J Neurol (2017) 264:749–757
DOI 10.1007/s00415-017-8413-3

ORIGINAL COMMUNICATION

Epidemiology of amyotrophic lateral sclerosis in Southern Germany

Angela Rosenbohm[1] · Raphael S. Peter[2] · Siegfried Erhardt[2] · Dorothée Lulé[1] · Dietrich Rothenbacher[2] · Albert C. Ludolph[1] · Gabriele Nagel[2] · The ALS Registry Study Group

Received: 12 October 2016 / Revised: 24 January 2017 / Accepted: 6 February 2017 / Published online: 20 February 2017

Abstract The objective of this study is to determine the current distribution of clinical phenotypes and to estimate future trends of ALS incidence in Western societies. We report on a clinical-epidemiological registry with a capture–recapture rate of >80% and population-based case–control study in ALS patients in South Western Germany. 1163 incidents of ALS were registered. Clinical and neuropsychological data were prospectively collected from 699 cases. The mean age at onset was 66.6 (SD = 11.6) years in prospective cases ($N = 699$). The site of onset was more frequently bulbar (34.1%) than lumbosacral (30.7%), cervical (27.0%), or thoracic (3.1%). Cognitive deficits (ranging from 27.5 to 42.1%, depending on the screening instrument) and behavioral changes (29%) were frequently detected. The incidence rate dropped markedly after 79 years of age, and bulbar onset as well as cognitive impairment were more frequent in ALS cases >75 years. The mean survival time of ALS cases from first paresis was 31 months. The age-standardized incidence rate (ASR) of ALS in 2012/2013 was found to be 2.4 (95% CI 2.2–2.7) per 100,000 person-years (resulting in an ASR of 3.1/100,000 with 100% coverage). Based on the predicted age distribution of the German population, the incidence of ALS was estimated to be 4.5/100,000 for men and 3.3/100,000 for women in the year 2050. ALS prevalence will rise to about 9.2–9.8/100,000 person-years in Germany in 2050. An increased proportion of patients with bulbar onset and/or cognitive deficits can be used as basic epidemiologic data on ALS for future health care decisions.

Keywords Amyotrophic lateral sclerosis · Registry · Aging · Cognitive impairment

Introduction

ALS is the most frequent adult-onset motor neuron disease, with a typical onset after 60 years of age, and disease progression leading to death, mostly by respiratory insufficiency within 3–5 years after onset. Thus, ALS is characterized by a high morbidity and high case-fatality rate, an urgent need of palliative care management, and intensive use of medical services [1]. Due to severity of symptoms, the lack of an efficient treatment, and relentless progression, ALS has a devastating impact on patients, their families, caretakers, and the society.

Over the past years, our understanding of the ALS pathomechanisms has greatly increased, with the identification of a number of causative mutations and the recognition of the sequential spreading pattern of clinical symptoms which is thought to mirror the patho-anatomical spreading of pTDP43 protein pathology [2, 3]. This new understanding resulted in revised classification criteria [4]. ALS is characterized by heterogeneous clinical phenotypes, including varying age and sites of onset, rates of progression of motor symptoms, as well as an occurrence of cognitive impairment related to the dysfunction of the

The members of the ALS registry Study Group are listed in Acknowledgements.

Electronic supplementary material The online version of this article (doi:10.1007/s00415-017-8413-3) contains supplementary material, which is available to authorized users.

✉ Albert C. Ludolph
albert.ludolph@rku.de

[1] Department of Neurology, Ulm University, Oberer Eselsberg 45, 89081 Ulm, Germany

[2] Institute for Epidemiology and Medical Biometry, Ulm University, Helmholtzstr. 22, 89081 Ulm, Germany

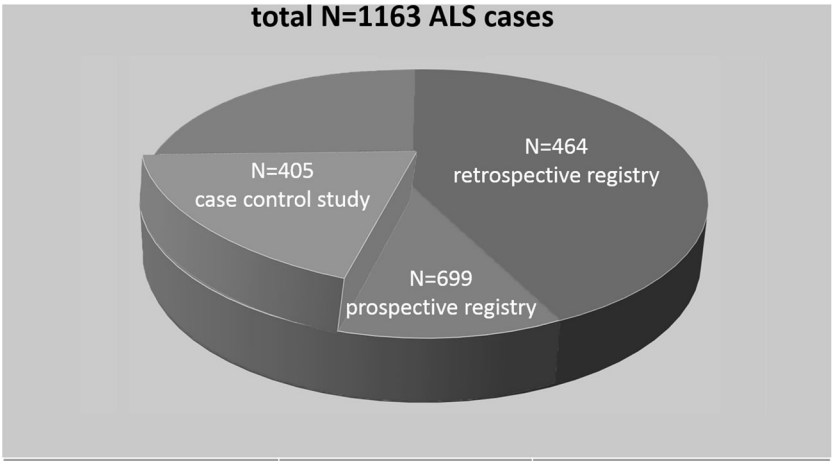
frontal cortex. Importantly, this clinical heterogeneity appears to influence prognosis, with older age or a bulbar site of onset associated with a worse prognosis. Symptoms of frontal dysfunction may also be risk factors for rapid progression, since ALS registries in USA and Europe have reported cognitive changes to predict ALS progression [5, 6]. However, the screening of cognitive profiles is a time-consuming task. Despite it has a potential high prognostic and clinical value, it remains scarcely reported.

In Western societies, characterized by progressive aging of the population, the incidence of ALS is expected to consecutively increase. Furthermore, the aging of the population might alter the pattern of clinical and cognitive phenotypes of ALS patients towards phenotypes associated with older age. In 2010, we initiated the ALS Registry Swabia in South Western Germany [7], which is now among the largest European ALS registries [8]. A capture–recapture rate of 81.1% indicates a high level of completeness, mandatory for predicting reliable future incidence rates [9]. The objective of this study was to characterize the core epidemiologic and clinical data of ALS in Southern Germany and to predict how the epidemiology of ALS will be altered by 2050, if current demographic trends are maintained.

Methods

The ALS Registry Swabia has been described previously [7, 9]. From 01.10.2010 to 31.12.2014, the ALS data ($N = 699$) were collected prospectively (Fig. 1) in the catchment area of 36,386 km^2 with 8,478,200 inhabitants (in 2009 according to the Federal Statistical Office). In 2012, about 12% of the population was made up of immigrants in Southwest Germany, of which about 40% came from other European countries (Statistics Baden Württemberg http://www.baden-wuerttemberg.de/de/unser-land/land-und-leute/bevoelkerung, accessed 11 Jan 2017). Regional collaboration partners (neurologists at currently 41 inpatient and outpatient clinics) identified ALS patients, obtained written informed consent, and then notified the ALS registry at Ulm University. Duplications of records were excluded within the database. Completeness is estimated to be 81.1% in the catchment area in a capture–recapture analysis without any statutory reporting requirement. To deal with the double reporting of ALS cases, ascertainment was estimated by five data sources (registry, university clinics, clinical centers, small hospitals, and private neurological practice doctors) and estimated with log-linear model approach. The percentage of missing ALS cases in the target population was estimated to be 18.9% [9]. All participants underwent full neurological and neurophysiological examination performed by the collaborating neurologists. A standardized data collection sheet was used to record the patients' demographic data, clinical history, date of onset (first paresis), date of diagnosis, site of onset, disease phenotype, and results of the diagnostic assessment (electromyography, laboratory values, MRI). If possible, interviews were conducted during individual home visits.

We reviewed the medical records of all prospective ALS cases aged 18 years and older; the diagnosis was verified and classified according to the original El Escorial diagnostic criteria (EEC) [10, 11]. Clinical phenotypes of motor neuron diseases were defined as lower motor neuron predominant (PLMD) (second motor neuron involvement in at



design	observation period	Age at diagnosis (years), mean (std)
retrospective	01.10.2008 - 30.09.2010	65.5 (± 12.1)
prospective	01.10.2010 - 31.12.2014	67.2 (± 11.6)
case control	01.10.2010 - 31.12.2014	65.5 (± 11.0)

Fig. 1 Overview of ALS cases in the ALS registry Swabia diagnosed between 10/2008 and 12/2014 and the embedded population-based case–control study

least two body regions) and upper motor neuron predominant (PUMN) (primary lateral sclerosis cases with only minor signs of second motor neuron involvement). Patients with PUMN and PLMN were also prospectively included in the registry. ALS mimic syndromes like spinal muscular atrophy, spinobulbar muscular atrophy (Kennedýs disease), cervical myelopathy, inclusion body myositis, and multifocal motor neuropathy were excluded.

Based on the prospective registry, a case–control study ($N = 405$ ALS cases) has been implemented [12]. All living patients in the target population had the chance to participate in the case–control design and were included if they wished. Two age- and sex-matched controls for each patient were randomly sampled from the same geographic area. In this study, we focus on data of ALS patients prospectively recruited in the registry and ALS patients with comprehensive neuropsychological testing recruited in the case–control study.

In addition, prospectively registered ALS patients were actively followed-up by interview on an annual basis. For all cases, vital status was checked annually by record linkage with the state of Baden-Wuerrtemberg central registration database and requests in the regional registration offices. Censoring date for the survival analyses was June 18, 2015.

Full ethical approvals of the Ethical Committee of the University of Ulm (No. 11/10), the Medical Association of the state of Baden-Wuerttemberg (Landesaerztekammer, No. B-F-2010-062), and the Medical Association of the state of Bayern (No. 7/11300) were obtained.

Neuropsychological screening

$N = 348$ ALS patients (of the 405 patients included in the embedded case–control study) underwent cognitive screening ($N = 57$ were physically incapable to perform neuropsychological tests or had to be excluded due to incomplete tests). $N = 214$ were screened with the Montreal Cognitive Assessment (MOCA) and the Frontal Assessment Battery (FAB). The Edinburgh Cognitive and Behavioral ALS Screen (ECAS) was established in 2013, and thereafter, this ALS-specific neuropsychological screening tool was used in $N = 138$ ALS cases; 4 cases involved in MOCA, FAB, and ECAS. Cognitive impairment was defined as total scores below the standardized cut-off scores (for MOCA <26 points [13]; for FAB $\leq$12 points [14]; for ECAS, age- and education-adjusted scores were used according to Lulé et al. [15]). For FAB and MOCA, patients with motor impairment received an adjusted total score (total score achieved divided by total score possible to achieve). As ECAS is adapted to motor impairments, no such adjusted score had to be provided. In addition, behavioral data were acquired for $N = 110$ patients with ECAS interviews of caregivers (all first-degree relatives).

Statistical analysis

Crude and age-standardized incidence rates (ASR) were calculated using the European standard population for the year 2013. We calculated rates for the complete years 2012 and 2014 only. Corresponding confidence intervals were based on normal approximation. The prevalence rate was estimated as product of the incidence rate and mean survival. Forecasts of age-standardized incidence rates by 2050 were based on population projections for the Federal Republic of Germany [16] and the observed cumulated case count within the ALS Registry Swabia, from 2012 to 2013. Prediction models were calculated for two scenarios of demographic aging, one with high increase (scenario 1) and the other with moderate increase of the older population (scenario 2).

Statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA) and IBM® SPSS Version 21.0. Categorical data are described as absolute frequencies and ratios. The Kaplan–Meier method was used to calculate survival probabilities. All statistical tests were two-sided and the significance level was set at $p = 0.05$.

Results

Clinical phenotype

We analyzed data from 699 registered ALS patients after the first 6 years of observation in the study region (Fig. 1). As expected, ALS was more prevalent in men than in women over the whole observation period (ratio 1.24:1), in the prospective arm of the registry (ratio 1.33:1) as well as in the subpopulation included in the case–control study (ratio 1.35:1). Information on the onset and the diagnosis during the prospective phase could be collected in $N = 648$ patients. Bulbar ($N = 221$; 34.1%) was more common than lumbosacral ($N = 199$; 30.7%), cervical ($N = 175$, 27.0%), or thoracic ($N = 20$; 3.1%) onset (Table 1) with similar distribution in the case–control sample. In the remaining patients (5.1%), onset could not be clearly defined retrospectively. The mean duration from onset to diagnosis was 6.8 (SD = 6.1) months. 15.2% had predominant lower motor neuron disease and 2.7% primary lateral sclerosis (data not shown).

Neuropsychological screening

In the cognitive screening tests performed in the case–control study ($N = 347$), 27.5% were cognitively impaired

Table 1 Characteristics of ALS cases in the prospective part of the ALS registry Swabia, in Southwest Germany (10/2010–12/2014) and the embedded case–control study

	Prospective registry	Case–control study
N	663[a]	405
Age at onset (years), mean (std)	66.6 (±11.6)	64.9 (±11.0)
Male ($N = 379$)	66.0 (±12.1)	64.2 (±11.3)
Female ($N = 284$)	67.5 (±10.8)	66.0 (±10.4)
Cognitively impaired ($N = 133$)[b]		68.1 (±10.3)
Male ($N = 83$)		67.3 (±10.9)
Female ($N = 50$)		69.5 (±9.0)
Without cognitive impairment ($N = 215$)[b]		63.0 (±10.4)
Male ($N = 125$)		62.7 (±11.1)
Female ($N = 90$)		63.4 (±9.6)
Onset site, *N* (%)	648	401
Bulbar	221 (34.1)	126 (31.4)
Cervical	175 (27.0)	113 (28.2)
Thoracic	20 (3.1)	15 (3.7)
Lumbar	199 (30.7)	129 (32.2)
Uncertain	33 (5.1)	18 (4.5)
Revised El Escorial criteria, *N* (%)	661	405
Clinically suspected	123 (18.6)	69 (17.0)
Clinically possible	87 (13.2)	48 (11.9)
Clinically probable	211 (31.9)	140 (34.6)
Clinically probable—lab.-supported	149 (22.5)	101 (24.9)
Clinically definite	91 (13.8)	47 (11.6)
Diagnostic delay (months), mean (std)	6.8 (±6.1)	6.5 (±5.9)
Survival from diagnosis (months), mean (std)	25.1 (±0.77)	27.7 (±0.94)
Survival from onset (months), mean (std)	31.0 (±0.72)	33.5 (±0.88)
ALSFRS score, mean (std)		37.2 (±7.4)
Male ($N = 232$)		37.8 (±7.5)
Female ($N = 169$)		36.4 (±7.2)
Family history of ALS/FTLD, *N* (%)	28 (4.2)	17 (4.2)

Sum may not always add up to total because of missing values for items

[a] Of 699 prospective cases, information on onset and diagnosis was available for 663

[b] Neuropsychological screening was available for 348 patients within the case–control study

when applying cutoffs of ECAS, 42.1% with MOCA, and 12.4% with FAB.

According to the diagnostic evaluation of the corresponding neurologists, 3.1% of prospectively observed ALS patients fulfilled the criteria of behavioral frontotemporal lobar degeneration (bvFTD) and an additional 1.6% was diagnosed with suspected FTD. For those with behavioral data ($N = 110$), 32 patients (29%) exhibited behavioral changes. Ten patients (9%) were abnormal in more than three domains and, therefore, fulfilled the criteria of a behavioral variant of FTD. Apathy was the most common behavioral change ($N = 19$), followed by loss of compassion ($N = 14$), stereotyped behavior ($N = 8$), hyperorality ($N = 7$), and loss of empathy ($N = 5$).

During the median follow-up (from date of onset) of 37.0 months of 646 patients, 392 (61%) died. Overall, the 1-year case-fatality rate from diagnosis was 28% (95% CI 25–32%). Concerning the case-fatality by site of onset, bulbar onset showed a worse prognosis than cervical onset (p value 0.0002, log rank test) (Fig. 2). Prognosis of patients with criteria defining higher levels of certainty (definite or probable ALS) was worse compared to lower levels of certainty (suspected or possible) (p value <0.0001). Patients with cognitive impairment also had a worse prognosis than cognitively normal individuals (p value 0.0065).

Epidemiology

During the prospective phase, mean onset age of ALS was 66.6 (±11.6) years, with a peak of the age-adjusted incidence between 75 and 79 years (Fig. 3, panel A,

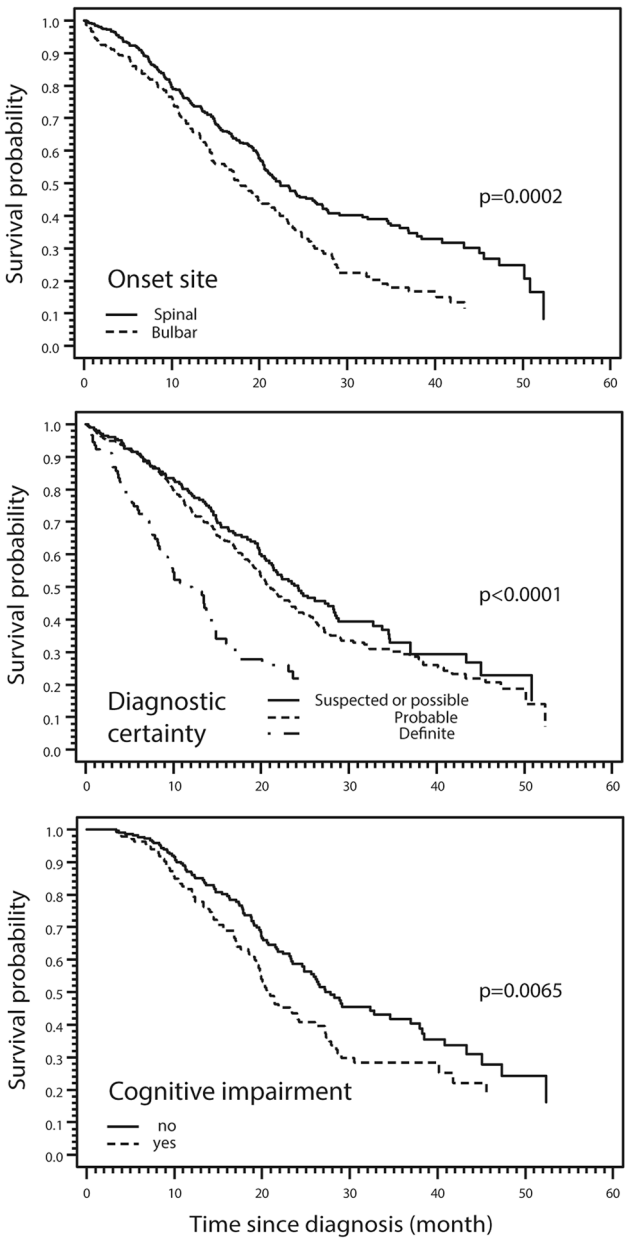


Fig. 2 Kaplan–Meier curves to depict prognosis of ALS after diagnosis in the prospective part of the ALS registry Swabia by common onset sites ($N = 605$) and diagnostic certainty ($N = 645$) as well as cognitive impairment ($N = 348$) in screening tests

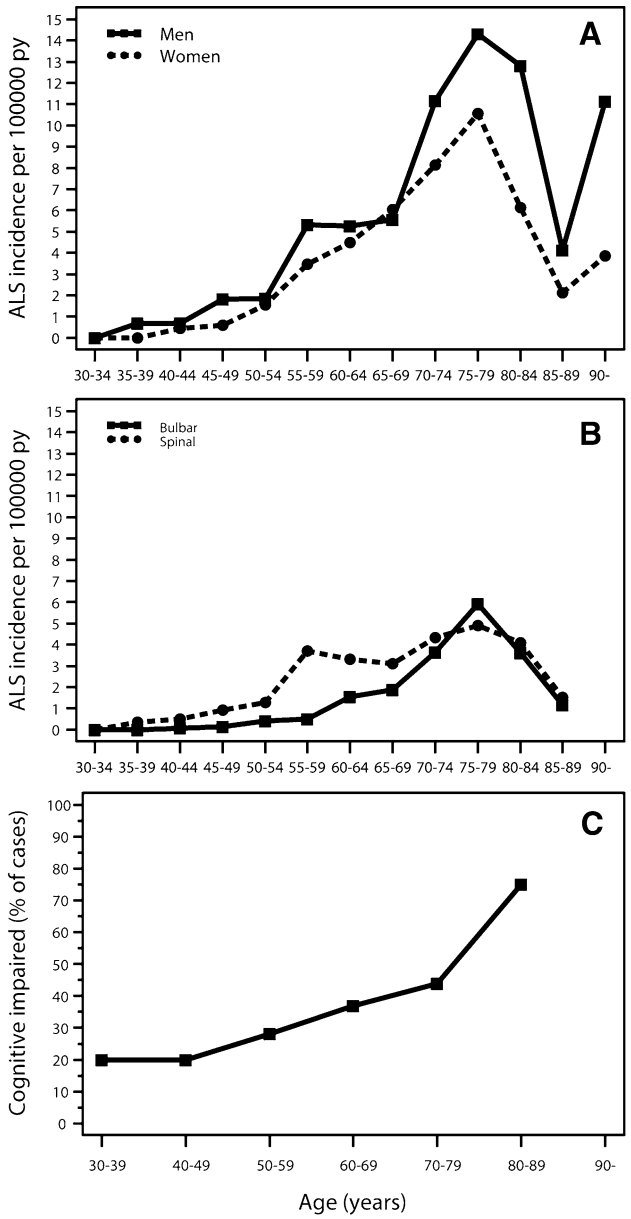


Fig. 3 Observed ALS incidence by age at diagnosis in the prospective part (2012/2013, $N = 399$) of the ALS registry Swabia. Panel **a** by sex, panel **b** by onset type of ALS, and panel **c** proportion of cognitive impaired by age

supplemental Table 2). The mean age of onset was similar in men (66.0 years) and women (67.5 years). Incidence rates markedly decreased in the age groups over 79 years. Bulbar onset has its peak in the older age groups >75 years and showed a more pronounced age-related pattern than spinal onset (Fig. 3, panel B). The percentage of cognitive impairment also rose after 70 years (Fig. 3, panel C).

The ASR was 2.5 (95% CI 2.3–2.8) in the period 2009/10 and 2.4 (95% CI 2.2–2.7) per 100,000 person-years (PY) in the period 2012/2013. The comparison of ASRs at county level revealed two areas with an incidence of over 4 per 100,000 PY in 2012/2013 (supplemental Fig. 5). Considering the coverage of 81.1% of our registry, this results in an expected age-adjusted incidence rate in Swabia of 3.1/100,000. With a mean survival of 31.0 months (from date of onset), the prevalence of ALS is about 8 per 100,000 person-years, meaning that about 6400 patients with ALS are currently living in Germany.

Based on extrapolation algorithms for the year 2050 [16], the predicted incidence rate for moderate demographic change (scenario 1) was estimated with 3.7 (95%

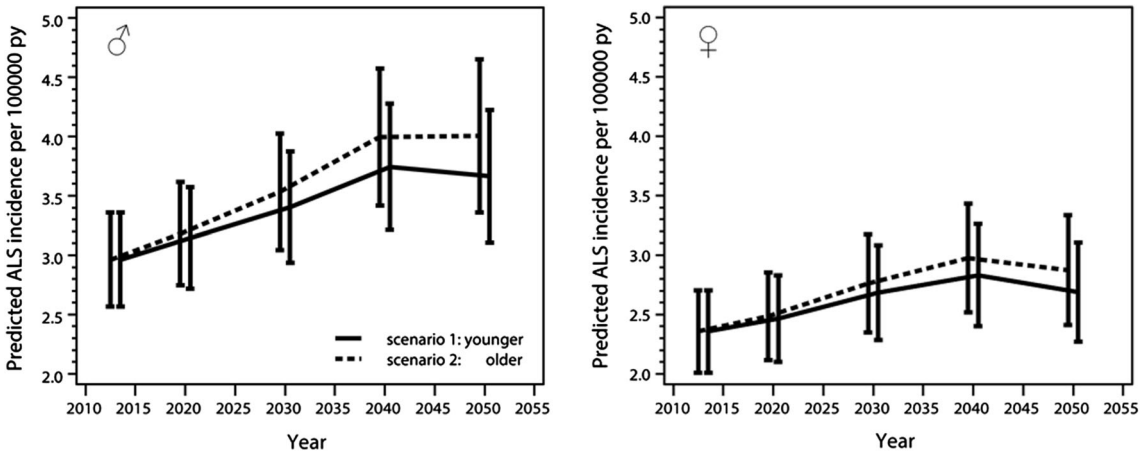


Fig. 4 Predicted ALS incidence till 2050 by sex using the observed ALS cases in the years 2012/2013 ($N = 399$) based on two population projections. *Scenario 1* younger population: high birth rate (1.6 children/woman), low life expectancy (when born in 2060: boys 84.8/girls 88.8 years), and high migration balance (200,000/year). Scenario *2* older population: low birth rate (1.4 children/woman), high life expectancy (when born in 2060: boys 86.7/girls 90.4 years), and low migration balance (100,000/year)

CI 3.1–4.2) for men and 2.7 per 100,000 PY (95% CI 2.3–3.1) for women (Fig. 4) without extrapolation of the coverage rate. With extrapolation to a 100% coverage rate, the predicted incidence rate rises to 4.5 for men and 3.3 for women with a 100% coverage. For more accelerated demographic change (scenario 2), the numbers were 4.0 (95% CI 3.4–4.7) and 3.7 (95% CI 3.1–4.2) per 100,000 PY, respectively. This would results in an estimated incidence rate of 4.9 for males and 4.6 for females and a prevalence of 9.2–9.8 per 100,000 if we assume 100% coverage.

Discussion

In this population-based registry study that followed 699 prospective ALS cases, we observed age-adjusted incidence rates within the reported range of other European countries. The highest age-specific rates were found in older age. Our projections for the year 2050, based on expected demographic changes, indicate a considerable increase of both the incidence and the prevalence of cases with bulbar onset and cognitive impairment. This will result in a meaningful impact of the ALS-related burden of disease, both for the individual as well as for society.

The ALS registry in Swabia has registered more than 1100 ALS cases since 2008. Clinical characteristics like the age of onset and the gender ratio in South Western Germany were consistent with German data from Rhineland-Palatinate [17, 18] and other European data from Piemont, Scotland, France, The Netherlands, and Ireland [19–23]. In addition, the incidence rate of ALS with 3.1 estimated cases per 100,000 person-years (PY) in the ALS registry Swabia was within the upper range of other European registries [8, 24, 25]. As we applied the same methods for retrospective and prospective data collection, a comparable capture-recapture-rate of 81% (estimated for retrospective data only) can be assumed for the prospective data [9]. Compared to other industrialized countries, we estimated higher incidence rates compared to reports from Olmsted, USA (Mayo clinic: incidence 1.7/100,000 $N = 77$) [26]. In some Western countries, such as France, Sweden, and Finland, a so far unexplained rise in incidence has been reported [27–29]. However, the registry in Olmsted reported no increase in incidence over an observation period of 73 years (1925–1998).

Consistent with our results, age-adjusted incidence in Europe is reported to be the highest in the age group of 70–74 year-old individuals [8, 21, 30]. This is also a characteristic pattern for many cancer types with the incidence increasing up to a maximum at about age 75+ years followed by a decline or a leveling off at the oldest ages [31]. Whether the leveling off for the oldest-old is real or an artifact caused by selection and less accurate diagnosis can only be addressed in registries with high coverage and access to old patients under neurological care. The ratio of males to females has been reported to be as high as 2.6:1 [24], but due to the demographic changes, gender ratio seems to be converging as described in recent studies [32, 33].

The demographic change in industrialized countries will inevitably lead to an increasing incidence of all age-related diseases, including ALS. The predicted incidence rates by 2050 build on two assumptions: a stable diagnostic approach to ALS and the available predictive models for the German population. Both scenarios revealed increasing incidence rates for coming decades. Until now, the burden regarding ALS patients, caregivers, health care systems,

and society has scarcely been investigated. Valid risk factor assessments and epidemiologic estimations for the future are highly important for both individual prognosis and the national health care system. In case of ALS, an increase in bulbar onset variants and cognitively impaired patients can be expected, since a trend towards older onset in cognitively impaired status and bulbar onset is already detectable now.

The diagnostic delay in our study was in the range of half a year and lower than in many previous studies (8–15 months) [19–21, 26, 34], possibly indicating improvement in the diagnostic process and the awareness of ALS within well-established registries and networks for ALS.

In our registry, the 1-year case-fatality rate from diagnosis was 28%, which is comparable with studies finding 34% in another German region [17], 22% in Europe [32], 18% in Italy [35], and 34% in Washington State (USA) [36]. As expected, in all mentioned studies, bulbar onset was associated with the worst prognosis, compared to spinal onset. These observations are consistent with our findings. Our observation, that high prognostic certainty is a negative prognostic factor in ALS, is also consistent with other studies [17, 35].

There were no substantial differences between the patients selected in the case–control study and the entire prospective group. A potential bias could be that only patients in better health conditions consented to an interview/home visit. However, due to lack of differences in core epidemiologic and clinical features, we assume that case–control data can represent the whole prospective part of the registry.

The three neuropsychological screening tools used in this study provided different results as they measure different cognitive domains. The FAB is designed to check for frontal cortical deficits, whereas the MoCA is designed to detect signs of Alzheimeŕs disease. Only the ECAS is specific for cognitive domains known to be involved in ALS and adjusted to motor impairments in patients. Outcome measures of the cognitive performance in ECAS were comparable to previous studies [13]. We see a higher frequency of FTD when neuropsychological screening tests are rigorously applied. Therefore, we recommend early and, if possible, longitudinal testing for fronto-temporal deficits. The exact estimation of the expected degree of behavioral deficits and number of FTD cases is important for prognostic estimates, especially bearing in mind the heavy impact on the burden of care [37].

Another study also reported a more aggressive disease phenotype in cognitively impaired patients with faster motor and cognitive decline [5]. This observation is consistent with our mortality data.

Among the strengths of our study are the prospective design and the standardized data collection with a capture–recapture rate of 81.1% in the target population which makes selection bias less likely [9]. A weakness could be the restriction to neurologists as referring cooperation partners and, therefore, a lack of patients that are diagnosed and treated otherwise.

In conclusion, the basic clinical characteristics in our data are consistent with other European studies, confirming an incidence of >3/100,000 and a prevalence of >6.2/100,000. Standardized neuropsychological screening is warranted for correct evaluation of accompanying cognitive, in particular frontal deficits, since cognitive impairment is a risk factor for faster motor decline and mortality. Epidemiological core data allowed the forecast of an increasing ALS incidence by 2050. The expectation of increasing ALS incidence may guide future public health decisions concerning palliative care, and forms a basis for informative estimation of ALS-related costs within the aging society. This is in accordance with a recently published study on the projected increase of global ALS incidence by Arthur et al. [38] proposing an increase of ALS patients by 20% in Europe by 2040. An increase in age-dependent bulbar onset variants and cognitively impaired patients can be expected. Thus, accompanying fronto-temporal dementia cannot longer be an exclusion criterion for ALS as suggested by the revision of El Escorial criteria 2015.

Acknowledgements We thank P. Weydt and L. Dupuis for critical reading of the manuscript. We thank the study nurses I. Kraft-Oberbeck, N. Lämmle, and I. Dobias for their excellent field work, and the medical documentation team T. Brehme, S. Enderle, G. Feike, and B. Och for their excellent technical support. This study was supported by the German Research Council (Deutsche Forschungsgemeinschaft, DFG Grant Number LU 336/15-1).

The following cooperation partners provided data for the ALS registry Swabia:

The ALS Registry Study Group.

Andres F., Kreiskliniken Reutlingen, Department of Neurology.

Arnold G., Klinikum Sindelfingen-Böblingen, Department of Neurology.

Asshauer I., Klinikum Friedrichshafen, Department of Psychiatry and Psychotherapy.

Baezner H., Bürgerhospital Stuttgart, Department of Neurology.

Baier H., ZFP Südwürttemberg Weissenau, Department of Epileptology.

Beattie J., Ostalb-Klinikum Aalen, Department of Neurology.

Becker T., University of Ulm, Klinikum Günzburg, Department of Psychiatry and Psychotherapy II.

Behne F., ZFP Südwürttemberg Weissenau, Department of Epileptology.

Bengel D., Oberschwabenklinik Ravensburg, Department of Neurology.

Boertlein A., Bürgerhospital Stuttgart, Department of Neurology.

Bracknies, V., Klinik Dietenbronn, Department of Neurology.

Broer R., Klinikum am Weissenhof, Weinsberg, Department of Psychiatry and Psychotherapy.

Burkhard, A., Klinikum Günzburg, Department of Neurology.

Connemann B., University of Ulm, Department of Psychiatry and Psychotherapy III.

Dempewolf S., Klinikum Ludwigsburg, Department of Neurology.
Dettmers C., Schmieder Kliniken Konstanz, Department of Neurology.
Dieterich M., LMU München, Department of Neurology.
Etzersdorfer E., Furtbachkrankenhaus Stuttgart, Department of Psychiatry and Psychotherapy.
Freund, W., private practice, Biberach.
Gersner T., ZfP Zwiefalten, Department of Psychiatry and Psychotherapy.
Gold H.-J., Klinikum am Gesundbrunnen Heilbronn, Department of Neurology.
Hacke, W., University of Heidelberg, Department of Neurology.
Hamann G., Klinikum Günzburg, Department of Neurology.
Hecht M., Bezirkskrankenhaus Kaufbeuren, Department of Neurology.
Heimbach B., University of Freiburg, Department of Neurology.
Hemmer B., TU Muenchen, Department of Neurology.
Hendrich C., Klinikum Friedrichshafen, Department of Neurology.
Herting B., Diakonie-Klinikum Schwäbisch Hall, Department of Neurology.
Huber R., Klinikum Friedrichshafen, Department of Neurology.
Huber-Hartmann K., Kliniken Landkreis Heidenheim, Department of Neurology.
Hülser P.-J., Fachklinik Wangen, Department of Neurology.
Jüttler E., Ostalb-Klinikum Aalen, Department of Neurology.
Kammerer-Ciernioch J., Klinikum am Weissenhof, Weinsberg, Department of Psychiatry and Psychotherapy.
Kaspar A., Oberschwabenklinik Ravensburg, Department of Neurology.
Kern R., Klinikum Kempten, Department of Neurology.
Kimmig H., Kliniken Schwenningen, Department of Neurology.
Klebe, S., University of Würzburg, Department of Neurology.
Kloetzsch C., Schmieder Kliniken Allensbach, Department of Neurology.
Klopstock, T., LMU München, Department of Neurology.
Kohler, A., Klinikum am Gesundbrunnen Heilbronn, Department of Neurology.
Kuethmann A., Bezirkskrankenhaus Memmingen, Department of Psychiatry and Psychotherapy.
Lewis D., Marienhospital Stuttgart, Department of Neurology.
Lichy C., Klinikum Memmingen, Department of Neurology.
Lindner A., Marienhospital Stuttgart, Department of Neurology.
Mäurer M., Caritas Krankenhaus Bad Mergentheim, Department of Neurology.
Maier-Janson W., private practice, Ravensburg.
Metrikat J., Bundeswehrkrankenhaus Ulm, Department of Neurology.
Meudt O., Klinikum Memmingen, Department of Neurology.
Meyer A., Weissenau, Department of Neurology.
Müller vom Hagen J., University of Tuebingen, Department of Neurology.
Naegele A., Christophsbad Göppingen, Department of Neurology.
Naumann M., Klinikum Augsburg, Department of Neurology.
Neher K.-D., Vinzenz von Paul Hospital, Rottweil, Department of Neurology.
Neuhaus O., Kliniken Landkreis Sigmaringen, Department of Neurology.
Neusch C., private practice, Singen.
Niehaus L., Klinikum Winnenden, Department of Neurology.
Opherk C., Klinikum am Gesundbrunnen Heilbronn, Department of Neurology.
Raape J., ZFP Südwürttemberg Weissenau, Department od Neurology.
Ratzka P., Klinikum Augsburg, Department of Neurology.
Rettenmayr C., Klinikum Esslingen, Department of Neurology.
Riepe MW., Klinikum Günzburg, Department of Gerontopsychiatry.
Rothmeier J., ZFP Südwürttemberg Weissenau, Department of Neurology.
Sabolek M., Klinik Biberach, Department of Neurology.
Schabet M., Klinikum Ludwigsburg, Department of Neurology.
Schell C., Kreiskliniken Reutlingen, Department of Neurology.
Schlipf T., Klinikum Winnenden, Department of Psychiatry and Psychotherapy.
Schmauss M., Bezirkskrankenhaus Augsburg, Department of Psychiatry and Psychotherapy.
Schoels L., University of Tübingen, Department of Neurology.
Schuetz K., Kliniken Schwenningen, Department of Neurology
Schweigert B., Caritas Krankenhaus Bad Mergentheim, Department of Neurology.
Sommer N., Christophsbad Göppingen, Department of Neurology.
Sperber W., Kliniken Esslingen, Department of Neurology.
Steber C., Bezirkskrankenhaus Augsburg, Department of Psychiatry and Psychotherapy.
Steber R., Bezirkskrankenhaus Memmingen, Department of Psychiatry and Psychotherapy.
Stroick M., Klinikum Memmingen, Department of Neurology.
Synofzik, M., University of Tübingen, Deartment of Neurology.
Trottenberg T., Klinikum Winnenden, Department of Neurology.
Tumani H., Klinikum Dietenbronn, Department of Neurology.
Wahl C., Klinikum Kempten, Department of Neurology.
Weber F., Bundeswehrkrankenhaus Ulm, Department of Neurology.
Weiler M., University of Heidelberg, Department of Neurology.
Weiller C., University of Freiburg, Department of Neurology.
Wessig C., University of Würzburg, Department of Neurology.
Winkler A., TU München, Department of Neurology.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical standards All persons gave their informed consent prior to their inclusion in the ALS Registry Swabia. The ALS Registry Swabia was approved by the local ethics committee of the University of Ulm (no. 11/10).

References

1. Oliver D, Borasio GD, Voltz R et al (2014) The development of a concensus paper on palliative care in neurology: the implications for ALS care. Amyotr Lateral Scler Frontotemp Degener 15:117–118
2. Braak H, Brettschneider J, Ludolph AC, Lee VM, Trojanowski JQ, Del Tredici K (2013) Amyotrophic lateral sclerosis—a model of corticofugal axonal spread. Nat Rev Neurol 9(12):708–714
3. Chiò A, Traynor BJ (2015) Motor neuron disease in 2014. Biomarkers for ALS–in search of the promised land. Nat Rev Neurol 11(2):72–74
4. Ludolph A, Drory V, Hardiman O et al (2015) A revision of the El Escorial criteria. Amyotroph Lateral Scler Frontotemporal Degener 16(5–6):291
5. Elamin M, Bede P, Byrne S et al (2013) Cognitive changes predict functional decline in ALS: a population-based longitudinal study. Neurology 80(17):1590–1597
6. Robinson KM, Lacey SC, Grugan P, Glosser G, Grossman M, McCluskey LF (2006) Cognitive functioning in sporadic

amyotrophic lateral sclerosis: a six month longitudinal study. J Neurol Neurosurg Psychiatry 77:668–670
7. Nagel G, Uenal H, Rosenbohm A, Ludolph AC, Rothenbacher D (2013) ALS Registry Study Group. Implementation of a population-based epidemiological rare disease registry: study protocol of the amyotrophic lateral sclerosis (ALS)—registry Swabia. BMC Neurol 13:22
8. Logroscino G, Traynor BJ, Hardiman O et al (2010) Incidence of amyotrophic lateral sclerosis in Europe. J Neurol Neurosurg Psychiatry 81(4):385–390
9. Uenal H, Rosenbohm A, Kufeldt J et al (2014) Incidence and geographical variation of amyotrophic lateral sclerosis (ALS) in Southern Germany—Completeness of the ALS Registry Swabia. PLoS One 9(4):e93932. doi:10.1371/journal.pone.0093932
10. Brooks BR (1994) El Escorial World Federation of Neurology criteria for the diagnosis of amyotrophic lateral sclerosis: Subcommittee on Motor Neuron Diseases/Amyotrophic Lateral Sclerosis of the World Federation of Neurology Research Group on Neuromuscular Diseases and the El Escorial Clinical Limits of Amyotrophic LateralSclerosis workshop contributors. J Neurol Sci 124(suppl):96e107
11. Brooks BR, Miller RG, Swash M, Munsat TL (2000) World Federation of Neurology Research Group on Motor Neuron Diseases. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disord 1(5):293–299
12. Nagel G, Unal H, Rosenbohm A, Ludolph AC, Rothenbacher D, ALS Registry Study Group (2013) Implementation of a population-based epidemiological rare disease registry: study protocol of the amyotrophic lateral sclerosis (ALS)—registry Swabia. BMC Neurol. 17(13):22
13. Nasreddine ZS, Phillips NA, Bédirian V et al (2005) The montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 53(4):695–699
14. Dubois B, Litvan I (2000) The FAB: a frontal assessment battery at bedside. Neurology 55(11):1621–1626
15. Lulé D, Burkhardt C, Abdulla S et al (2015) The Edinburgh Cognitive and Behavioural Amyotrophic Lateral Sclerosis Screen: a cross-sectional comparison of established screening tools in a German-Swiss population. The Edinburgh Cognitive and Behavioural Amyotrophic Lateral Sclerosis Screen: a cross-sectional comparison of established screening tools in a German-Swiss population. Amyotroph Lateral Scler Frontotemporal Degener 16(1–2):16–23
16. Statistisches Bundesamt (2015) (ed.) Bevölkerung Deutschlands bis 2060—13. koordinierte Bevölkerungsvorausberechnung, Wiesbaden. https://www.destatis.de/DE/Publikationen/Thematisch/Bevoelkerung/VorausberechnungBevoelkerung/BevoelkerungDeutschland2060.html
17. Wolf J, Wöhrle JC, Palm F et al (2014) Incidence of amyotrophic lateral sclerosis in Rhineland-Palatinate, Germany. Amyotroph Lateral Scler Frontotemporal Degener 15(3–4):269–274
18. Wolf J, Safer A, Wöhrle JC et al (2014) Variability and prognostic relevance of different phenotypes in amyotrophic lateral sclerosis—data from a population-based registry. Variability and prognostic relevance of different phenotypes in amyotrophic lateral sclerosis—data from a population-based registry. J Neurol Sci 345(1–2):164–167
19. O'Toole O, Traynor BJ, Brennan P et al (2008) Epidemiology and clinical features of amyotrophic lateral sclerosis in Ireland between 1995 and 2004. J Neurol Neurosurg Psychiatry 79(1):30–32
20. Marin B, Gil J, Preux PM, Funalot B, Couratier P (2009) Incidence of amyotrophic lateral sclerosis in the Limousin region of France, 1997–2007. Amyotroph Lateral Scler 10(4):216–220
21. Huisman MH, de Jong SW, van Doormaal PT et al (2011) Population-based epidemiology of amyotrophic lateral sclerosis using capture-recapture methodology. J Neurol Neurosurg Psychiatry 82(10):1165–1170
22. Chio A, Calvo A, Moglia C, Mazzini L, Mora G (2011) PARALS study group. Phenotypic heterogeneity of amyotrophic lateral sclerosis: a population based study. J Neurol Neurosurg Psychiatry 82(7):740–746
23. Forbes RB, Colville S, Parratt J, Swingler RJ (2007) The incidence of motor neuron disease in Scotland. J Neurol 254(7):866–869
24. Al-Chalabi A, Hardiman O (2013) The epidemiology of ALS: a conspiracy of genes, environment and time. Nat Rev Neurol 9(11):617–628
25. Kiernan MC, Vucic S, Cheah BC et al (2011) Amyotrophic lateral sclerosis. Lancet 377(9769):942–955
26. Sorenson EJ, Stalker AP, Kurland LT, Windebank AJ (2002) Amyotrophic lateral sclerosis in Olmsted County, Minnesota, 1925–1998. Neurology 59:280–282
27. Fang F, Valdimarsdottir U, Bellocco R et al (2009) Amyotrophic lateral sclerosis in Sweden, 1991–2005. Arch Neurol 66(4):515–519
28. Neilson S, Robinson I, Alperovitch A (1994) Rising amyotrophic lateral sclerosis mortality in France 1968–1990: increased life expectancy and inter-disease competition as an explanation. J Neurol 241(7):448–455
29. Maasilta P, Jokelainen M, Loytonen M, Sabel CE, Gatrell AC (2001) Mortality from amyotrophic lateral sclerosis in Finland, 1986–1995. Acta Neurol Scand 104(4):232–235
30. Piemonte and Valle d'Aosta Register for Amyotrophic Lateral Sclerosis (PARALS) (2001) Incidence of ALS in Italy: evidence for a uniform frequency in Western countries. Neurology 56(2):239–244
31. Pedersen JK, Engholm G, Skytthe A, Christensen K (2016) Academy of Geriatric Cancer Research (AgeCare) Cancer and aging: epidemiology and methodological challenges. Acta Oncol 55(supp1):7–12
32. Logroscino G, Traynor BJ, Hardiman O et al (2008) Descriptive epidemiology of amyotrophic lateral sclerosis: new evidence and unsolved issues. J Neurol Neurosurg Psychiatry 79(1):6–11
33. Blasco H, Guennoc A-M, Veyrat-Durebex C et al (2012) Amyotrophic lateral sclerosis: a hormonal condition? Amyotroph Lateral Scler 13(6):585–588
34. Paganoni S, Macklin EA, Lee A et al (2014) Diagnostic timelines and delays in diagnosing amyotrophic lateral sclerosis (ALS). Amyotroph Lateral Scler Frontotemporal Degener 15(5–6):453–456
35. Millul A, Beghi E, Logroscino G, Micheli A, Vitelli E, Zardi A (2005) Survival of patients with amyotrophic lateral sclerosis in a population-based registry. Neuroepidemiology 25(3):114–119
36. Del Aguila MA, Longstreth WT, McGuire V et al (2003) Prognosis in amyotrophic lateral sclerosis. A population based study. Neurology 60(5):813–819
37. Watermeyer TJ, Brown RG, Sidle KC et al (2015) Impact of disease, cognitive and behavioural factors on caregiver outcome in amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener 16(5–6):316–323
38. Arthur KC, Calvo A, Proce TR et al (2016) Projected increase in amyotrophic lateral sclerosis from 2015 to 2040. Nat Commun 11(7):12408. doi:10.1038/ncomms12408