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ORIGINAL COMMUNICATION

Prognostic factors in ALS: a comparison between Germany and China

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Abstract

Objective Several independent prognostic factors, such as age of onset, type of onset, body mass index (BMI), and progression rate have been identified for amyotrophic lateral sclerosis (ALS) in Caucasians. The aim of this study was to identify such factors in Chinese patients and to compare their impact with German patients.

Methods Comparison of prognostic factors was based on two hospital-based registries. The registry of the German Network for Motor Neuron Diseases contains 3100 patients with ALS. The Chinese registry comprises 2101 patients who were collected between 2003 and 2015 in the metropolitan area of Beijing.

Results Disease progression was slower in China [median loss of 0.50 points (IQR 0.26–0.87 points) versus 0.55 points (IQR 0.28–1.00 points) of ALS functional rating scale revised (ALS-FRS-R) score per month; $p < 0.0001$]. Survival of patients with ALS was similar in Germany and China ($p > 0.05$). We found that younger age of onset ($p < 0.0001$), spinal onset ($p < 0.0001$), high BMI ($p < 0.0001$) and low progression rate ($p < 0.0001$) were positive prognostic factors in China as well as in Germany.

Interpretation Prognostic factors, which are known to modify the course of disease in Caucasians, apply to Chinese patients as well. The results indicate that despite the apparent differences regarding genotype and clinical phenotype, findings from interventional studies in Caucasians aiming at disease-modifying prognostic factors (such as body weight) may be transferred to Chinese patients.

Keywords Amyotrophic lateral sclerosis · Motor neuron disease · Prognostic factors · Survival · Germany · China

Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease characterized by a loss of both upper and lower motor neurons, usually leading to progressive paresis and death due to failure of the respiratory muscles after an average survival of 2–5 years. Since the pathomechanisms of ALS and related neurodegenerative diseases are still largely unknown, it is of crucial importance to identify genetic and environmental risk factors as well as disease-modifying prognostic factors and to describe similarities and differences in various populations.

Due to the current lack of causal therapeutic options, increasing attention has recently been directed towards disease-modifying prognostic factors to identify possible additional therapeutic targets. For example, as a higher body mass index has been identified as a positive prognostic factor in ALS [1], high-caloric nutrition has been established in ALS therapy and has been found to prolong survival in patients with percutaneous endoscopic gastrostomy [2], while its impact on oral feeding patients is currently investigated in a large multi-center trial (LIPCAL study—clinicaltrials.gov identifier NCT02306590). Further potential therapeutic targets include the fat and carbohydrate metabolism,

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since both dyslipidemia [3] and type II diabetes mellitus [4] have been suspected to be protective factors.

However, since all findings of randomized controlled trials are derived from Caucasian patients, it is completely unclear if they can be transferred to other populations, especially since genetic and clinical features in ALS vary greatly between populations.

Epidemiological and clinical data on ALS in Asia are rarely reported, but seem to differ markedly from those obtained in Caucasian countries [5]. Studies in Caucasians report ALS to be a disease of older age [6, 7], whereas in China and other Asian countries, epidemiologic data show a much younger age of onset [8–10]. Despite scarcely receiving disease-modifying therapy such as riluzole or ventilatory support, Chinese and Indian ALS patients were reported to have a longer median survival [9, 11]. One comparative study between Chinese and German ALS patients found apparent differences with regard to clinical phenotype, including age at onset (67 years in Germany vs. 53 years in China), gender distribution, bulbar onset percentage, and cognitive dysfunction [11]. However, a major limitation was an inhomogeneous cohort composition (epidemiologic registry in Germany vs. hospital-based registry in China), and prognostic factors were not evaluated.

Therefore, we aimed to compare two hospital-based national registries in Germany and China to be able to compare prognostic factors in two large comparable cohorts.

Methods

Study design and participants

We compared data of two national registries for patients with amyotrophic lateral sclerosis (ALS):

The German registry comprises data of 3100 patients which were collected within the German network for motor neuron diseases (MND) by 21 centers across the country (Aachen, Berlin, Bochum, Dresden, Erlangen, Essen, Göttingen, Halle/Saale, Hannover, Jena, Leipzig, Mannheim, München, Münster, Regensburg, Rostock, Ulm, Wiesbaden, and Würzburg) between August 2012 and May 2018.

The Chinese registry comprises data of 2101 patients which were collected in the University Third Hospital (PUTH), Beijing, China. Between January 2003 and December 2015, all patients who visited the clinic for motor neuron diseases at PUTH and were diagnosed with sporadic ALS were included.

Both registries contained patients with typical ALS as well as variants of ALS including primary lateral sclerosis (PLS), progressive muscular atrophy (PMA), flail arm syndrome (FAS), and flail leg syndrome (FLS). All participants underwent full neurological and neurophysiological examination performed by the collaborating neurologists.

Other motor neuron diseases such as spinal muscular atrophy or Kennedy's syndrome were excluded. All patients with ALS fulfilled the revised El Escorial criteria for possible, probable or definite ALS [12].

Outcome parameters

Standardized, electronic forms were used for data collection for both registries, including demographic data, medical history, medication, neurological examination, diagnostic criteria, body mass index (BMI), ALS functional rating scale revised (ALS-FRS-R; [13]), and date of death.

In Germany, patients were included in the registry at their first visit, and follow-up data were collected about every 3 months in the outpatient clinics. In China, follow-up visits were conducted by phone call every 3 months.

The date of disease onset was defined as the time when the patient noticed first paresis. To address the importance of natural disease progression as highlighted by several recent clinical studies [14, 15], we calculated the progression rate for two different time periods: The "early" progression rate was calculated by subtracting the loss of ALS-FRS-R score between onset of disease and first visit and dividing the result by the number of months between both time points. For the calculation of "late" progression rate the same method was applied for the period between first and last visit.

Statistical analysis

For analysis of epidemiological data, the whole data set comprising 5201 patients was used. For survival analysis, we excluded patients who were lost to follow-up after the first visit, leaving 3804 patients (1836 German and 1968 Chinese patients) for survival analysis.

The Mann–Whitney *U* test for continuous variables was used for comparison between the two countries. The chi-square test was used for the comparison of categorical variables between the two countries. All continuous data are given as median and interquartile range (IQR). Categorical data are presented as frequencies and percentages.

For survival analysis, Kaplan Meier method and the log rank test were used. For patients lost to follow-up, the date of last contact was used as censoring time. To estimate the effect of prognostic factors, we used the Hazard ratio (HR) from the Cox proportional hazard regression model, including the 95% confidence interval (CI).

The level of significance was set at $p = 0.05$ (two-sided). For statistical analyses, SPSS Statistics Version 21.0 (IBM, Armonk, USA), SAS version 9.4 (SAS Institute, Cary, NC, USA), and GraphPad Prism 7.04 (GraphPad Software, La

Jolla, USA) were used. Because of the explorative nature of this study, all results from the statistical tests have to be interpreted as hypothesis generating only and not as confirmatory. No adjustment for multiple testing was done.

Results

Demographic and clinical data

Demographic data of both cohorts are shown in Table 1.

Median age of onset was 61.0 (IQR 52.0–69.0) years in Germany, and 51.0 (IQR 43.0–59.0) years in China, therefore, the median age of onset in China was 10 years younger ($p < 0.0001$). The male to female ratio was higher in China (1.69:1) compared to Germany (1.53:1), although this difference was not significant ($p = 0.083$). The type of onset was equally distributed between Germany (spinal 80.0%, bulbar 20.0%) and China (spinal 78.8%, bulbar 21.2%, $p = 0.351$).

German patients displayed a faster disease progression. Between onset of disease and diagnosis, German patients showed a median loss of 0.55 (IQR 0.28-1.00) points of ALS-FRS-R score per month compared to a loss of 0.50 (IQR 0.26–0.87) points of ALS-FRS-R score per month in Chinese patients ($p < 0.0001$). During the later stages of the disease (between first and last visit), German patients lost 0.75 (IQR 0.28–1.34) points of ALS-FRS score per month compared to a loss of 0.67 (IQR 0.25–1.17) points of ALS-FRS-R score per month in Chinese patients ($p < 0.0001$).

Regarding ALS subforms, primary lateral sclerosis (PLS, 2.9% vs. 0.7%) and progressive muscular atrophy (PMA, 13.2% vs. 2.1%) were diagnosed more frequently in Germany ($p < 0.0001$), whereas the frequency of FAS and FLS (6.9% vs. 7.5%) was similar.

German patients showed a higher median BMI [24.5 (IQR 22.0-27.2) kg/m^2 vs. 23.0 (IQR 20.8–25.2) kg/m^2; $p < 0.0001$] and a higher incidence of type II diabetes (10.2% vs. 7.0%, $p < 0.0001$). The median age of onset was higher in patients with diabetes compared to patients without diabetes in both cohorts [Germany: 66 (IQR 58–71) vs. 61 (IQR 52–69) years, $p = 0.0013$; China: 58 (IQR 50.8–63) vs. 52 (IQR 45–60) years; $p = 0.0007$].

Riluzole was more frequently prescribed in Germany than in China (86.3% vs. 46.1%, $p < 0.0001$). Non-invasive ventilation (NIV, 41.1% vs. 14.0%) and percutaneous endoscopic gastrostomy (PEG, 32.7% vs. 4.1%) were more frequently used in Germany ($p < 0.0001$).

Prognostic factors and survival

Although German patients showed a faster disease progression, median survival between German and Chinese patients was not different ($p = 0.183$, Fig. 1). An age of onset older than the median was associated with

Table 1 Demographic and clinical data of German and Chinese patients. Descriptive statistics are given as median and interquartile rage (IQR)

	Germany	China	*p* value
Number of patients	3100	2101	
Age of onset	61 (IQR 52–69)	51 (IQR 43–59)	**< 0.0001**
Male to female ratio	1.53:1	1.69:1	0.083
Type of onset	Spinal 80% Bulbar 20%	Spinal 78.8% Bulbar 21.2%	0.351
ALS subforms	PLS 2.9% PMA 13.2% FAS/FLS 6.9%	PLS 0.7% PMA 2.1% FAS/FLS 7.5%	**< 0.0001**
BMI (kg/m^2)	24.5 (IQR 22.0–27.2)	23.0 (IQR 20.8–25.2)	**< 0.0001**
Diabetes	10.2%	7.0%	**< 0.0001**
Riluzole	86.3%	46.1%	**< 0.0001**
NIV[a]	41.1%	14.0%	**< 0.0001**
PEG[a]	32.7%	4.1%	**< 0.0001**
Early disease progression (Loss of ALS-FRS-R/month)	0.55 (IQR 0.28-1.00)	0.50 (IQR 0.26–0.87)	**< 0.0001**
Late disease progression (loss of ALS-FRS-R/month)	0.75 (IQR 0.28–1.34)	0.67 (IQR 0.25–1.17)	**< 0.0001**

Statistically significant differences are marked with bold font

PLS primary lateral sclerosis, *PMA* progressive muscular atrophy, *FAS* flail arm syndrome, *FLS* flail leg syndrome, *NIV* non-invasive ventilation, *PEG* percutaneous endoscopic gastrostomy

[a]Subgroup of deceased patients with follow-up of at least 6 months (Germany $n = 248$, China $n = 680$)

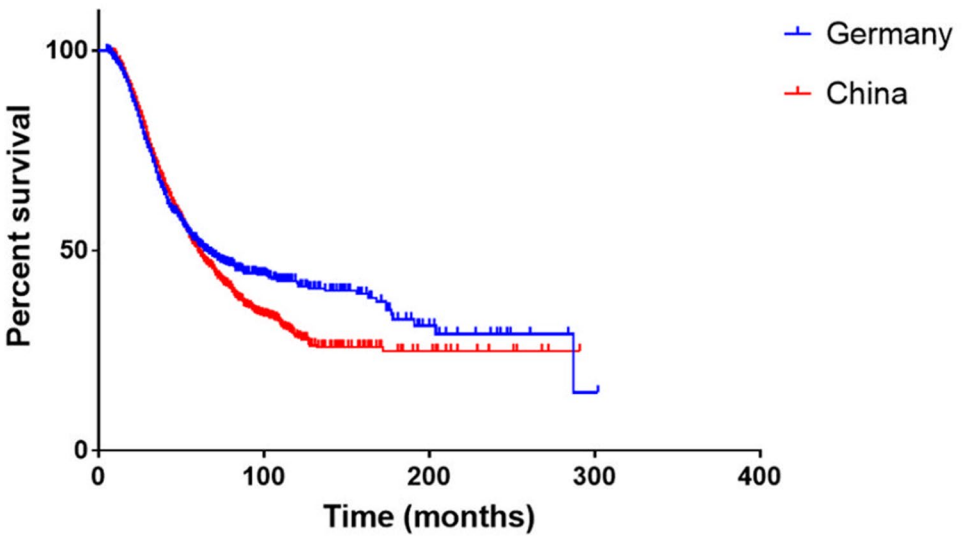

Fig. 1 Survival of ALS patients in Germany and China. Survival curves show survival of patients in Germany (blue) and China (red). Survival was not different ($p = 0.183$)

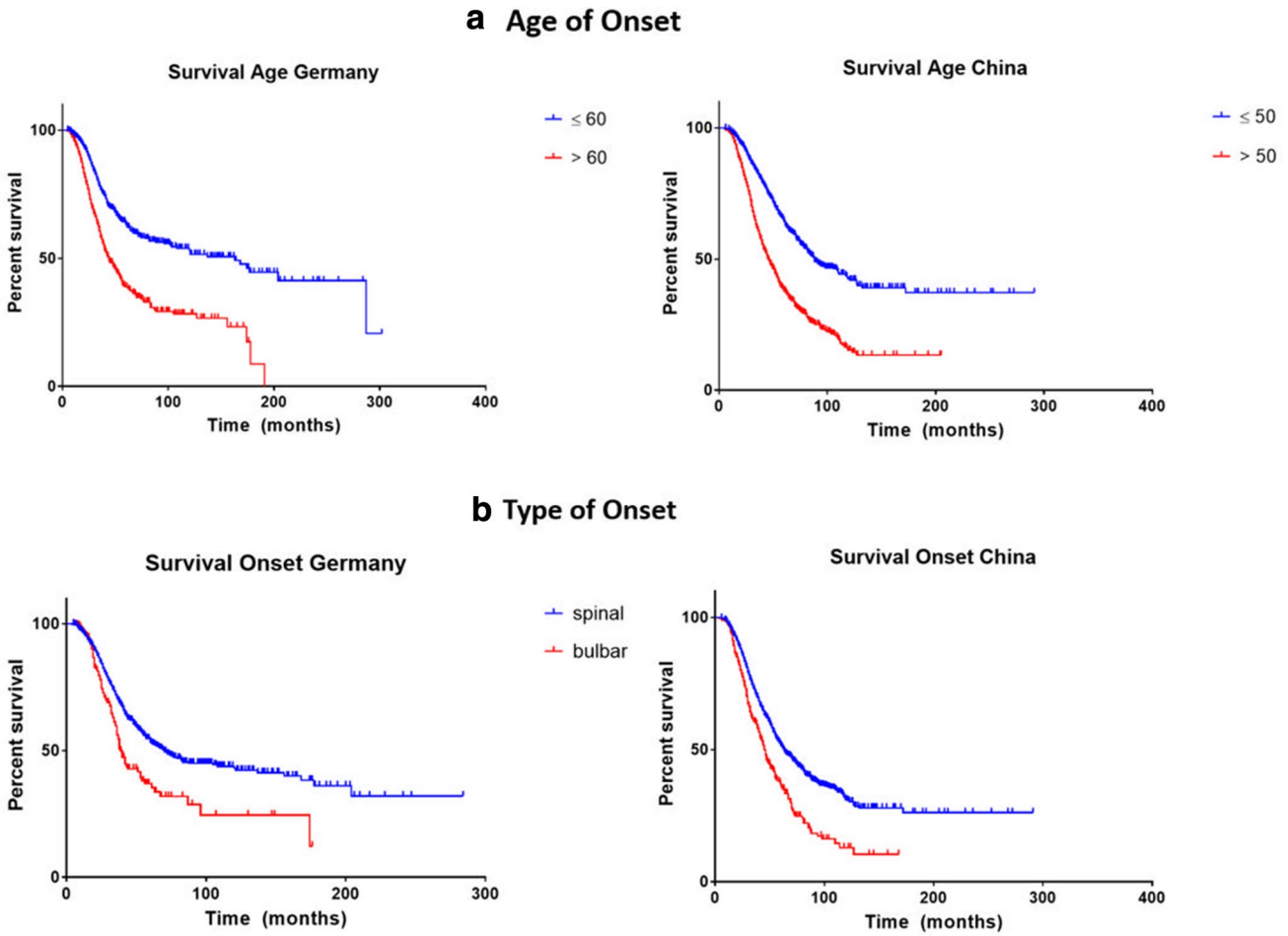

Fig. 2 Prognostic factors for survival in Germany and China—age of onset and type of onset. Survival curves show survival of patients in Germany (left) and China (right). **a** Age of onset: Patients with age of onset above median had a shorter survival in both countries ($p < 0.0001$). b Type of onset: Patients with bulbar onset had a shorter survival than patients with spinal onset in both countries ($p < 0.0001$)

a shorter survival in both countries (Germany: HR 2.08 (95% CI 1.78–2.44), China: HR 2.16 (95% CI 1.90–2.44); $p < 0.0001$; Fig. 2a).

Gender did not affect survival in either cohort. In Germany, male patients had a longer survival (HR 1.15 (95% CI 0.98–1.35; $p = 0.063$), while in China, female patients had a longer survival [HR 1.13 (95% CI 1.00–1.29); $p = 0.055$], but in both cases the differences were not statistically significant. Patients with PLS had the longest survival, followed by PMA, FAS/FLS, and classical ALS in both cohorts.

Patients with bulbar onset had a worse prognosis compared to patients with spinal onset in both countries [Germany HR 1.62 (95% CI 1.27–2.05); $p < 0.0001$; China HR 1.62 (95% CI 1.36–192); $p < 0.0001$; Fig. 2b].

Patients with faster disease progression during the early [Germany: HR 5.08 (95% CI 4.25–6.06); China: HR 2.94 (95% CI 2.57–3.36); $p < 0.0001$; Fig. 3a] as well as the later [Germany: HR 5.31 (95% CI 4.17–6.78); China: HR 3.46 (95% CI 2.99–4.01); $p < 0.0001$] stages of the disease had a shorter survival in both countries.

Patients with BMI above median (Germany: 24.5 kg/m^2; China: 23 kg/m^2) at the time of their first visit had a longer survival in both cohorts [Germany: HR 1.37 (95% CI 1.16–1.61), $p = 0.0002$; China: HR 1.34 (95% CI 1.18–1.53); $p < 0.0001$; Fig. 3b]. The prevalence of type II diabetes did not affect survival.

Hazard ratios of all investigated variables are displayed in Fig. 4.

Discussion

Demographic and clinical data

Various studies have investigated the genetic and clinical characteristics of ALS in China in recent years. Although several differences have been described between Chinese and Caucasian patients, direct comparative studies with synchronized databases and similar selection criteria are missing. Therefore, the validity of existing literature is limited

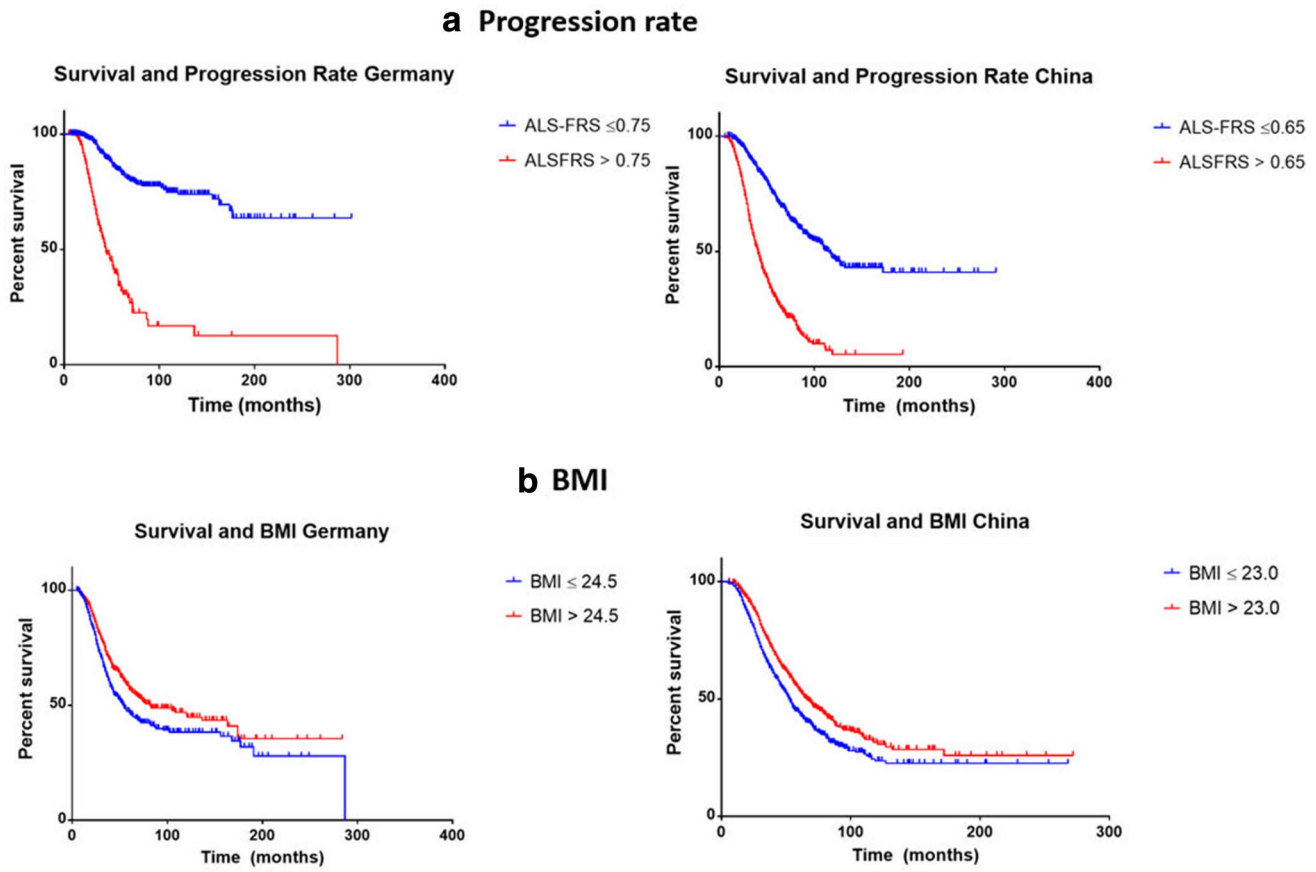

Fig. 3 Prognostic factors for survival in Germany and China—progression rate and body mass index. **a** Progression rate: Patients with faster early progression rate (loss of ALS functional rating scale revised (ALS-FRS-R) per month above the median during the time between onset of disease and diagnosis) as well as patients with faster later progression rate (not shown) had a shorter survival in both countries ($p < 0.0001$). **b** Body mass index (BMI): Patient with BMI above median at the time of their first visit had a longer survival in both countries (Germany $p = 0.0002$, China $p < 0.0001$)

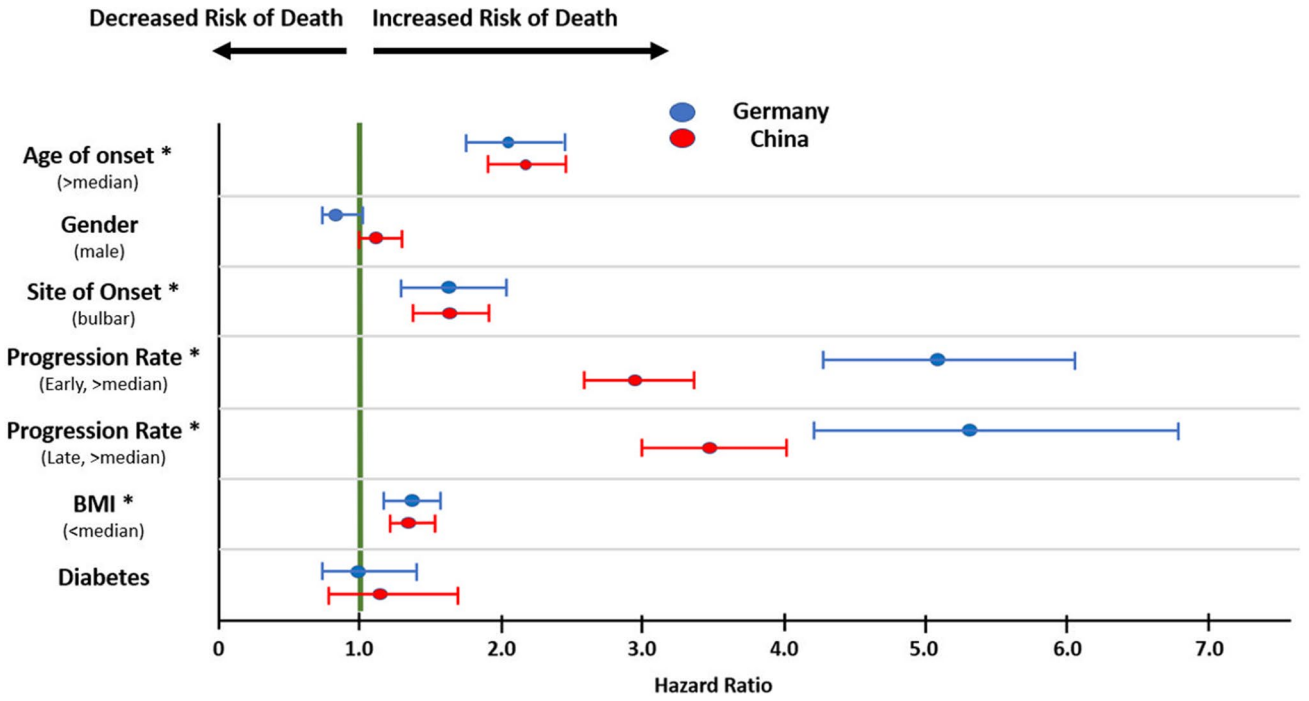

Fig. 4 Effect of prognostic factors on survival. Figure shows Hazard Ratios (HR) for alle tested variables in Germany (blue) and China (red) as an estimation of their effect on survival. Statistically significant variables are marked with asterisk

and possibly severely biased. In this study, we compared two national hospital-based datasets with more than 5000 patients to identify similarities and differences regarding prognostic factors in ALS.

Age of onset of Chinese patients was about 10 years younger compared to German patients. Median age of onset in China was 51 years, confirming previous studies which reported slightly higher values between 52.6 and 54.3 years [11, 16–18]. This finding seems to constitute the most significant demographic difference between Chinese and Caucasian patients. We also found a higher male to female ratio in China (1.69:1 compared to 1.53:1), which was not significant. Similar results have been reported before with gender distributions ranging between 1.45:1 and 1.63:1 [11, 17–19].

The ratio of spinal and bulbar patients (80.0% spinal and 20.0% bulbar in Germany vs. 78.8% spinal and 21.1% bulbar in China) was similar. Regarding type of onset in China, previously reported ratios of bulbar patients range between 14 and 22.8% [8, 11], therefore, existing literature is not as consistent compared to other demographic variables, hinting at a possible selection bias based on the type of data acquisition. It may be hypothesized that bulbar patients are less inclined to travel long distances to specialized ALS centers because of their on average more advanced state of disability, since a bulbar onset is associated with worse prognosis, faster disease progression, and impaired communication. This may also explain why a former study comparing Caucasian and Chinese patients found a significantly higher share of bulbar patients (35.9% vs. 22.8%) in Caucasians: since the Caucasian cohort was based on a population-based registry and the Chinese cohort on a specialized hospital setting, a selection bias may have been present in the Chinese, but not in the Caucasian cohort.

Of note, we found that the German patients had a faster disease progression as measured by loss of ALS-FRS-R score per month. Considering the importance of disease progression not only for prognosis but also for the response to different therapeutic approaches as shown by the edaravone and rasagiline trials [14, 15], we opted for two different ways of calculating the ALS-FRS-R loss per month. The first method covered the early stages of the disease (between onset of disease and first visit), the second method the later stages of the disease (between first and last visit). German patients showed a significantly faster loss of ALS-FRS-R in both periods (0.55 vs. 0.50 per month in the early interval, 0.75 vs. 0.67 per month in the later interval phase).

Regarding ALS subforms, we found about similar rates of FAS and FLS (6.9% vs. 7.5%), but higher rates of PLS (2.9% vs. 0.7%) and PMA (13.2% vs. 2.1%) in Germany. The numbers in both countries are probably overestimated, since many patients were still alive at cut-off date and may have developed clinical signs of first (in case of PMA) and second (in case of PLS) motoneuron during the later stages of the disease, changing the diagnosis to classical ALS accordingly. Other studies have partially found higher rates of PMA in China up to 10.4% [18], while reported rates of

PLS in China are consistently low between 0.5 and 0.9% [8, 18]. Therefore, it can be assumed that PLS is relatively rare in China, although additional data is needed in this regard. However, non-consistent diagnostic criteria might make comparisons difficult [20].

In recent years, metabolic changes have increasingly been recognized in ALS, including an increased incidence of type II diabetes and impaired glucose tolerance in ALS [21], as well as hypermetabolism as the potential main reason for loss of body weight [22].

We found that German ALS patients had a significantly higher BMI (24.5 kg/m^2 vs. 23.0 kg/m^2) and a significantly higher prevalence of diabetes compared to Chinese patients (10.2% vs. 7.0%). Metabolic parameters are supposed to be heavily influenced by cultural differences in nutrition. Higher intake of fatty and high-caloric food in the German population might explain the observed differences. Confirming the influence of BMI on prognosis, obese patients had a better prognosis in both countries. However, although German patients had a higher BMI, the survival of both cohorts did not differ significantly, indicating that other factors (such as natural disease progression and younger age of onset) compensated for it.

Prognostic factors and survival

As opposed to a previous study [11], we found no survival differences for German and Chinese patients with ALS. The former study compared two different types of registries (a German population-based and a Chinese hospital-based registry), resulting in a considerably lower share of bulbar patients in the Chinese cohort as explained above. Because patients with bulbar onset have a worse prognosis, the lower share of bulbar patients in the Chinese cohort might have caused the survival differences in the former study.

Although German patients showed a faster disease progression during the early as well as the later stages of the disease as measured by loss of ALS-FRS-R score per month (see above), survival rates were comparable. We believe that this might be explained by the fact that the medical standard for the treatment of patients especially in far advanced disease stages may be higher in Germany, including a higher share of patients treated with NIV and PEG. These therapeutic measures affect survival, but not ALS-FRS-R. The share of patients with NIV or PEG can not be derived directly from our data, since many patients were observed over a limited period of time or were still alive at the cut-off date. However, comparing the subgroups of deceased patients with a follow-up period of at least 6 months ($n = 248$ German and $n = 680$ Chinese patients), we found that the share of patients with NIV (41.1% vs. 14.0%) and PEG (32.7% vs. 4.1%) was significantly larger in Germany compared to China. Furthermore, more patients received riluzole in Germany (86.3% vs. 46.1%). Riluzole is known to prolong survival by several months [23], but does not affect functional status [24].

Therefore, it seems justified to hypothesize that the natural course of disease is more benign in China, which is just about compensated by a higher standard of symptomatic medical care in Germany. Accordingly, survival curves show a slight survival advantage for Chinese patients during the early stages, but a more pronounced advantage for German patients during the later stages of the disease, when advanced life-supporting measures become meaningful. Our finding of a more benign natural disease progression in Chinese patients might be associated with their younger age of onset or protective genetic factors.

The main focus of this study was to identify prognostic factors for ALS in China and to compare their effect with Caucasian patients. We expected significant differences, since Caucasian and Chinese patients show clear genetic and clinical differences. A recent meta-analysis showed that mutations in the C9ORF72 gene are most common in European and American patients (33.7%), followed by SOD1 (14.8%), TDP-43 (4.2%), and FUS (2.8%) [25]. In China, SOD1 mutations constitute the most frequent gene mutations (30%), while C9ORF72 mutations are far less common (2.3%) [25]. As mentioned above, a younger age of onset and a more benign natural course of disease are the most significant clinical differences in Chinese patients compared to Caucasians.

Surprisingly, we found that despite these obvious differences, prognostic factors were similar in both cohorts. All relevant factors which are known to modify the course of disease in Caucasian patients, i.e., age of onset, site of onset (spinal vs. bulbar), BMI, and disease progression rate, turned out to be independent prognostic factors in the Chinese cohort as well. Furthermore, effect sizes as measured by hazard ratios were comparable as well, with the exception of disease progression rate, which showed a higher impact in the German patients. This can be attributed to the generally more rapidly progressive natural course of disease in the German cohort. Interestingly, female patients had a longer survival in China, while male patients had a longer survival in Germany, although both results were statistically not significant.

Diabetes was not associated with survival, but patients with diabetes had a delayed onset of disease, which is in line with recent publications [4]. Although significance as well as etiology of this finding has not been fully understood to date, the most common hypothesis relies on the strong association between diabetes and a specific protective metabolic profile, including a high BMI [26].

The finding of similar prognostic factors in Caucasian and Chinese patients has important therapeutic implications, since many current approaches either depend on

specific prognostic subgroups (e.g. only faster progressive patients may benefit from edaravone [14] or rasagiline [15]) or directly aim at the alteration of prognostic factors, such as high-caloric food supplements to stabilize body weight (e.g. the LIPCAL study—clinicaltrials.gov identifier NCT02306590). Therefore, the results of this study support the hypothesis that conclusions from clinical studies in Caucasian ALS patients might be transferable to Chinese patients.

Strengths and limitations

The main strengths of this study are the high numbers of patients, their detailed clinical characterization and their regular follow-up in both cohorts. Furthermore, both databases were comparable with regard to data acquisition (hospital-based registries) and showed a large overlap with regard to collected variables. However, we assume that various selection biases based on vastly different cultural and health-economic conditions are still present in both countries, e.g., Chinese patients are more likely to come from urban areas, since large travel distances from rural areas impede specialized care in ALS centers. Furthermore, information about some other known prognostic factors (diagnostic delay, cognition, genetics, respiratory status) was not collected. Another limitation is that follow-up information of Chinese patients was collected by phone calls instead of on-site visits.

Summary

We can summarize the following results:

1.) Chinese patients have a 10 years earlier age of onset and a slower disease progression compared to German patients, confirming previous studies.
2.) We could not confirm the lower proportion of bulbar patients and the longer survival of Chinese patients as previously reported. We believe that the different types of data acquisition (hospital-based vs. population-based registry) caused the effects in the former study.
3.) All known prognostic factors in Caucasians (age of onset, type of onset, BMI, and disease progression rate) were confirmed as independent prognostic factors in China as well. Effect sizes are similar with the exception of disease progression rate, which has a higher impact in German patients.

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Compliance with ethical standards

Conflicts of interest The German network for motoneuron diseases was funded by Bundesministerium für Bildung und Forschung (BMBF; 01GM1103A). Dr. Lu Chen has received funding from the National Natural Science Foundation of China (81701248). Prof. Dongsheng Fan has received funding from the National Natural Science Foundation of China (81873784). JDo, LC, AR, JS, AH, JDr, TM, UW, AH, JHW, JK, JW, TG, TH, PL, JCK, AS, JG, MM, JW, ASW, TK, MB, SJ, AS, BS, DZ, XL, LT, DSF, and ACL declare that they have no conflict of interest. SP reports honoraria as speaker/consultant from Biogen Idec, Novartis, Cytokinetics, TEVA Pharmaceuticals, Desitin. BG reports honoraria by Grifols, Bayer, DGN. Funding by DFG (GE 2249/1–3) and BMBF (01GM1511A).

Human participants and/or animals The research involved human participants. The study has been approved by the local ethics committees of all participating centers and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent All patients gave their written informed consent for data collection and analysis.

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