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Incidence and Survival Rates of Frontotemporal Lobar Degeneration

Population-Based Registry Study

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Abstract

Background and Objectives

Frontotemporal lobar degeneration (FTLD) can present as a behavioral or language variant (bvFTLD or a primary progressive aphasia [PPA], or as a syndrome with parkinsonism, such as corticobasal syndrome [CBS] or progressive supranuclear palsy [PSP]). The incidence of FTLD varies in epidemiologic studies, reaching 3 per 100,000 person-years. Only few data exist regarding survival times. We evaluated incidence and survival rates in a population-based registry with high coverage in Southern Germany.

Methods

The epidemiologic ALS-FTLD registry Swabia covers a population of 8.4 million inhabitants in south-west Germany. Raw and age-standardized incidence rates, as well as incidence rate ratios (IRR) with 95% CIs were calculated. Median survival time was estimated for different FTLD variants using the Kaplan-Meier method.

Results

Between 2015 and 2022, 515 patients with FTLD (mean age at diagnosis 68.0 ± 9.5 years, 59.8% men) were registered. The median diagnostic delay was 24.8 months. The most common variant was bvFTLD (n = 185, 35.9%; 66.5% men), followed by PPA (n = 147, 28.5%; 51.0% men), PSP (n = 133, 25.8%; 62.9% men), and CBS (n = 22, 4.3%; 50% men). The overall FTLD

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Supplementary Material

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Glossary

ALS = amyotrophic lateral sclerosis; **bvFTD** = behavioral variant frontotemporal dementia; **CBD** = corticobasal degeneration; **CBS** = corticobasal syndrome; **FTLD** = frontotemporal lobar degeneration; **IQR** = interquartile range; **lvPPA** = language variant PPA; **nfvPPA** = nonfluent variant PPA; **PPA** = primary progressive aphasia; **PSP** = progressive supranuclear palsy; **svPPA** = semantic variant PPA.

incidence was 0.77 (95% CI 0.71–0.84), and the age-standardized incidence was 0.76 (95% CI 0.69–0.82) per 100.000 person-years. The age-standardized incidence was higher in men than in women, with an IRR of 1.73 (95% CI 1.44–2.00). In men, incidence increased from the age 50 years, primarily due to bvFTD, whereas in women this rise was primarily due to PSP. The median survival (N = 392) from diagnosis was 53.6 months (95% CI 50.9–62.0) overall, 73.1 months (95% CI 63.6–82.8) for patients with PPA, 42.8 months (95% CI 35.1–64.3) for patients with bvFTD, and 49.5 months (95% CI 39.2–53.7) for patients with PPS/CBS.

Discussion

We observed a raw incidence rate of 0.77, thus considerably lower than in most previous reports. Incidence was substantially higher in men than in women. The prognosis from the time of diagnosis depended highly on the specific FTLD subtype. Our data are based on the large sample size and high capture rate of a central European population-based registry.

Introduction

Frontotemporal lobar degeneration (FTLD) is a neurologic condition characterized by predominant neuronal loss in the frontal and/or temporal cerebral cortex. Patients with FTLD usually present with 1 of the 2 phenotypic variants, the behavioral variant frontotemporal dementia (bvFTD) or, less frequently, a primary progressive aphasia (PPA), which may be nonfluent (nfvPPA) or the semantic type (svPPA). Primary tauopathies such as corticobasal syndrome (CBS) or progressive supranuclear palsy (PSP) are also included in the FTLD spectrum.[1,2]

The incidence and prevalence of FTLD are largely unknown in most countries. To date, our understanding of the frequency of FTLD is mainly based on smaller clinical study samples.[3-6] Data from a large consortium[7] revealed an annual incidence rate of 2.36 cases per 100,000 person-years in Europe, with the highest FTLD incidence and prevalence rates reported for the 45–65 age groups. FTLD has been suggested to be more common in men than in women, but larger epidemiologic studies documented only a minor increase in male patients.[3,7] In Olmsted County, an increase in incidence was observed between 1995 and 2010 based on only 35 patients. Initially there was a balanced ratio, but after 2000, the rate was higher in male patients.[8]

A meta-analysis[4] revealed a large heterogeneity of median survival times ranging from 7 to 12 years across different clinical cohorts. A population-based study in Italy reported a median survival time of 5.4 years after diagnosis.[9]

Epidemiologic parameters may be biased by differences in diagnostic criteria, study design, and populations studied. Most studies to date have covered small populations or were based on patients with FTLD reported by specialized FTLD care centers only.[3,4,6,7] However, only population-based registries covering large populations with a high completeness (i.e., a high capture-recapture rate, including patients not referred to specialized centers), facilitates estimates of the actual FTLD rates in a given region in a valid manner.

The aims of this study were to estimate the raw and age-standardized incidence as well as median survival times of FTLD from a population-based, highly complete register of a defined geographic region. Second, we aimed to investigate the distribution of subtypes, as well as age-dependent and sex-dependent effects in the ALS-FTLD registry Swabia.

Methods

The amyotrophic lateral sclerosis (ALS) registry Swabia was implemented as a clinical-epidemiologic registry in the year 2010[10,11] in a target population in South-West Germany comprising 8.4 Mio inhabitants. Data were collected on all newly diagnosed patients with ALS since 2010. From 2014, also patients with FTLD have been recruited in the same area using the same infrastructure. The registry was then renamed to ALS-FTLD registry Swabia. The cooperation partners contributing to the registry comprised 39 sites in total including neurologic clinics or private practices and psychiatric clinics within the target region.[10,11] The study protocol, diagnostic criteria, and standard operating procedures for FTLD were established and discussed at regular meetings with the collaborators. Several information events or lectures on FTLD were offered and held on site. For the recruitment of patients with FTLD, standard instruments were applied by trained interviewers.[12-14] Diagnosis and files were reviewed for consistency.

After informed consent was given, patients were registered and the data were collected, curated, and checked for duplicates. The current analysis takes into account sex as biological category, sociodemographic information, date of diagnosis, age at diagnosis, onset of the first symptom, and the clinical phenotype.

All patients underwent a neurologic and neuropsychological examination performed by the collaborating neurologists or psychiatrists. For the clinical diagnosis the patient's clinical presentation, neuroimaging results, the outcome of neuropsychological tests, and genetic testing were used. The registry staff collected copies of the medical records including these results. After receiving written consent, an experienced study nurse visited the patients. Standardized questionnaires were used to collect information on bvFTLD,[12] PPA,[13] PSP,[15] and corticobasal degeneration (CBD),[16] as well as Edinburgh Cognitive and Behavioral ALS Screen (2014) and Questionnaire for the Assessment of Risk Factors and Symptoms of Frontotemporal Dementia in the Context of ALS. Based on the collected information the diagnosis of FTLD was reviewed by an experienced neurologist in the registry. FTLD was diagnosed according to the Rascovsky criteria for bvFTD or the Gorno-Tempini criteria for the language variants.[12,13] FTLD syndromes associated with parkinsonism (PSP and CBS) were diagnosed according to Litvan et al. and Boeve et al.,[14-16] respectively. Ambiguous cases were followed-up to clarify the diagnosis. For this purpose, all available information, medical records, and MRIs, as well as information on regional hypometabolism in fluorodeoxyglucose-PET, were used to confirm the diagnosis. Because of the small number of patients with CBS and its neuropathologic similarities, we analyzed CBS together with PSP. Mortality follow-up was performed by regular record query from the regional registration offices for the entire study sample. Queries were performed before each 2-year follow-up for individual patients, or for the entire cohort (most recent query performed on January 15, 2023).

To take into account the start of recruitment in 2014 and the reporting delay between notification and data entry in 2023 and 2024, we used the reports for the period January 1, 2015, to December 31, 2022, to calculate the incidence rates. From January 1, 2015, to December 31, 2022, 515, patients with FTLD were registered in the ALS-FTLD registry Swabia, including 123 for which no follow-up data were available. The distribution of incidence in patients with FTLD by district is shown in eTable 1.

Statistics

We calculated the raw incidence of FTLD in the target population per 100,000 person-years with a 95% CI overall and by sex, age group, and district based on the population of the corresponding year using the forward projection of the population status based on the 2011 census of the Federal Statistical Office of Germany.[17] The age groups presented are based on the age groups for which population data were available. For the age-standardized incidence rate, the 2013 European Standard Population[18] was applied and depicted by sex and age groups. Age-adjusted incidence rate ratios (IRRs) were calculated to appraise sex differences. Heterogeneity of raw and age-standardized incidence rates for the years 2015–2022 in the target population was explored by district of the main residence at diagnosis (eTable 1).

Survival time since diagnosis was calculated based on the date of death, dates of last contact, or of last record linkage. Complete follow-up survival data were available for 392 patients with FTLD. The median survival time was estimated for different FTLD variants using the Kaplan-Meier method. In addition, we tested a possible modifying effect of sex and FTLD variants on survival time using an accelerated failure time model. The statistical software packages SAS (release 9.4 SAS Institute Inc., Cary, NC) and R version 4.3.2 were used for the statistical analyses.

Standard Protocol Approvals, Registrations, and Patient Consents

This study received approval by the ethical committee for both the analysis reported within this proposal and any related publications (ethical review boards of Ulm University, approval No. 11/10 with an amendment in 2020 and the regional physician chambers ["Landesärztekammer Baden-Wuerttemberg" and "Landesärztekammer Bayern"]). Written informed consent was obtained from all participants. The report of this study followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline.

Data Availability

Owing to the ethical restrictions regarding data protection issues and the study specific consent text and procedure, the data cannot be made publicly available, but the data are available from the corresponding author on reasonable request.

Results

During 66,584,586 person-years of observation, 515 patients with FTLD were identified (median age at diagnosis 68.7 years; n = 308 male patients [59.8%]) (Table 1). The age at study inclusion ranged between 29.4 and 88.9 years. The most common phenotypes were bvFTD (n = 185, 66.5% men), followed by PPA (n = 147, 51.0% men), PSP (n = 133, 62.9% men), and CBS (n = 22, 50% men). Forty-two patients (11.7%) had received an ALS diagnosis at the same time, and 18 even before (median 3 months) the FTLD diagnosis (ALS + FTLD). Overall, the median diagnostic delay, from FTLD symptom onset to FTLD diagnosis, was 24.8 (interquartile range [IQR] 13.5–44.1) months. The median diagnostic delay was 26 months (IQR 15–49), 3 in men, and 23 months (IQR 12–38) in women.

Table 1 Characterization of Registered Male and Female Patients With FTLD (2015–2022)

	Men (n = 308)	Women (n = 207)	Total (N = 515)
Age at diagnosis, y, mean (SD)	68.3 (9.5)	67.6 (9.4)	68.0 (9.5)
Age at diagnosis, y, median (Q1, Q3)	69.6 (61.0, 75.9)	68.0 (60.9, 75.7)	68.7 (61.0, 75.8)
Diagnostic delay, mo, median (Q1, Q3)	26 (15, 49)	23 (12, 38)	24.8 (13.5, 44.1)
Variants, n (%)[a]			
PPA	75 (24.4)	72 (34.8)	147 (28.5)
nfvPPA	17 (5.5)	18 (8.7)	35 (6.8)
svPPA	18 (5.8)	15 (7.3)	33 (6.4)
lvPPA	20 (6.5)	26 (12.6)	46 (8.9)
PPA not further specified	21 (6.8)	15 (7.3)	36 (7.0)
PSP/CBS	95 (30.8)	56 (27.1)	151 (29.3)
PSP	86 (27.9)	47 (22.7)	133 (25.8)
CBS	11 (3.6)	11 (5.3)	22 (4.3)
bvFTD	123 (39.9)	62 (30.0)	185 (35.9)
FTLD not further specified	29 (9.4)	26 (12.6)	55 (10.7)
ALS + FTLD	41 (13.3)	19 (9.2)	60 (11.7)
ALS + PPA	5 (1.6)	1 (0.5)	6 (1.2)
ALS + PSP/CBS	4 (1.3)	0 (0.0)	4 (0.8)
ALS + bvFTD	25 (8.1)	15 (7.3)	40 (7.8)
ALS + FTLD not further specified	9 (2.9)	3 (1.5)	12 (2.3)

Abbreviations: ALS = amyotrophic lateral sclerosis; bvFTD = behavioral variant frontotemporal dementia; CBS = corticobasal syndrome; FTLD = frontotemporal lobar degeneration; lvPPA = language variant PPA; nfvPPA = nonfluent variant PPA; PPA = primary progressive aphasia; PSP = progressive supranuclear palsy; svPPA = semantic variant PPA.
[a] The sum of the variants may add up to >100% because of an overlap of few patients.

The average annual raw incidence was 0.77 (95% CI 0.71–0.84) per 100,000 person-years, and the age-standardized raw incidence was 0.76 (95% CI 0.69–0.82) per 100,000 persons-years (Table 2). In the target population, the age-standardized incidence rates ranged between 0 and 1.90 per 100.000 person-years. In general, only small differences between the raw and age-adjusted rates were observed. Thus, we further focus and report the age-standardized values.

The age-standardized incidence rate was higher in men (0.96 per 100,000 person-years [95% CI 0.86–1.07]) than in women (0.55 per 100,000 person-years [95% CI 0.48–0.64]), with an IRR of 1.73 (95% CI 1.44–2.08). There was little difference in the incidence rates between phenotypes, with 0.27 (95% CI 0.24–0.32) for bvFTD, 0.23 (95% CI 0.19–0.27) for PSP/CBS, and 0.21 (95% CI 0.18–0.25) per 100.000 person-years for PPA. However, sex-specific differences for incidence rates were in particular evident for bvFTD and PSP/CBS. For bvFTD, the IRR of 2.23 (95% CI 1.63–3.05) doubled the one of females, with respective incidence rates of 0.38 (95% CI 0.32–0.45) and 0.17 (95% CI 0.13–0.22). A similar pattern was observed for PSP/CBS with an IRR of 2.02 (95% CI 1.44–2.83), and incidence rates of 0.31 (95% CI 0.25–0.37) and 0.15 (95% CI 0.12–0.20) for male and female patients, respectively. By contrast, the IRR of 1.25 (95% CI 0.90–1.75) in the PPA/CBS patient group was only moderately increased, with similar incidence rates for both sexes 0.23 (95% CI 0.19–0.29) and 0.19 (95% CI 0.14–0.24).

Figure 1 shows the age-specific incidence rates by sex. In men, FTLD incidence peaked in the 65–74 age group at 3.78 (95% CI 3.15–4.54) and 1.47 (95% CI 1.10–1.96) for PSP/CBS. The highest age-specific incidence rates in women were observed in the 60–64 and 65–74 age groups at 1.84 (95% CI 1.35–2.51) and 1.88 (95% CI 1.47–2.40), respectively. Regarding phenotypes (eTable 2), the age-standardized incidence of PPA peaked at 0.78 (95% CI 0.49–1.26) in the 60–64 age group, whereas the incidence rates of PSP and bvFTD were similar in the 65–74 age group (0.59 [0.38–0.91] and 0.56 [0.36–0.88], respectively). The overall incidence rate in men, started to rise slightly earlier than that in women. This increase began in the

Table 2 FTLD Incidence Rates (per 100,000 Person-Years) in the ALS-FTLD Registry Swabia in Men and Women (2015–2022)

	Male: 33,113,957 person-years			Female: 33,470,629 person-years			Male vs female	Total: 66,584,586 person-years		
	Patients	Raw rate (95% CI)	Age-standardized[a] rate (95% CI)	Patients	Raw rate (95% CI)	Age-standardized[a] rate (95% CI)	Age-adjusted IRR (95% CI)	Patients	Raw rate (95% CI)	Age-standardized[a] rate (95% CI)
FTLD spectrum	308	0.93 (0.83–1.04)	0.96 (0.86–1.07)	207	0.62 (0.54–0.71)	0.55 (0.48–0.64)	1.73 (1.44–2.08)	515	0.77 (0.71–0.84)	0.76 (0.69–0.82)
PPA	75	0.23 (0.18–0.28)	0.23 (0.19–0.29)	72	0.22 (0.17–0.27)	0.19 (0.14–0.24)	1.25 (0.90–1.75)	147	0.22 (0.19–0.26)	0.21 (0.18–0.25)
PSP/CBS	95	0.29 (0.23–0.35)	0.31 (0.25–0.37)	56	0.17 (0.13–0.22)	0.15 (0.12–0.20)	2.02 (1.44–2.83)	151	0.23 (0.19–0.27)	0.23 (0.19–0.27)
bvFTD	123	0.37 (0.31–0.44)	0.38 (0.32–0.45)	62	0.19 (0.14–0.24)	0.17 (0.13–0.22)	2.23 (1.63–3.05)	185	0.28 (0.24–0.32)	0.27 (0.24–0.32)

Abbreviations: ALS = amyotrophic lateral sclerosis; bvFTD = behavioral variant frontotemporal dementia; CBS = corticobasal syndrome; FTLD = frontotemporal lobar degeneration; IRR = incidence rate ratio; PPA = primary progressive aphasia; PSP = progressive supranuclear palsy.
[a] Standardized to the European standard population 2013.

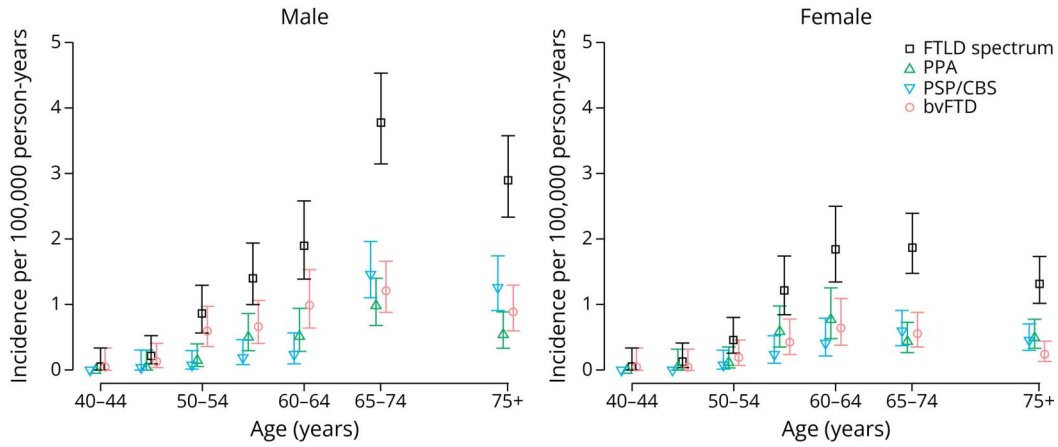
50–54 age group (0.86 [95% CI 0.57–1.29] vs 0.46 [95% CI 0.26–0.81]) and was primarily driven by bvFTD (0.60 [95% CI 0.37–0.98] vs 0.19 [95% CI 0.08–0.46]).

Survival data were available for 392 patients with FTLD (eTable 3), with similar age and sex distribution as in the entire cohort. The median survival time by age groups with 95% CI of all patients with FTLD is shown in Figure 2 and eTable 4. During a follow-up time of 15,595 person-months in 392 patients, 209 deaths occurred. Overall, the median survival from diagnosis was 53.6 (95% CI 50.9–62.0) months. By phenotypic subgroup, the median survival was 73.1 (95% CI 63.6–82.8) months for PPA, 49.5 (95% CI 39.2–53.7) months for PPS/CBS, and 42.8 (95% CI 35.1–64.3) months for patients with bvFTD. The shortest median survival was observed for patients with ALS-FTLD with 12.6 months (95% CI 9.6–27.6). Overall, there was no statistically significant difference in survival times by sex (survival time ratio for females vs males: 1.18 [95% CI 0.93–1.49]).

Discussion

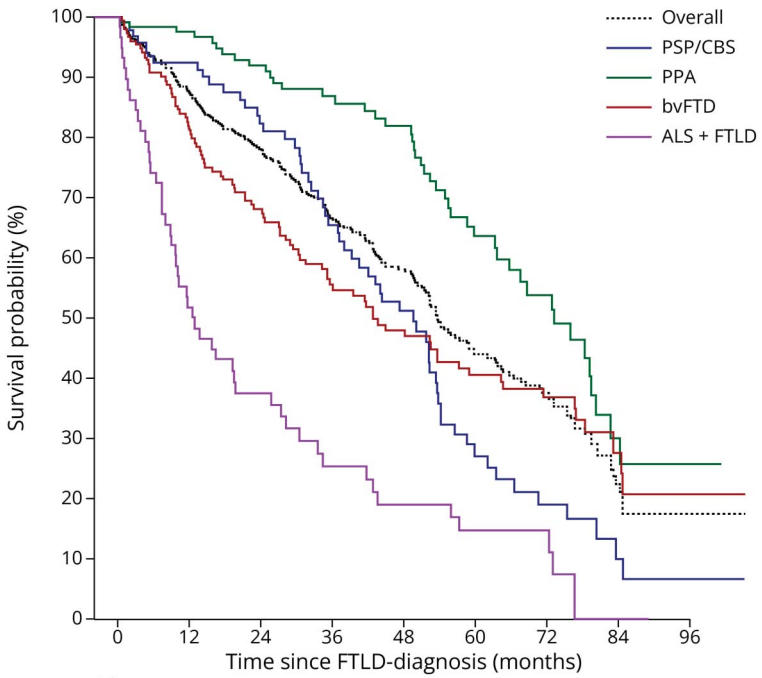
Previous data on incidence and survival times of patients with FTLD are scarce and mostly based on small sample sizes and/or from registries that are not population-based. Here, we present results from the large population-based ALS-FTLD registry Swabia, which provides population-based data with a high capture rate from a defined geographically region in southwestern Germany.

Figure 1 Age-Specific FTLD Incidence Rates With 95% CI (per 100,000 Person-Years) in Men and Women in the ALS-FTLD Registry Swabia (2015–2022)



ALS = amyotrophic lateral sclerosis; bvFTD = behavioral variant frontotemporal dementia; CBS = corticobasal syndrome; FTLD = frontotemporal lobar degeneration; PPA = primary progressive aphasia; PSP = progressive supranuclear palsy.

Figure 2 Survival Probability by FTLD Variant in the ALS-FTLD Registry Swabia (2015–2022) Based on 392 Patients With Available Survival Data



Events at risk:

0	49	82	119	141	175	188	206	209
392	316	271	192	153	93	63	18	5

ALS = amyotrophic lateral sclerosis; bvFTD = behavioral variant frontotemporal dementia; CBS = corticobasal syndrome; FTLD = frontotemporal lobar degeneration; PPA = primary progressive aphasia; PSP = progressive supranuclear palsy.

The age-standardized incidence rates in the ALS-FTLD registry were much lower than the estimated annual incidence rate for FTLD in other European studies. A previous study, which included patients from 9 different European countries,[7] calculated an incidence of 2.36 patients per 100,000 person-years. However, this study only recruited 267 patients from several European countries, and it was not population-based. High regional variability was reported across different countries, with age-adjusted incidence rates ranging from 7.01 (4.24–10.91) in Northern Sava in Finland to 0.42 (0.05–1.52) in Zuid-Holland Zuid, the Netherlands.[7] Incidence rates based on the Swedish Dementia Registry in defined regions in Sweden were substantially lower and closer to the figures obtained in this study, ranging from 1.17 (Stockholm) to 2.07 (Lund).[19]

Turcano et al.[8] found an age-standardized and sex-standardized incidence of 4.3 per 100,000 person-years in Olmsted County, Minnesota, based on record-linkage and the identification of ICD codes. By using a population-based referral system Coyle-Gilchrist et al.,[20] identified patients and estimated an age-standardized incidence rate of 1.61 per 100,000 person-years for patients with FTLD in the United Kingdom. More previous publications using a population-based approach have revealed incidence rates from 2.7 to 4.1,[3] or approximately 1.3 per 100,000 person-years in Spain.[21] These results suggest that the type of study and the geographic region substantially influence the estimated incidence rates. Considering the strong genetic contribution to the pathogenesis of most FTLD subtypes, it is not surprising that incidence rates could vary across different European regions. Furthermore, population-based studies (which are more quantitative) usually tend to reveal lower incidence rates of FTLD than those reported to date.

Our finding that the incidence rate of FTLD was 73% higher in men than in women is consistent with previous reports.[7,8] However, other studies have reported only minor sex-dependent differences in FTLD incidence in population-based[20] or clinical settings,[22] or even higher incidence rates in women.[19] Turcano et al. analyzed 15 years data from the medical records in Olmsted County (1995–2010) and found the overall incidence rate of 4.3 per 100,000 person-years, based on 35 patients. Their data showed an increase in the incidence of FTLD in men and women from 2002 onward, which may indicate increasing awareness or changing demographics.

In our study, sex differences were primarily attributed to the approximately two-fold higher incidence rates of bvFTD and PSP/CBS in men when compared with women. For the other FTLD phenotypes, the sex differences were less pronounced. This phenotypic pattern of sex-dependent incidence rates is consistent with other reports from Europe[7,22,23] as well as North and South America.[8,24]

The age distribution in our study was consistent with that in previous population-based studies.[7,19,20] In the FRONTIERS study, more than 60% of patients with FTLD were aged 65 years or older and the incidence peaked at 71 years of age.[7] Coyle-Gilchrist et al.[20] observed a similar pattern, which is mainly related to the distribution of bvFTD. However, in this study, the incidence rate of PSP peaked at 70–74 years, and the incidence rates of CBS and nfvPPA at 75–79 years, which was higher than in our study.[20]

The bvFTD phenotype was the most frequent subtype in our study, consistent with previous reports.[9,17] The distribution of phenotypes may reflect a greater degree of robustness, and therefore homogeneity of incidence, of the diagnostic criteria for PPA compared with those of CBS or PSP across centers. Alternatively, differences in the coverage of movement disorder phenotypes across referral centers[7,25] or a real heterogeneity of the frequency of CBS or PSP phenotypes or a combination of these factors,[6] may also be relevant.

In line with previous reports, we found that the median survival from diagnosis was longer in PPA than in the other clinical FTLD subtypes.[8] A meta-analysis by Kansal et al.[4] reported that bvFTD (8.17 years) and nfvPPA (8.11 years) had the longest mean survival times from onset. PSP (6.38 years) and CBD (6.40 years) generally had shorter survival than bvFTD. However, FTLD was also found to be a relatively homogeneous disease in terms of survival. In a registry-based Italian study, the median survival was 8.16 years from disease onset and 5.38 years from diagnosis.[9] In this study, survival rates did not differ between phenotypes. In our study, however, the overall median survival of patients with PPA was 29 months longer than that of patients with PSP/CBS. Among the patients with PSP/CBS, we observed the longest survival in the 50–54 age groups, whereas survival was shorter in older patients. These differences could be explained by a later diagnosis or by the higher prevalence of comorbid conditions in older age groups. In a review El-Wahsh et al.[26] identified potential clinical indicators, such as phenotype, as well as genetic, metabolic, and radiologic factors, as being associated with survival. We found no statistically significant difference in survival times by sex. In a study focusing on bvFTD, the mean survival time was longer in men than in women.[25]

In addition, variations in the incidence rates and median survival could have been influenced by differences in age and sex distributions and variations in phenotypes. In the ALS-FTLD registry Swabia, 515 patients were recruited between 2015 and 2022, and during 15,595 person-months of observation, 209 deaths occurred in 392 patients. Previous reports suggest that the awareness of the diagnosis has evolved over time alongside the definition of the phenotypes.[8,27] Onyike et al.[27] reported wide variations in the prevalence and incidence of FTLD worldwide. These authors suggested that these differences may be partially because of cultural influences on symptom expression.[27]

The diagnosis of FTLD is challenging and is based on clinical and neuropsychological assessment. In our study, patients with unclear or suspicious diagnoses were followed up clinically, and only longitudinally verified disease cases were registered. All available information, including medical reports and MRI scans, were used to confirm the FTLD diagnosis. The presentation of symptoms is heterogeneous, and the overlap of motor and cognitive symptoms (e.g., PSP and CBS) adds to the complexity. In our study, 22 patients (4.3%) presented with symptoms from 2 and 1 patient presented with symptoms from 3 phenotypes, highlighting that distinguishing between the FTLD variants clinically is often difficult and challenging for diagnosis.[6]

To date, data on FTLD remain limited, and further research into the natural history of the disease is required to improve the understanding of the differences in the clinical presentation and their underlying causes. The diagnostic criteria have been adapted in recent years, and their application may depend on the clinical discipline and setting.[27,28]

The strengths of this study include the high standards of data collection, the extensive neurologic and psychiatric network involved, and the ascertainment of case diagnoses in the established and trained ALS-FTLD registry Swabia. Newly diagnosed patients were interviewed and reviewed by experienced board-certified neurologists and psychiatrists strictly according to established diagnostic criteria.[12-14] A large number of caregivers (clinics and private practices) were contacted to identify patients in the target population. However, the possibility of underreporting in one or another district of our target region cannot be completely ruled out. We accounted for this in a sensitivity analysis (excluding 7 districts with age-standardized rates <0.35 per 100,000 person-years) (eTable 5). However, owing to the otherwise stable incidence numbers, the overall age-standardized incidence rate remained almost unchanged (eTable 5). In addition, misclassification of other psychiatric and neurologic diagnoses, as well as delays in diagnosis, may have biased the completeness of the registry.

Compared with the literature, we observed a low incidence rate, with men having a 75% higher incidence rate than women. In men, the incidence increased in the age group around 50 years old, primarily caused by patients with bvFTD. In women, the incidence increased slightly later, at around 55 years of age, and was mainly related to PSP. The median survival time for patients with PSP/CBS was substantially shorter than that of patients with PPA. The best prognosis had young-onset cases, at age 50 years.

Further research is needed to understand the interaction between ethnicity, environment, and social background of the FTLD spectrum. Cultural factors should also be considered in the diagnostic procedure because FTLD phenotypes are defined according to the profile of disability and dysfunction, behavioral changes, language deficits, or a combination of cognitive and neurologic symptoms.

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Author Contributions

G. Nagel: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. R.S. Peter: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. Z. Uzelac: major role in the acquisition of data. D. Wernecke: analysis or interpretation of data. L. Niehaus: major role in the acquisition of data. T. Trottenberg: major role in the acquisition of data. M. Jöbges: major role in the acquisition of data. C. Dettmers: major role in the acquisition of data. H. Bäzner: major role in the acquisition of data. A. Börtlein: major role in the acquisition of data. K. Althaus: major role in the acquisition of data. K. Mayer-Freitag: major role in the acquisition of data. P. Ratzka: major role in the acquisition of data. M. Naumann: major role in the acquisition of data. A. Lindner: major role in the acquisition of data. A. Chatzikonstantinou: major role in the acquisition of data. F. Andres: major role in the acquisition of data. G. Arnold: major role in the acquisition of data. M. Blickhan: major role in the acquisition of data. C. Opherk: major role in the acquisition of data. B. Knier: major role in the acquisition of data. M. Ertl: major role in the acquisition of data. J. Metrikat: major role in the acquisition of data. R. Huber: major role in the acquisition of data. C. Thomas: major role in the acquisition of data. R. Kozian: major role in the acquisition of data. H. Kimmig: major role in the acquisition of data. K. Demuth: major role in the acquisition of data. M. Hecht: major role in the acquisition of data. C. Foerch: major role in the acquisition of data. C. Kloetsch: major role in the acquisition of data. M. Reinhard: major role in the acquisition of data. D. Bengel: major role in the acquisition of data. O. Neuhaus: major role in the acquisition of data. M. Buttmann: major role in the acquisition of data. J. Volkmann: major role in the acquisition of data. E. Pinkhardt: major role in the acquisition of data. C. Lichy: major role in the acquisition of data. C. Laske: major role in the acquisition of data. J. Beattie: major role in the acquisition of data. J. Häckert: major role in the acquisition of data. S. Jesse: major role in the acquisition of data. D. Brenner: major role in the acquisition of data. J. Weishaupt: major role in the acquisition of data. M. Otto: major role in the acquisition of data; analysis or interpretation of data. I. Uttner: analysis or interpretation of data. S. Anderl-Straub: major role in the acquisition of data; analysis or interpretation of data. D.E. Lulé: major role in the acquisition of data; analysis or interpretation of data. D. Rothenbacher: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design. A. Rosenbohm: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. A.C. Ludolph: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

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Appendix Coinvestigators

Coinvestigators are listed at Neurology.org/N.

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