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# Survival in a German Population with Frontotemporal Lobar Degeneration

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**Key Words**
Frontotemporal dementia · Frontotemporal lobar degeneration · Survival · Causes of death

**Abstract**
***Background:*** The present study aimed at analysing survival of patients with behavioural-variant frontotemporal dementia (bvFTD), semantic dementia (SD) and progressive nonfluent aphasia (PNFA). Furthermore, the objective of the study was to identify prognostic factors associated with survival and to examine causes of death. ***Methods:*** Interviews were performed with the proxies of 124 patients with frontotemporal lobar degeneration (FTLD). ***Results:*** Survival from the onset of first symptoms was significantly longer in SD than in bvFTD (10.5 years). Median survival in PNFA was 12.6 years. Age at onset, gender, education and severity of dementia at diagnosis did not significantly influence survival. We did not identify any phenocopy cases. The most frequent cause of death as reported by caregivers was respiratory system disorder. ***Conclusion:*** This study adds to the growing literature on survival in patients with FTLD and provides insights into the causes of death.

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## Introduction

In the general population, dementia caused by frontotemporal lobar degeneration (FTLD) is a rare disorder with an estimated prevalence of 18 per 100,000 inhabitants [1]. Current consensus diagnostic criteria distinguish three major clinical variants. (1) Behavioural-variant frontotemporal dementia (bvFTD) is the most common clinical phenotype of FTLD. Cerebral dysfunction predominantly in the frontal lobes generates a clinical syndrome characterized by early decline in social behaviour and personal conduct, emotional blunting, and early loss of insight. Patients present with marked changes in behaviour, often displaying a mixture of apathy and disinhibition [2, 3]. (2) Semantic dementia (SD) is defined as a disorder of language, semantics and recognition of visual percepts caused by predominantly anterior temporal pathology. The most prominent clinical picture of SD is a progressive semantic impairment. Patients are significantly impaired in word comprehension and confrontation naming [4]. Although semantic deficits dominate the clinical picture, behavioural alterations also occur [5, 6]. (3) Progressive nonfluent aphasia (PNFA) is caused by asymmetric degeneration of the frontotemporal cortex in the language-dominant hemisphere. Clinical features include a progressive loss of

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**Table 1.** Patient characteristics (mean ± standard deviation)

| | FTLD (all) | bvFTD | SD | PNFA | p |
|---|---|---|---|---|---|
| Number of patients | 124 | 81 | 21 | 22 | |
| Male/female, % | 62/38 | 65/35 | 57/43 | 54/46 | n.s. |
| Age at onset, years | 60.8 ± 9.0 | 59.8 ± 9.8 | 60.6 ± 5.3 | 64.8 ± 8.6 | n.s. |
| Age at diagnosis, years | 64.0 ± 8.8 | 63.1 ± 9.8 | 64.0 ± 4.7 | 67.5 ± 8.1 | n.s. |
| Years of education | 12.9 ± 3.2 | 12.9 ± 3.1 | 13.1 ± 3.8 | 12.5 ± 2.8 | n.s. |
| MMSE score at diagnosis | 21.8 ± 6.0 | 22.4 ± 5.6 | 22.1 ± 6.1 | 19.4 ± 6.9 | n.s. |
| CDR at diagnosis 0.5/1/2/3, % | 31/46/19/4 | 24/49/24/4 | 38/43/10/9 | 50/37/14/0 | n.s. |

n.s. = Not significant.

language function with non-fluent and agrammatic speech. Other cognitive domains are relatively spared in the early stages of the disease [2, 7–9].

FTLD is associated with reduced life expectancy. The median survival time from onset is 3–14 years, depending on the clinical and pathological subtype [10–19]. In clinical practice, patients and carers frequently inquire about the progression and prognosis of the disease. However, there are little published data to guide clinicians and counsellors when advising patients and their families. The aims of the present study were to analyse survival and causes of death in a large group of patients with clinically diagnosed FTLD and to identify factors potentially influencing survival.

## Methods

*Participants*

We conducted a prospective follow-up study on 146 patients with FTLD who had been consecutively referred to our memory clinic between 1998 and 2008. The initial diagnostic evaluation was obtained by consensus of two psychiatrists with extensive experience in the field of FTLD (J.D.-S. and A.K.). The diagnosis of FTLD was established according to the 1998 Consensus Criteria published by Neary et al. [2] and was based on information from a thorough neurological and psychiatric examination, informant interview, routine blood sampling, neuropsychological examination, structural neuroimaging (computed tomography or magnetic resonance imaging) and $^{18}$F-FDG positron emission tomography in all cases. The onset of the first symptoms of FTLD was determined retrospectively at the initial diagnostic evaluation based on caregivers' information.

*Procedures*

All patients and their health care proxies were followed up regularly – in most cases in 1-year intervals – either by a visit of the patients and their proxies at the memory clinic or by telephone. For the present study, we analysed the data gathered in interviews with the health care proxies in 2009. Informant interviews were conducted with 124 out of 146 patients who had been initially diagnosed with FTLD. Of these, 81 had bvFTD, 21 had SD and 22 had PNFA. Twenty-two patients were excluded for the following reasons: lost to follow-up (n = 20), and diagnosis of FTLD combined with motor neuron disease (MND; n = 2). Information was collected on the current status. If applicable, caregivers were asked about circumstances, cause and time of death. Informed consent according to the Declaration of Helsinki was available for all patients. The study protocol was approved by the local ethics committee.

*Statistical Analyses*

Patient characteristics are described as means ± standard deviations. The $\chi^2$ test, or if appropriate Fisher's exact test, was used to compare frequencies. For all other demographic and neuropsychological factors, a one-way analysis of variance was performed to compare mean values between the three diagnostic subgroups. Survival analyses were conducted using Kaplan-Meier methods (95% confidence intervals). Survival curves across diagnostic groups were examined with log rank tests. The effect of possible confounders (demographic and neuropsychological factors) on survival was examined by using Cox's proportional hazards regression. Estimates of hazard ratios are presented with 95% confidence intervals. All statistical tests were performed two-sided, and a p value less than 0.05 was considered to indicate statistical significance.

## Results

*Patient Characteristics*

Characteristics of the patients are shown in table 1, including 72 patients who were still alive at the time of the interview and 52 patients who had already died before the interview.

In the bvFTD group, men were overrepresented, but there was no statistically significant difference between the diagnostic categories regarding gender distribution.

**Table 2.** Stratification of survival by CDR status

| CDR | n | Survival from onset median (95% CI) | Survival from diagnosis median (95% CI) |
|---|---|---|---|
| All | 124 | 11.8 (10.3–13.3) | 6.9 (4.3–9.5) |
| 0.5 | 38 | 12.5 (7.5–17.5) | 9.1 (5.2–12.9) |
| 1 | 57 | 11.6 (9.0–14.1) | 6.0 (3.3–8.7) |
| 2 | 24 | 11.8 (7.4–16.2) | 8.8 (5.5–12.1) |
| 3 | 5 | 6.7 (6.5–6.9) | 4.6 (3.2–6.1) |

The age at onset of first symptoms in the whole FTLD group was 60.8 ± 9.0 years and the age at diagnosis was 64.0 ± 8.8 years. On average the patients had 13 years of education. The mean diagnostic latency, defined as the time between onset and diagnosis, was 3.2 years. For these variables, no significant differences between the subgroups were detected. The Mini Mental State Examination (MMSE) score at diagnosis was available for 110 of 124 patients; the mean score was 21.8 ± 6.0. The average observational period between diagnosis and death or the final interview was 4.8 ± 2.8 years.

Clinical Dementia Rating (CDR) was assessed in all 124 patients at the diagnostic visit (table 2). Severity of dementia according to the CDR score was questionable (CDR = 0.5) in 33.0%, mild (CDR = 1) in 44.4%, moderate (CDR = 2) in 20.2% and severe (CDR = 3) in 2.4%. There were no significant differences (Fisher's exact test, p = 0.055) regarding severity of dementia between diagnostic subgroups.

*Survival Analysis*

During the observational period, 52 out of the 124 patients died (42 with bvFTD, 3 with SD, and 7 with PNFA) (table 3). Forty-eight percent of the deceased patients had died in a nursing home, 22% in a hospital and 30% at home. The mean age at death was 67.5 ± 10.8 years (range: 44–90 years). Median survival in patients with FTLD was 6.9 years from diagnosis to death and 11.8 years from the onset of symptoms to death. A stratification of survival by CDR status is provided in table 2.

Among the three diagnostic subtypes, patients with bvFTD showed a significantly shorter survival time as compared to SD patients (from diagnosis to death: p = 0.005; from onset to death: p = 0.009) (fig. 1).

Median survival in the bvFTD group was 5.9 years from diagnosis and 10.5 years from symptom onset. Median survival in the SD group could not be defined because less than half of the patients had died at the end of the observational period. Median survival in PNFA was intermediate between the other subtypes with 9.0 years since diagnosis and 12.6 years since age onset.

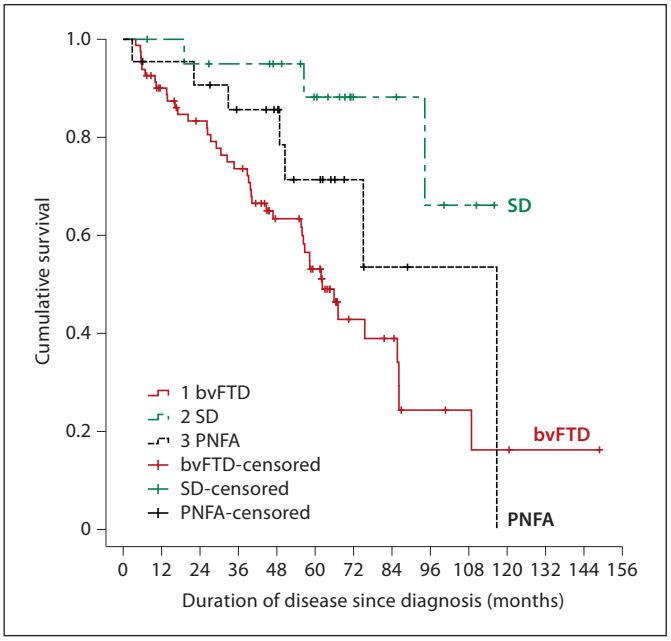


**Fig. 1.** Kaplan-Meier survival curves for bvFTD, SD and PNFA patients. Disease duration is given in months since diagnosis; + denotes censored cases.

In a Cox proportional hazard model, the contribution of age at onset, sex, years of education, MMSE and CDR at diagnosis to risk of death was analysed (table 4). Neither the demographic factors nor the MMSE results or severity of dementia were significantly associated with survival, neither in the whole group nor in the three subgroups.

*Causes of Death*

In 11.5% of the patients, the cause of death was unknown. The most common causes of death were respiratory system disorder (27%), circulatory system disorder (19%) and cachexia (14%). Within the respiratory system group, pneumonia accounted for more than half of the causes of death followed by choking on food. 11.5% of the patients died of cancer. Fourteen patients died within 5 years after symptom onset. Of these rapid cases, the cause of death was unknown in 29%, 29% died of pneumonia, 14% of cachexia, 14% of carcinoma, 7% of circulatory system disorder and 7% due to an accident.

In 7 cases (6 FTD, 1 SD), a relatively sudden death (death within hours in patients who had been considered

**Table 3.** Characteristics of the deceased patients (mean ± standard deviation)

| | FTLD (all) | bvFTD | SD | PNFA | p |
|---|---|---|---|---|---|
| Number of patients who died | 52 | 42 | 3 | 7 | <0.01* |
| Age at death, years | 67.5 ± 10.8 | 66.9 ± 11.1 | 72.0 ± 2.6 | 73.0 ± 5.9 | n.s. |
| Duration of illness from onset to death, years | 8.35 ± 5.5 | 8.2 ± 5.9 | 8.7 ± 2.9 | 8.9 ± 4.9 | n.s. |

* SD < bvFTD; n.s. = not significant.

**Table 4.** Hazards since onset and diagnosis

| | From onset to death | | From diagnosis to death | |
|---|---|---|---|---|
| | p value | HR (95% CI) | p value | HR (95% CI) |
| Age at onset | 0.185 | 1.03 (0.98–1.07) | 0.593 | 1.01 (0.97–1.05) |
| Gender | 0.748 | 0.90 (0.46–1.75) | 0.351 | 0.73 (0.38–1.41) |
| Education | 0.262 | 0.93 (0.83–1.05) | 0.225 | 0.93 (0.83–1.04) |
| MMSE at diagnosis | 0.822 | 0.99 (0.94–1.05) | 0.342 | 0.97 (0.92–1.03) |

HR = Hazard ratio.

as physically healthy) was described. In one of these cases, ventricular fibrillation was diagnosed; in all other cases, the cause of the sudden death remained unclear.

A comparison with the causes of death of the general population aged 45 years and older provided by the German official statistics of 2007 *(Statistisches Bundesamt)* [20] revealed that circulatory system disorder (45%) and neoplasm (27%) were more frequent in the general population compared to patients with FTLD, whereas respiratory system disorder (8%) and cachexia (1%) were less frequent.

## Discussion

In a large group of patients with FTLD, we found a mean survival of 11.8 years from disease onset and 6.9 years from diagnosis, which is longer than it has been shown in patients with Alzheimer's disease, i.e. 4.2 years for men and 5.7 years for women [21]. Our findings are similar to the results of a recent study in Korea [12]. However, we found a somewhat longer median survival time in the bvFTD subgroup (10.5 years) compared to a number of previous studies which reported median survival times of 7.6 [16] and 8.7 years [14] from symptom onset to death and 4.2 years from initial evaluation to death [15]. A thorough review of the patients' files did not reveal any 'phenocopy' cases that might have explained a longer survival time in our patient sample. Phenocopy cases have previously been described as fulfilling clinical bvFTD criteria while showing a relatively preserved functioning of activities of daily living (non-progressors) [22, 23]. All patients in our study showed a continuous – although sometimes slow – progressive course of their illness with a significant functional decline: in all patients with a CDR of 0.5 or 1 at the diagnostic visit, the CDR sum of the boxes increased with time. Most likely, the consequent (as far as possible) exclusion of patients with MND caused the longer survival time in our sample. In numerous studies, it has been shown that the progression to death is fastest in patients with bvFTD with coexisting MND [10, 14, 24]. In most survival analyses, patients with FTD-MND are included, so that survival times found in these studies might not be representative for patients with FTLD without MND and might therefore not be useful for advising patients, caregivers and health care institutions in clinical practice. An exception is the study of Xie et al. [25] who have excluded patients with clinical MND in their survival analysis of autopsy-proven FTLD. With a median survival of 6.6 years from onset, survival in this study was shorter than in most other studies (even those including FTLD with MND) so that it cannot be exclud-

ed that the subjects enrolled in the autopsy program were sicker – as the authors discuss themselves.

Survival in all three diagnostic groups was very variable. Patients with FTLD died between a few months and 12 years after diagnosis. In accordance with the results of a recent study on SD, we found that patients with SD survived significantly longer than patients with bvFTD [11]. The reasons for this difference are still unclear. The clinical impression is that in contrast to bvFTD and PNFA, patients with SD develop neurological deficits and dysphagia very late in the disease course. These symptoms have been shown to be associated with shorter survival [26].

The results of our study do not allow an individual prognosis in patients with clinically diagnosed FTLD. Apart from diagnosis, we were unable to identify any risk factors for a shorter survival. Age at onset, gender, education and severity of dementia (measured with CDR and MMSE) at the initial visit were not significantly associated with mortality as has been shown by Roberson et al. [14] before. Whereas a previous study of survival times including 106 patients with FTLD at our centre had shown that the mortality risk was significantly higher in patients with early onset [27], this result was not replicated with the larger patient sample and longer observational periods of the present study.

Future studies will need to analyse whether the clinical management of patients with FTLD (i.e. drug treatment, speech therapy, physiotherapy, institutionalization) has any impact on survival. A biomarker which reliably predicts the rapidity of disease progression might be identified in the future.

The most frequent cause of death in FTLD was respiratory system disorder followed by circulatory system disorder and cachexia. Within respiratory system disorder, the most common cause was pneumonia followed by choking on food. These results are consistent with the findings of a study that investigated the causes of death in 890 elderly individuals with dementia of various aetiology in nursing homes [28]. The 3 most prevalent causes of death were cachexia, cardiovascular disorders and pulmonary disease, mainly pneumonia. Dysphagia and swallowing problems (leading to cachexia and/or aspiration pneumonia) are typical symptoms in FTLD. In a recent study, the patients' ability to swallow liquids and foods was assessed and abnormalities were found in 12 of 21 patients [29]. A study of Gräsbeck et al. [30], which retrospectively analysed predictors of mortality in FTLD based on a review of clinical records, showed that patients with dysphagia had a shorter survival time.

A general limitation of the present study is that postmortem examination was only available for 7 patients, confirming the clinical diagnosis in all cases. Second, survival statistics should be based upon a neuropathologically confirmed series. Third, a survival bias cannot be excluded completely. Fourth, in most cases the causes of death that were reported by the patients' caregivers were not proven by autopsy, death certificates or medical records. Unfortunately, the German National Register on Cause of Death is based on strictly anonymized death certificates, so that additional information is not available from this source. The competent authority is not allowed to give information about the cause of death, unless it was explicitly designated by the patient in life. However, the reliability of diagnoses is probably high in patients who died in a hospital or in a nursing home, which was the case for the majority of patients in this study. Fifth, the small sample sizes of the SD and PNFA patient groups limit the informative value to a certain degree.

Nonetheless, the present study on a large patient sample with FTLD adds to the growing literature on survival in patients with FTLD and provides new insights into causes of death.

## Disclosure Statement

There are no conflicts of interest.

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