimate the ratio of wrongly coded discharge diagnoses in Austria (misclassification ratio) we evaluated the records of patients discharged from two tertiary referral centres and from four non-tertiary hospitals with an ICD-10 code of G12.2. Cases not fulfilling the El Escorial criteria for definite, probable, possible or suspected ALS were considered being wrongly coded. The coding quality between tertiary and nontertiary hospitals was compared, and, finally, IR and PR were corrected for this ratio.

Statistical Analysis

All variables were analysed using descriptive statistics including mean, median, 95% confidence interval (CI) and interquartile range (IQR). Comparisons between medians were made with the Mann-Whitney U test and between categorical variables with a χ^2 test. For IR and PR 95% CI were calculated assuming a Poisson distribution. Kaplan-Meier analysis and log-rank test were used to assess survival. For the Kaplan-Meier analysis in dependence of riluzole use, the Gehan-Breslow-Wilcoxon test was performed additionally, which emphasises the information at the beginning of the survival curves. A multivariate Cox regression model for non-proportional hazards was used to study the effect of riluzole on ALS survival [11]. Riluzole exposure was expressed as a categorical variable (riluzole use = 1, no riluzole = 0). We adjusted for the following potential confounding factors: gender, age at diagnosis, the total duration of all inpatient stays during the study period and comorbidities (quantified in the CDS). To adjust for immortal time we also used a time-varying covariate for the exposure to riluzole. To further assess whether the effect of riluzole therapy on survival was dependent on the treatment duration we employed Kaplan-Meier analyses for five groups with increasing therapy ratios (group 1: ≤0.2, group 2: 0.21–0.4, group 3: 0.41–0.6, group 4: 0.61–0.8, group 5: ≥0.81). To adjust for the above-mentioned potential confounding factors we performed the Cox proportional hazard regression model using the riluzole therapy ratio as a continuous variable. The Pearson's correlation coefficient was calculated to assess the correlation between riluzole therapy ratios and the duration of riluzole therapy. A p value <0.05 was considered significant (two-sided). Data processing was performed using the statistical package SPSS v20 (IBM Corp. Released 2011).

Results

Incidence and Prevalence of ALS

During the study period 911 individual ALS patients were identified by the two data sources (362 patients captured by the PD and 549 patients captured by the HDD).

Table 1. Estimation of the number of unobserved cases by the two-way capture-recapture analysis

	Observed cases			Capture-recapture analysis		
	HDD	PD	both sources	unobserved	estimated total	95% CI
Incidence	187	91	279	64	621	592–649
Prevalence	433	398	732	254	1,817	1,736–1,903

There were 167, 215 and 175 incident and 441, 534 and 588 prevalent ALS cases in the years 2009, 2010 and 2011. By the capture-recapture method the number of unobserved cases were identified, which resulted in a total of 621 incident and 1,817 prevalent cases in all three years (table 1). After age-standardisation to the corresponding Austrian population (excluding the population below 20 years of age) the average annual incidence was calculated to be 4.20/100,000 person-years (95% CI, 3.72 to 4.70) and the average annual prevalence to be 12.26/100,000 persons (95% CI, 11.44 to 13.14) (online suppl. table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000369813).

To allow a better comparison with previous studies we also performed age-standardisations to the corresponding US Census population. Adjusted to the US 1990 Census population the IR was calculated as 3.48/100,000 person-years (95% CI, 3.39 to 3.56) and the PR as 10.18/100,000 persons (95% CI, 10.03 to 10.33), respectively. Adjusted to the US 2010 Census population the IR was 3.87/100,000 person-years (95% CI, 3.79 to 3.95) and the PR was 11.39/100,000 persons (95% CI, 11.25 to 11.53), respectively (online suppl. table 1).

To correct the HDD for misclassified other neurological disorders we evaluated the inpatient records of 585 patients from six different neurological departments in Austria (395 patients from two tertiary referral centres and 190 patients from four non-tertiary hospitals). In 77 cases (13.2%) the discharge diagnosis of ICD-10 G12.2 (ALS) was considered incorrect after reviewing the medical charts (32 misclassified cases (16.8%) in non-tertiary hospitals and 45 misclassifications (11.4%) in tertiary referral centres). There was no significant difference of the misclassification ratio between tertiary and non-tertiary centres ($p = 0.07$; χ^2 test). None of the misclassified cases was prescribed riluzole. Taking the misclassification ratio for the identification of ALS cases by the HDD (but not by the PD) into account the IR and PR may have been overestimated by 5.9%. Applying this correction the IR

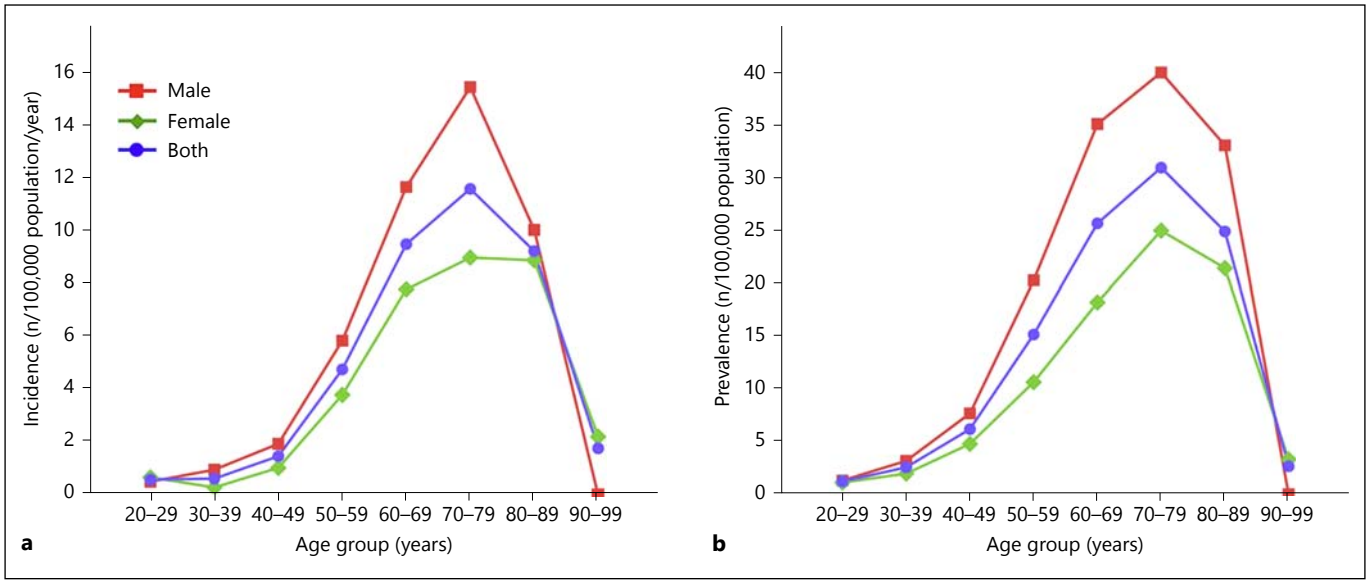


Fig. 1. Age- and gender-specific incidence rates (**a**) and prevalence ratios (**b**).

was calculated as 3.95/100,000 person-years (95% CI, 3.50 to 4.42) and the PR as 11.54/100,000 persons (95% CI, 10.77 to 12.36), respectively. After including the population below 20 years of age (20.8% of the total Austrian population in the years 2009, 2010 and 2011) the IR was calculated as 3.13/100,000 person-years (95% CI, 2.77 to 3.50) and the PR as 9.14/100,000 persons (95% CI, 8.53 to 9.79).

Gender Distribution in ALS

In both sexes IR and PR increased with age reaching their maximum in the seventh decade and decreasing again thereafter (fig. 1; online suppl. table 2a and b). The median age at diagnosis was significantly higher in women than in men (68.0 and 64.1 years, respectively). The IR and PR were higher for men than for women in all but the last decade. Over all decades, the male-to-female crude IR ratio was 1.31 and the male-to-female crude PR ratio was 1.50. Although there was the impression of a continuous decline of the male-to-female IR ratios with rising age (fig. 2), this difference was not significant.

Survival Time and Prognostic Factors in ALS

Of the 911 individually identified ALS patients 473 (51.9%) deceased during the study period (table 2). Median overall survival from diagnosis was 676 days (95% CI, 591 to 761). Twenty-five patients captured by the HDD died during their initial inpatient stay and, thus, were excluded from the survival analysis. A younger age at diagnosis (≤65 years) was clearly associated with a longer survival (with a 17 and 25% higher cumulative survival in the younger age group at 12 and 24 months after diagnosis, respectively). With the survival curves of men and women not being significantly different we could find no evidence for an influence of gender on survival (fig. 3a; table 3). Although women were significantly older than men at the time of death (71.0 and 68.0, respectively) this corresponded to women's higher age at diagnosis.

Survival in dependence of riluzole therapy showed a more complex relationship. As can be seen in the Kaplan-Meier curves there was a beneficial effect of riluzole treatment on survival for about 6 months after diagnosis with a gradual reversal of its effect thereafter (fig. 3c). At 540 days after diagnosis the survival curves crossed each other with the riluzole-naive group showing a better prognosis in the following time period. Survival was 15% higher in the riluzole group than in the riluzole-naive group at 6 months after diagnosis but 14% lower at 48 months after diagnosis (online suppl. table 3).

Correspondingly, the unadjusted hazard ratio (HR) of mortality for riluzole therapy increased over time suggesting a beneficial effect just until 230 days after diagnosis (HR <1) and a detrimental effect thereafter (HR >1) (fig. 4a). After adjusting for potentially confounding factors the overall picture did not change. Riluzole therapy

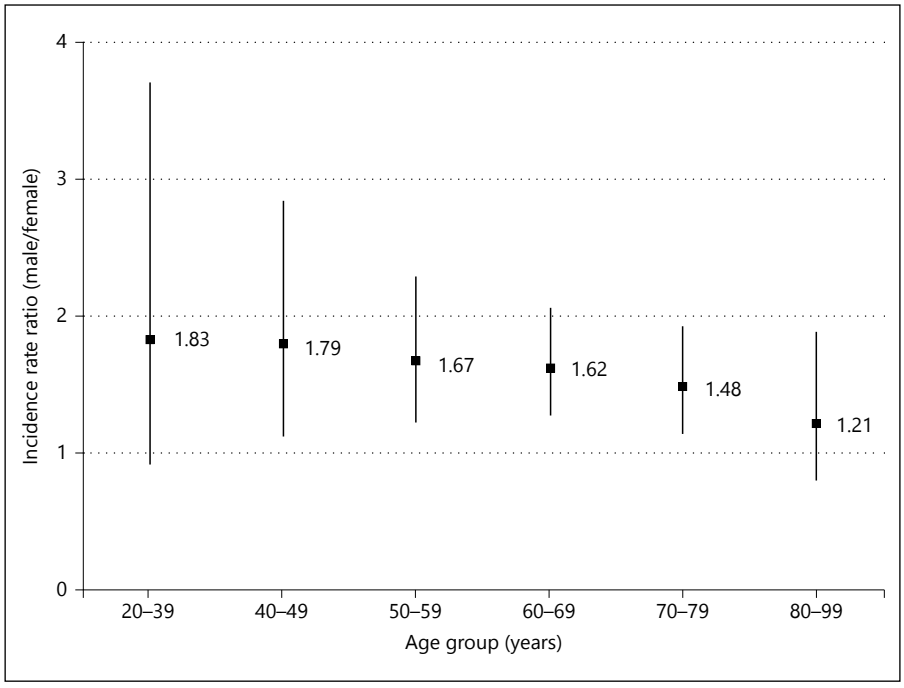


Fig. 2. Incidence rate ratios of men and women. The IR ratios show a continuous decline with increasing age. Because of the low case numbers in the second/third and eighth/ninth age decade, respectively, ALS patients of those age groups were put together.

Table 2. Characteristics of 911 ALS patients in Austria

	Overall	PD	HDD	p value
Number of ALS patients (%)	911	362 (39.7)	549 (60.3)	
Age at the time of diagnosis, years				
Median (IQR)	66.0 (56.8–73.2)	65.1 (56.0–71.9)	67.0 (57.2–74.8)	0.07
Mean (95% CI)	64.5 (63.7–65.3)	63.9 (62.6–65.1)	64.9 (63.8–66.0)	
Deceased patients (%)	473 (51.9)	185 (51.1)	288 (52.5)	0.69
Age at time of death, years				
Median (IQR)	69.0 (62.0–76.0)	68.0 (62.0–75.0)	70.0 (62.0–78.0)	0.13
Mean (95% CI)	68.2 (67.2–69.3)	67.6 (66.0–69.2)	68.6 (67.2–70.0)	
Duration of riluzole use, days				
Median (IQR)	297 (140–588)	364 (141–672)	252 (140–448)	0.001
Mean (95% CI)	398 (370–427)	463 (418–509)	325 (295–355)	
Median delay of riluzole start from diagnosis, days				
Median (IQR)	0.0 (0.0–3.0)	0.00 (0.00–0.00)	4.0 (1.0–21.0)	<0.001
Mean (95% CI)	16.4 (9.9–22.9)	0.00 (0.00–0.00)	34.9 (21.4–48.4)	
Median riluzole therapy ratio				
Median (IQR)	0.34 (0.00–0.91)	0.70 (0.08–0.97)	0.00 (0.00–0.79)	<0.001
Mean (95% CI)	0.42 (0.40–0.45)	0.57 (0.53–0.61)	0.33 (0.29–0.36)	
Duration of inpatient stays, days				
Median (IQR)	9.0 (1.0–23.0)	0.0 (0.0–10.0)	15.0 (7.0–30.0)	<0.001
Mean (95% CI)	17.8 (16.1–19.5)	8.8 (6.8–10.7)	23.7 (21.4–26.1)	
CDS				
Median (IQR)	0.0 (0.0–3.0)	1.0 (0.0–4.0)	0.0 (0.0–2.0)	<0.001
Mean (95% CI)	1.9 (1.7–2.1)	2.5 (2.2–2.8)	1.4 (1.2–1.7)	
Survival time (days)				
Median (IQR)	676 (591–761)	756 (608–904)	646 (538–754)	0.10
Mean (95% CI)	843 (797–889)	886 (815–956)	816 (755–876)	

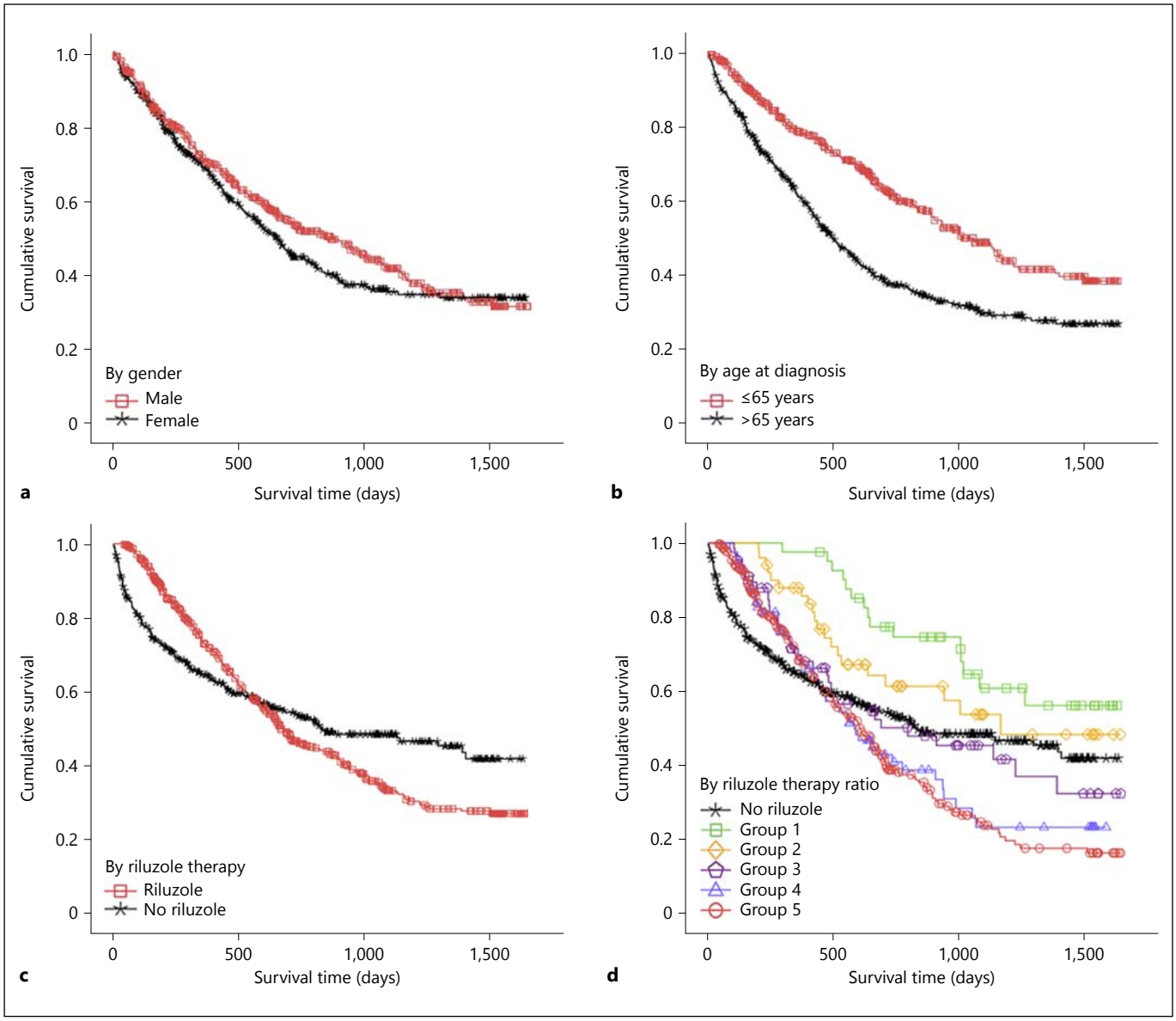
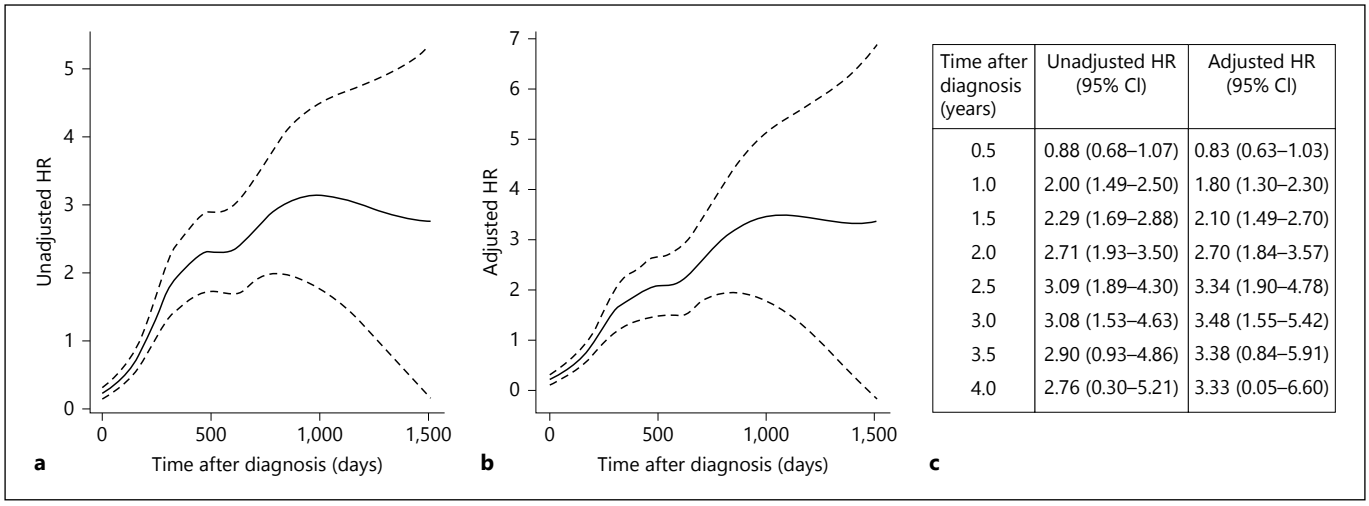


Fig. 3. Kaplan-Meier (KM) survival curves of patients with amyotrophic lateral sclerosis. **a** KM curve according to gender. **b** KM curve according to age at diagnosis (with the median age at diagnosis as the cut off). **c** KM curve according to riluzole use. There was no significant difference using the log-rank test (p = 0.61) but using the Gehan-Breslow-Wilcoxon test (p = 0.006). **d** KM curve according to five groups of increasing riluzole therapy ratios: group 1: ≤0.2, group 2: 0.21–0.4, group 3: 0.41–0.6, group 4: 0.61–0.8, group 5: ≥0.81. Survival improved with shorter riluzole therapy ratios (survival was significantly longer in group 1 and significantly shorter in group 5 compared to ALS patients without riluzole). Twenty-five patients died during their initial hospitalisation and, thus, were excluded from the survival analyses (n = 886).

was associated with a better survival for about 180 days after diagnosis (HR <1) and a poorer survival thereafter (HR >1) (fig. 4b).

We next wondered whether the effect of riluzole treatment might in some way be time-dependent (i.e. change with the duration of treatment). To evaluate this possibility we stratified patients into five groups defined by their therapy ratios (i.e., duration of riluzole therapy divided by the survival time). Patients without any riluzole treatment were given a therapy ratio of 0 and assigned to a sixth group. There was a significant correlation between therapy ratios and the duration of riluzole therapy (p <



Time after diagnosis (years)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
0.5	0.88 (0.68–1.07)	0.83 (0.63–1.03)
1.0	2.00 (1.49–2.50)	1.80 (1.30–2.30)
1.5	2.29 (1.69–2.88)	2.10 (1.49–2.70)
2.0	2.71 (1.93–3.50)	2.70 (1.84–3.57)
2.5	3.09 (1.89–4.30)	3.34 (1.90–4.78)
3.0	3.08 (1.53–4.63)	3.48 (1.55–5.42)
3.5	2.90 (0.93–4.86)	3.38 (0.84–5.91)
4.0	2.76 (0.30–5.21)	3.33 (0.05–6.60)

c

Fig. 4. Multivariate Cox regression analysis for non-proportional hazards comparing ALS patients with and without riluzole. A time-varying covariate for riluzole exposure was used to adjust for immortal time (defining exposed patients' survival time before the first riluzole prescription as the unexposed follow-up time). **a** Unadjusted time-dependent HR increasing over time with values <1 until 230 days after diagnosis and reaching its peak of 3.07 at 980 days after diagnosis. **b** Time-dependent hazard ratio adjusted for gender, age at diagnosis, total duration of inpatient stays and the chronic disease score. The HR increased over time passing the threshold of 1 at 180 days after diagnosis and reaching its peak of 3.44 at 1,070 days after diagnosis. **c** Time-dependent unadjusted and adjusted hazard ratios corresponding to plot **a** and **b**.

Table 3. Kaplan-Meier analysis of survival times (days)

By age at diagnosis	Ratio ≤65/>65 years	Survival time, days		p value
		≤65 years (95% CI)	>65 years (95% CI)	
Overall	436/450	1,015 (868–1162)	495 (425–565)	<0.0001
Men	265/208	1,065 (907–1223)	489 (399–579)	<0.0001
Women	171/242	1,003 (890–1,116)[a]	719 (635–802)[a]	<0.0001
By gender	**Male/female**	**Male (95% CI)**	**Female (95% CI)**	**p value**
Overall	473/413	860 (691–1,029)	641 (563–719)	0.14
Riluzole	280/248	815 (637–993)	636 (564–708)	0.34
≤65 years	159/107	1,004 (881–1,127)	760 (415–1,105)	0.99
>65 years	121/141	479 (377–581)	530 (452–608)	0.94
No riluzole	193/165	1,142 (711–1573)	786 (439–1,133)	0.16
≤65 years	106/64	1,050 (922–1,179)[a]	1,027 (837–1,216)[a]	0.46
>65 years	87/101	564 (389–739)	403 (248–558)	0.68
By riluzole prescription	**User/non-user**	**User (95% CI)**	**Non-user (95% CI)**	**p value**
Overall	528/358	666 (578–754)	829 (449–1,209)	0.61 0.006[b]
Riluzole therapy ratio groups				
Group 1 (≤0.2)	41/358	1,255 (1,105–1,404)[a]	908 (829–987)[a]	0.010
Group 2 (0.21–0.4)	50/358	1,089 (910–1,268)[a]	908 (829–987)[a]	0.09
Group 3 (0.41–0.6)	67/358	794 (240–1,348)	829 (449–1,209)	0.77
Group 4 (0.61–0.8)	82/358	582 (433–731)	829 (449–1,209)	0.28
Group 5 (≥0.81)	288/358	601 (518–684)	829 (449–1,209)	0.026

[a] Mean was used (instead of median), because cumulative survival was >0.5 during the study period.
[b] Gehan-Breslow-Wilcoxon test was used (instead of the log-rank test), which gives more weight to deaths at early time points.

0.0001; R = 0.36). Interestingly, this analysis clearly demonstrated that lower therapy ratios and thus shorter riluzole treatment periods were associated with longer survival times than longer treatment periods (fig. 3d and online suppl. table 4). After adjusting for potential confounding factors, as above, higher therapy ratios were still associated with poorer survival (HR 2.98, 95% CI 1.96–4.55; $p < 0.0001$).

Discussion

This is the first epidemiological study on ALS in Austria using a comprehensive hospital discharge and prescription registry of more than 5 million people. The registry covers the majority of the total Austrian population and can thus be taken as representative for the whole country.

The incidence and prevalence of ALS in this study are on the upper end of the wide range discussed in the literature and comparable to other recent reports [12–14]. Data from previous studies are heterogeneous with a variation of the IR between 0.3 and 3.6/100,000 person-years and of the PR between 1.0 and 11.3/100,000 population [15–18]. Methodological differences of the studies as well as a true variation of ALS frequency have been discussed to contribute to the disparity of the rates [15, 19].

The application of the capture-recapture method, which corrects for an incomplete case ascertainment by estimating the number of unobserved cases, has contributed to the high IR and PR reported in our study. The proportion of unobserved cases in epidemiological studies on ALS has previously been estimated to be as high as 28% [14, 20]. Not accounting for such an important bias is therefore likely to lead to a substantial underestimation of the true IR and PR [10, 21]. In our study 10.3% of the incident and 14.0% of the prevalent cases from 2009 to 2011 were determined by the use of the capture-recapture method. This approach will, to a large extent, have captured ALS patients without any hospitalisation or riluzole therapy, who would have otherwise been missed. Another reason for our high IR and PR could be seen in the inclusion of suspected or possible ALS cases.

In accordance with previous studies, IR and PR increased with age reaching their maximum in the eight decade and decreased again thereafter [12–14]. The decline of IR and PR after the age of 80 years could theoretically be attributed to problems with case ascertainment [22]. Difficult access to medical care centres, comorbidities and a more severe disease course leading to earlier death would result in more unobserved cases in the very old age groups. We corrected for this potential error by applying the capture-recapture method separately for each age and gender group. Therefore, we are confident that the susceptibility to ALS indeed declines after the peak age as suggested before [14, 22].

The use of automated hospital discharge and prescription databases harbours a number of potential risks and pitfalls [23]. (i) The data in our study were maintained primarily for administrative and financial purposes and lacked clinical details. The data from the hospital discharge registry were affected by errors due to diagnostic misclassification. We ascertained a false positive coding rate of 13.2% by evaluating discharge diagnoses in several tertiary and non-tertiary medical centres in Austria and were thus able to correct the IR and PR for positive misclassifications. Negative misclassifications (patients with ALS not being given the correct ICD-code) are not likely to bias our epidemiological data substantially, since we also used riluzole prescription data and applied the capture-recapture method correcting for false negative cases from the HDD. (ii) Another potential bias resulting from the use of the HDD and PD is that our analysis was not strictly population-based as not all patients were recorded in these databases, for example, – ALS patients managed exclusively as outpatients and not receiving riluzole due to mild symptoms or due to a too advanced disease stage. This could have introduced a selection bias affecting our survival analyses. (iii) Due to the lack of clinical data in the registries we could not completely eliminate another potential selection bias associated with the HDD. Preferential admissions of patients with advanced disease or due to complications would presumably be associated with a shorter survival time, whereas diagnostic admissions at early stages should be associated with a longer survival. To increase the likelihood that any hospitalisation with a main discharge diagnosis for ALS was the first-ever occurrence (and thus for diagnostic reasons) every patient was required to have had at least a 12 months event-free observation period without any prior riluzole prescription or ALS-discharge diagnosis. Those 25 patients who died during their first inpatient stay (presumably due to complications) were excluded from the survival analyses. Additionally, we adjusted the survival analyses for the total duration of all hospitalisations in order to mitigate this selection bias. (iv) The correct identification of patients exposed to a risk modifying medication (riluzole) is arguably another problematic issue in survival analyses when using administrative databases. The used prescription registry

lacked information on the use of over-the-counter drugs. However, since riluzole is available only on prescription in Austria, which invariably involves the insurance system, we are confident to have captured all patients on riluzole.

We observed higher IR and PR in men than in women. The reason for the well-known higher susceptibility of men to ALS is still a matter of contention. Based on some studies, a beneficial effect of endogenous female reproductive hormones has been proposed though this has been contradicted by other results [24–26]. If female sex hormones really exerted a protective influence one might expect to find a higher susceptibility to ALS in women after menopause. Yet, we could not find a significant difference in the male-to-female IR ratios between the pre- and post-menopausal age range. Our analysis does therefore not support a role of female sex hormones to ALS susceptibility or survival. This is in accordance with one other recent observational study [14]. Another explanation for the higher IR and PR in men could be that testosterone is a risk factor. This is possible, although testosterone is usually discussed as having a beneficial and not detrimental effect on motor neurons [27]. Alternatively, our data could be the consequence of differences in case ascertainment between men and women as previously discussed in the literature. This view is supported by recent findings of a trend towards more equal gender ratios [22, 28].

Analysing survival in dependence of riluzole treatment revealed a beneficial effect of the drug for the initial 6 months of therapy only, with a 15% reduction in mortality at 6 months. At approximately 18 months after diagnosis (and start of therapy) the survival curves of riluzole-treated and untreated patients crossed with untreated patients showing an apparently better survival thereafter. This observation is supported and more clearly illustrated by an analysis of how the hazard ratio of mortality in riluzole users changes over time. After adjustment for potential confounding factors a beneficial effect of riluzole therapy lasted only 180 days with an increase in the hazard ratio thereafter. To illuminate this apparent time-dependent effect of riluzole on survival further we analysed survival in dependence of riluzole therapy ratios as a measure for the treatment duration. We used this ratio instead of simply the duration of riluzole therapy because the latter could have introduced a bias with longer surviving patients resulting in longer treatment periods. This analysis was not influenced by patients without riluzole and was therefore not affected by a hidden selection bias between riluzole users and non-users. Confirming the above observations we detected a significant association of shorter riluzole treatment periods with longer survival times.

Interestingly, this effect does not seem to be a specific peculiarity of our survey as similar crossings of Kaplan-Meier curves at similar time points (ranging from 11 to 26 months) were published (though not commented on) by several other retrospective and prospective observational studies with well phenotyped ALS patients [4, 29–31]. An underlying true biology must, therefore, be considered. A reasonable interpretation of the data could be that, at least on a population level, riluzole's effect on survival diminishes over time and is lost approximately 6 months after starting treatment. Thus, it could be speculated that riluzole is more effective in rapidly worsening patients or just in certain stages of the disease. Further studies are needed to evaluate the long-term effect of riluzole in ALS patients.

Acknowledgments

We thank the Regional sickness funds of the counties Burgenland (BGKK), Vienna (WGKK), Lower Austria (NÖGKK), Upper Austria (OÖGKK), Carinthia (KGKK), Styria (StGKK), Salzburg (SGKK), Tirol (TGKK) and Vorarlberg (VGKK) for the provision of the data.

Funding

No external funding was obtained for this study.

Disclosure Statement

All authors state that there are no conflicts of interest to declare.

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