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Survival in Frontotemporal Lobar Degeneration and Related Disorders: Latent Class Predictors and Brain Functional Correlates

B. Borroni, M.D.,[1] M. Grassi, Ph.D.,[2] C. Agosti, M.D.,[1] E. Premi, M.D.,[1] A. Alberici, M.D.,[1] B. Paghera, M.D.,[3] S. Lucchini, M.D.,[3] M. Di Luca, Ph.D.,[4] D. Perani, M.D.,[5] and A. Padovani, M.D., Ph.D.[1]

Abstract

Background: Establishing survival rate in frontotemporal lobar degeneration (FTLD) is a clinical challenge for defining disease outcomes and monitoring therapeutic interventions. Using the latent profile analysis (LPA) approach, we have previously suggested that FTLD patients can be grouped into specific phenotypes—"pseudomanic behavior" (LC1), "cognitive" (LC2), and "pseudodepressed behavior" (LC3)—on the basis of neuropsychological, functional, and behavioral data.
Objective: The aim of this study was to evaluate the rate of survival in FTLD, to identify predictors of survival, and to determine the likely usefulness of LPA in defining prognosis.
Methods: A total of 252 FTLD patients entered the study. A clinical evaluation and standardized assessment were carried out, as well as a brain imaging study. LPA on neuropsychological, functional, and behavioral data was performed. Each patient was followed up over a 5-year period, and institutionalization or death was considered.
Results: The survival rate was associated neither with demographic characteristics, co-morbidities, family history for dementia, nor clinical diagnosis. The presence of the three LC phenotypes was confirmed by LPA. A different survival rate was predicted by LCs, the worse prognosis being found in LC1 (hazard ratio [HR] = 15.7, 95% confidence interval [CI] = 7.2–34.9, $p < 0.001$, reference LC3). LC2 had a worse prognosis compared to LC3 (HR = 2.07, 95% CI = 0.98–4.37, $p = 0.06$). Greater hypoperfusion in the orbitomesial frontal cortex was specifically associated with LC1 compared with the other LCs.
Conclusions: A data-driven approach regarding neuropsychological and behavioral assessment might be useful in clinical practice for defining a FTLD prognosis and hopefully will lead to the possibility of identifying patient groups for the evaluation of treatment response in future trials.

Introduction

Frontotemporal lobar degeneration (FTLD) is a collective term for disorders characterized by focal frontal and temporal lobar atrophy and clinically encompasses behavioral disturbances, language deficits, and extrapyramidal features.[1] Consensus criteria have defined three prototypical FTLD variants, represented by the behavioral variant frontotemporal dementia (bvFTD), semantic dementia (SD), and progressive non-fluent aphasia (PNFA).[2,3] Progressive supranuclear palsy (PSP) and corticobasal degeneration syndrome (CBDS) are considered to be part of the spectrum of tauopathies and have been shown to overlap both clinically and neuropathologically to FTLD; therefore, they are considered under the same label overall.[4] The discrete clinical presentation at disease onset depends on the initial focal atrophy and dysfunction on neuroimaging function.[5,6] However, during the disease course, a broad convergence of different syndromes has been observed frequently, arguing for considering these diverse conditions as a unitary continuum,

[1]Center for Aging Brain and Dementia, Department of Neurology, University of Brescia, Brescia, Italy.
[2]Department of Health Sciences, Section of Medical Statistics & Epidemiology, University of Pavia, Pavia, Italy.
[3]Nuclear Medicine Unit, Brescia Hospital, Brescia, Italy.
[4]Centre of Excellence for Neurodegenerative Disorders and Department of Pharmacological Sciences, University of Milan, Milan, Italy.
[5]Vita-Salute San Raffaele University, IRCCS San Raffaele, National Institute of Neuroscience (INN) and IBFM-CNR, Milan, Italy.

whereas others describe more discrete syndromes.[7] Pathological fractionation has not lagged behind, as histochemistry and molecular biology have yielded new features.[8] Because of excessive deposits of hyperphosphorylated tau protein in affected neurons and glia, the underlying pathology of FTLD was regarded as a tauopathy.[10] However, it has been recently demonstrated that the general label of FTLD includes cases in which tau protein was not found in the brain, and the vast majority of FTLD pathology is actually recognized by TDP43/ubiquitin-positive and tau-negative inclusions or by TDP43/tau-negative and ubiquitin-positive inclusions.

Despite the large body of knowledge about clinical features and neuropathological hallmarks, the prediction of disease progression rate and its outcomes is still poor in the clinical management of patients and their caregivers; the common experience for clinicians who follow patients with FTLD is the existence of large heterogeneity in natural history not merely explained by clinical phenotypes. A subgroup of these patients shows a benign prognosis over years; others progress to institutionalization with a malignant course.[11] Following clinical presentation of FTLD, the median patients survivals were documented to be shorter than those found in Alzheimer disease (AD), but the associated predictors are still unknown.[11,12–15] Neuropathological features, i.e., tau-positive and tau-negative pathologies, have been correlated with reduced survival, but with contrasting results.[7,12,15,16]

Beyond neuropathological features, the identification of clinical factors influencing the disease course would be useful for establishing prognosis in newly diagnosed patients. In fact, this issue is crucial to designing the natural history of FTLD to provide counseling for patients and their relatives, to evaluate response to disease modifiers, and to establish the sample size of patients needed in future clinical trials.[17] A few available clinical works have evaluated the demographic characteristics and the positive family history for dementia as predictors of survival, but none was associated with prognosis amongst FTLD patients.[12] Only patients with normal brain magnetic resonance imaging (MRI) patterns were found to have the best prognosis over the disease course.[11] The clinical phenotypes, but FTLD with motor neuron disease, were not demonstrated to be significantly related to different survival rates as well.[18] In keeping with these findings, it is clear that the use of these predefined clinical criteria seems to not be helpful in clinical practice for this purpose.

In a series of FTLD patients,[5] we have recently applied latent profile analysis (LPA), a latent variable model that is used to detect subgroups or syndromes based on the observed relationship between chosen continuous indicators or symptoms.[19] LPA was employed to rationalize a large clinical data set with a data-driven approach, allowing us to reveal three discrete clinical presentations. On the basis of the extended neuropsychological, behavioral, and functional assessment, and blinded to clinical diagnosis, these obtained clusters were named "pseudomanic behavior," "cognitive," and "pseudodepressed behavior."[5] The follow up of these clusters in longitudinal studies would be of interest for outlining the pattern of disease progression, and to single out whether this approach might add some information for defining FTLD prognosis.

With these caveats in mind, in the present work we sought to: (1) evaluate median survival time in an Italian sample of FTLD; (2) test whether background characteristics and co-morbidities are associated with different survival; (3) test whether clinical diagnosis is associated with different prognosis; (iv) validate the LPA approach in a larger sample of FTLD patients and investigate the usefulness of LPA in predicting survival rate; and (5) identify the brain functional correlates associated to survival predictors in patients with FTLD.

Methods

Subjects

This study is part of an ongoing research program aimed at evaluating the core features of FTLD and predictors of prognosis at the Centre for Aging Brain and Neurodegenerative Diseases at the University of Brescia, Italy, between 2001 and 2007.

All subjects underwent a somatic and neurological evaluation, routine laboratory examinations, a brain structural MRI study, and a brain functional single-photon emission tomography (SPECT) study.

The diagnostic assessment involved a review of the patient's full medical history, a semistructured neurological examination, and a complete mental status evaluation by two independent and experienced reviewers (B.B., C.A.). Only patients with full consensus agreement by the reviewers were enrolled.

Demographic characteristics, co-morbidities, and the estimated age at onset of symptoms were carefully recorded. The age at onset of symptoms was based on a family report of the earliest persistently abnormal clinical feature in the domains of language, social function or personality change, executive functioning, or movement disorder. In regard to co-morbidities, history of hypertension, diabetes mellitus, hypercholesterolemia, and cardiomiopathy were assessed in each subject. Hypertension was considered present either if systolic blood pressure was >40 mmHg and diastolic pressure >90 mmHg in more than three separate measurements, or if the subject was treated with antihypertensive drugs before recruitment.[20] The diagnosis of diabetes mellitus was established according with World Health Organization (WHO) criteria. Hypercholesterolemia was considered present either if cholesterol serum levels were >220 mg/dL or if the subject was under treatment with cholesterol-lowering drugs. The presence of atrial fibrillation, ischemic cardiomyopathy, or hypertensive cardiomyopathy was also considered, according to common clinical criteria.

Patients considered to have a positive family history were those who had a first-degree relative with dementia, Parkinsonism, or motor neuron disease. No patients belonging to the same family were included.

All participants were made fully aware of the research goals, and an informed consent signature was required from all subjects. The work was conducted in accordance with local clinical research regulations and in conformity with the Declaration of Helsinki.

Inclusion criteria

The Neary and McKhann criteria for FTLD were fulfilled by all subjects.[2,3] Moreover, clinical criteria for CBDS and

PSP were fulfilled.[21,22] FTD was defined by character change and disorder of social conduct. SD was defined by a prominent comprehension disorder (impaired understanding of word meaning and/or object identity), difficulty in naming, and asking for the name of nouns and objects. PNFA was diagnosed when the first symptom was an isolated disorder of expressive language when other aspects of cognition and daily living functions were relatively well preserved. CBDS exhibited unilateral rigidity and apraxia, some of them having "alien hand." In these patients, the extrapyramidal syndrome developed first and was followed by cognitive changes. PSP showed vertical gaze palsy, repetitive falls, axial rigidity, and pseudobulbar palsy; a poor response to L-dopa treatment was counted as an additional inclusion criterion.

Exclusion criteria

Stringent exclusion criteria were applied as follows: (1) cerebrovascular disorders, previous stroke, hydrocephalus, and intracranial mass documented by MRI; (2) a history of traumatic brain injury or another neurological disease (e.g., seizures, choreoathetosis, cerebellar ataxia); (3) another extrapyramidal syndrome (e.g., Parkinson disease, Lewy body disease, vascular Parkinsonism, multiple systemic atrophy) according to current clinical criteria; (4) significant medical problems (e.g., poorly controlled diabetes or hypertension; cancer within the past 5 years; clinically significant hepatic, renal, cardiac, or pulmonary disorders); (5) major depressive disorder, bipolar disorder, schizophrenia, substance abuse disorder, or mental retardation according to criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV); (6) FTLD with motor neuron disease.

Cognitive, behavioral, and functional assessment at enrollment

At first evaluation, global cognitive function assessment was made according to a standardized battery, including the Mini-Mental State Examination (MMSE). The neuropsychological assessment was made with the following tests: Story Recall Test, Raven Colored Progressive Matrices, Rey Complex Figure Copy and Recall, Controlled Oral Word Association Test and Category Fluency, Digit Span, Token Test, Trail Making Test A and B, and De Renzi Imitation Test. Instrumental Activities of Daily Living (IADL) and Basic Activities of Daily Living (BADL) were assessed as well. Motor impairment was evaluated using the motor subscale of Unified Parkinson Disease Rating Scale (UPDRS) III. Behavioral and psychiatric disturbances were evaluated by the Neuropsychiatry Inventory (NPI), and Frontal Behavioral Inventory (FBI).

Technetium-ethylcysteinate dimer SPECT acquisition image preprocessing and analysis

For brain functional data comparisons, a group of healthy subjects ($n = 15$, mean age $\pm$ standard deviation [SD] = 56.3 $\pm$ 15.4) were recruited among patients' spouses or relatives and were included as normal controls. They were interviewed, assessed for neurological or cognitive dysfunction, evaluated for diseases that were exclusion criteria for the patients group, and underwent a brain SPECT study.

Both patients and controls were administered an intravenous injection of 1110 MBq technetium-99m ethylcysteinate dimer (^{99m}Tc-ECD; Neurolite, Bristol-Myers Squibb Pharma) in a resting condition, lying supine in a quiet, dimly lit room. All subjects were imaged using a dual-head rotating gamma camera (VG MILLENIUM GE) fitted with a low-energy, high-resolution collimator, 30 min after intravenous injection of ^{99m}Tc-ECD. A 128 $\times$ 128-pixel matrix was used for image acquisition with 120 views over a 360° orbit (in 3° steps) with a pixel size and slice thickness of 1 mm, in 27 min or more if total counts were lower than 5×10^6. Image reconstruction was performed by a ramp filtered-back projection and three-dimensionally smoothed with a Metz filter (order 3, enhancement 1.24, FWHM 6.7 mm, cut-off 0.61 cycles cm^{-1}). The reconstructed images were corrected for gamma ray attenuation using the Chang method (attenuation coefficient, 0.11 cm^{-1}).

Statistical Parametric Mapping (SPM2, Welcome Department of Cognitive Neurology, University College, London) and Matlab 6.1 (Mathworks Inc., Sherborn, MA) were used for image preprocessing. Images were spatially normalized to a reference stereotactic template (Montreal Neurological Institute, MNI), and smoothed by a Gaussian kernel of 8 $\times$ 8 $\times$ 8mm FWHM.

SPECT data analysis was performed in blind to clinical diagnoses and latent classes. Global differences in the distribution and the effect of age on the tracer's uptake were covariated out for all voxels. Comparisons across the different groups were made using *t*-statistics with appropriate linear contrasts.[23] We considered any cluster above a statistical threshold set at $p < 0.001$, uncorrected. The results were explored at $p < 0.005$ as well.

Latent profile analysis

LPA was used to determine the number and composition of groups in which participants aggregated on the basis of their indicator values. LPA is a latent variable model that serves to cluster subjects. Latent class analysis (LCA) explains the clustering of cases, based on the relationship of a set of observed (manifest) categorical indicators by assuming that the patterns of values are determined by a latent (unobserved) categorical variable. Inversely, LPA allows continuous indicators to be present. For both, the number of categories of the latent variables (i.e., number of latent classes) represents the number of different clusters in subjects. In the classic form of the LPA used here, observed continuous indicators within each latent class were assumed to be uncorrelated. In other words, the model supposes that the pairwise correlations between the continuous outcomes are due to mixing an unknown number of different classes of individuals, each having unrelated outcomes. This is also referred as a conditional independence assumption, with the idea that if a sufficient number of classes is introduced, the conditional independence is more likely to hold. Thus, the latent categorical variable captures population heterogeneity, and the parameters of the model are latent class prevalences, indicator means within latent classes, and indicator variances common to all latent classes.

We performed a sequence of five LPA models, from one to five classes, with varying across-class indicator means and across-class common indicator variances. MMSE and other

neuropsychological tests (Story Recall Test, Raven Colored Progressive Matrices, Rey Complex Figure Copy and Recall, Controlled Oral Word Association Test, Category Fluency, Digit Span, Token Test, Trail Making Test A and B), functional impairment (IADL, BADL), and behavioral disturbance (NPI, FBI) were introduced in the LPA as observed continuous indicators. The neuropsychological tests were re-expressed according to Italian Equivalent scores (range 0–4, 0 = poor performance, 4 = better performance). The UPDRS-III and De Renzi Imitation Test were excluded, because in a preliminary data analysis UPDRS-III results were uncorrelated with the selected variables, and the De Renzi Test had negligible variation.

Model parameters were estimated using the maximum likelihood estimator (MLE) based on the expectation maximization (EM) algorithm. The Akaike information criterion (AIC = $-2 \times$ model log-likelihood + $2 \times$ number of model parameters) and Bayesian information criterion (BIC= $-2 \times$ model log-likelihood + log (n) − number of model parameters) were computed to compare such competing models, and the selected model was the one minimizing either AIC or BIC. The Lo–Mendell–Rubin likelihood ratio test comparing the improvement in fit between neighboring class models (i.e., comparing k-1 and the k-class models) was also performed, and the p values were used to determine if there is a statistically significant improvement in fit for the inclusion of one more class.

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Finally, using the entropy index, the quality of the resulting classification was evaluated in terms of the separation of the latent classes. Entropy denotes how possible it is to predict class membership given the observed indicators. Values range from 0 to 1, and high values (>0.90) indicate that the latent classes are highly discriminative. The statistical significance of the parameter estimates were evaluated by t-tests (= parameter/standard error [SE]) considering robust standard errors. Multiple comparisons procedures based on the Fisher least significant difference (LSD) testing of across latent class mean estimates were used to select discriminative indicators. The significance level was established at $p < 0.05$, two-sided. All models were fit using Mplus software (version 5.10 for Windows), and full details of the computing approach can be found in user's guide.[24]

Survival analysis

Each patient was followed up over a 5-year period from the time of the study enrollment/diagnosis. The binary end point was determined: entry to nursing home or other long-term care facility (institutionalization) and death (outcome = 1), and otherwise (outcome = 0). End points were determined by clinical periodic follow up when possible, or by a telephone semistructured interview.

Survival analyses were carried out by Cox proportional hazard models, fitting univariate models (single prognostic factor entered in the multiple models), and a multivariate model (all prognostic factors entered in a single model). The prognostic variables entered into the analysis were the background predictors: age at onset of symptoms, gender, positive family history, years of schooling, and co-morbidities (i.e., hypertension, hypercholesterolemia, diabetes, and cardiomyopathy). Also entered were the predictors at the time of study enrollment: clinical diagnosis, i.e., bvFTD, SD + PNFA, CBDS, and PSP, and the Latent Class groups. Hazard ratios (HR) are given with their respective 95% confidence intervals (CI), while the significance level was established at $p < 0.01$, two-sided. Kaplan–Meier curves with log-rank *post hoc* testing were also performed. The survival analyses were conducted by SPSS software version 16 (SPSS Inc, Chicago, Ill).

Table 1. Demographic and Clinical Characteristics of Included FTLD Patients

Diagnoses	*bvFTD* (n = *116*)	*SD* (n = *8*)	*PNFA* (n = *13*)	*CBDS* (n = *60*)	*PSP* (n = *55*)
Demographic variables					
Age at evaluation, years	68.8 ± 7.2	7.8 ± 7.3	70.3 ± 8.7	66.5 ± 8.2	76.1 ± 6.0
Estimated age at onset, years	63.6 ± 7.3	67.6 ± 7.9	64.4 ± 8.8	61.3 ± 8.6	69.8 ± 6.0
Gender, F%	41.4 (48)	62.5 (5)	76.9 (10)	41.7 (25)	47.3 (26)
FH[a]	50.0 (50)	25.0 (2)	46.2 (6)	33.9 (19)	33.3 (18)
Education, years	7.1 ± 3.1	9.5 ± 3.6	6.3 ± 2.3	7.7 ± 3.7	7.2 ± 4.3
Clinical variables					
UPDRS-III	9.4 ± 10.6	4.1 ± 4.8	11.0 ± 8.6	20.7 ± 10.2	26.4 ± 14.8
MMSE	23.3 ± 6.3	21.5 ± 6.6	17.0 ± 7.3	25.5 ± 3.8	24.7 ± 6.0
NPI	17.8 ± 14.1	10.2 ± 9.7	13.3 ± 17.5	9.2 ± 9.4	9.7 ± 9.2
FBI-A	10.4 ± 8.4	10.3 ± 8.2	10.2 ± 7.3	4.0 ± 5.0	4.2 ± 4.5
FBI-B	6.2 ± 6.5	3.5 ± 3.8	1.8 ± 2.3	1.0 ± 1.6	1.7 ± 3.1
FBI-AB	16.4 ± 13.9	13.8 ± 10.7	11.9 ± 8.8	5.0 ± 6.0	6.0 ± 6.3
BADL (lost)	0.6 ± 1.4	0.3 ± 0.7	0.1 ± 0.3	0.7 ± 1.5	1.3 ± 1.9
IADL (lost)	1.6 ± 2.2	1.7 ± 2.2	2.4 ± 2.9	0.7 ± 1.4	1.4 ± 2.1

Number of subjects between brackets.

[a]Missed values are due to unknown FH.

bvFTD, Behavioral variant of frontotemporal dementia; SD, semantic dementia; PNFA, slowly progressive aphasia; CBDS, corticobasal degeneration syndrome; PSP, progressive supranuclear palsy; N, number; F, female; FH, family history; UPDRS, Unified Parkinson Disease Rating Scale; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatry Inventory; FBI, Frontal Behavioral Inventory; BADL, Basic Activities of Daily Living; IADL, Instrumental Activities of Daily Living.

Table 2. Neuropsychological Assessment in FTLD Patients

Diagnosis	*bvFTD*	*SD*	*PNFA*	*CBDS*	*PSP*
Short story	7.3 ± 4.8 (41.4)	5.5 ± 2.7 (80.0)	2.64 ± 4.2 (83.3)	7.5 ± 4.2 (31.5)	8.0 ± 3.4 (47.3)
Raven colored progressive matrices	18.1 ± 6.5 (32.5)	24.0 ± 6.4 (25.0)	18.0 ± 7.5 (60.0)	19.6 ± 6.6 (22.0)	19.1 ± 6.2 (23.6)
Rey complex figure, copy	22.3 ± 9.9 (63.2)	26.8 ± 9.3 (50.0)	25.5 ± 10.3 (58.3)	23.7 ± 10.4 (57.6)	22.0 ± 9.6 (63.9)
Rey complex figure, recall	8.2 ± 7.0 (55.4)	8.8 ± 6.3 (37.5)	7.8 ± 7.1 (66.7)	8.4 ± 6.0 (49.2)	8.6 ± 6.7 (36.7)
Verbal fluency	17.8 ± 10.7 (33.6)	17.0 ± 15.7 (50.0)	7.5 ± 6.1 (69.2)	21.3 ± 9.9 (20.3)	18.1 ± 9.0 (36.4)
Category fluency	23.8 ± 10.5 (39.5)	13.5 ± 10.8 (62.5)	11.3 ± 9.8 (92.3)	28.6 ± 10.0 (18.6)	22.1 ± 8.4 (34.5)
Digit span	5.0 ± 1.2 (17.3)	4.7 ± 1.5 (28.6)	3.9 ± 1.8 (45.5)	5.2 ± 1.1 (7.4)	4.9 ± 1.1 (14.8)
Token test	29.5 ± 4.6 (28.2)	24.0 ± 5.2 (71.4)	29.4 ± 11.4 (49.2)	30.5 ± 5.1 (20.8)	29.3 ± 7.6 (25.0)
Trail making A	175.3 ± 175.7 (38.9)	245.4 ± 212.6 (50.0)	311.1 ± 208.9 (81.8)	153.5 ± 165.6 (27.6)	195.5 ± 171.4 (49.1)
Trail making B	358.0 ± 157.9 (57.5)	354.8 ± 157.8 (62.5)	281.3 ± 149.8 (90.9)	300.1 ± 162.7 (41.4)	366.3 ± 166.3 (51.3)

Percentage of subjects with pathological scoring according to Equivalent Score (ES = 0) between brackets (percentages > 50% are underlined).

bvFTD, Behavioral variant of frontotemporal dementia; SD, semantic dementia; PNFA, Progressive non-fluent aphasia; CBDS, corticobasal degeneration syndrome; PSP, progressive supranuclear palsy.

Results

Subjects

A total of 275 enrolled FTLD patients entered the study. Nine patients were excluded because their diagnosis was not fully confirmed by the two independent reviewers, and 14 were drop-out patients. The present analysis was carried out on 252 patients. Demographic and clinical characteristics according to clinical diagnosis are reported in Table 1. Overall, FTLD patients were mild for global cognitive decline. bvFTD diagnosis was the most prevalent (46.0%); SD and PNFA diagnoses were the less prevalent (3–5%). bvFTD showed higher behavioral disturbances (NPI and FBI) compared to SD and PNFA patients, who had a different pattern of behavioral disturbances (as illustrated by high loadings in FBI-A but low scores in FBI-B); CBDS and PSP, as expected, showed the worst motor impairment.

The neuropsychological profile in bvFTD, SD, PNFA, CBDS, and PSP patients is reported in Table 2. Neuropsychological tests that resulted in pathological profiles in more than 50% of cases, according to Italian equivalent scores (ES = 0) , are underlined: bvFTD showed greater deficits in tests of executive functions (Trail Making B and copy of the Rey Complex Figure), SD patients were more impaired in language (Token test and letter and category fluency), memory (Short Story), and executive functioning (Trail Making); PNFA patients had language deficits (verbal and category fluency) and were impaired in tests of executive functioning as well (planning of the copy of Rey Complex Figure copy and Trail Making B); CBDS and PSP showed deficits mainly of tests of visuo-spatial skills (copy of Rey Complex Figure).

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Table 3. Goodness of Fit Statistics and Class Frequencies for LPA Models from 1 to 5 Latent Classes

	LC (1)	*LC (2)*	*LC (3)*	*LC (4)*	*LC (5)*
Log-L (H0)	−8549.35	−7460.50	−7242.45	−7123.22	−7015.22
n parameters	32	49	66	83	100
AIC	17162.70	15019.00	14622.84	14412.38	14230.44
BIC	17275.64	15191.94	14789.27	14621.69	14482.62
Entropy		0.911	0.952	0.933	0.929
p value		<0.001	0.0471	0.0886	0.2729
Class frequencies (%)					
n_1	252 (100)	120 (47.6)	46 (18.3)	28 (11.1)	37 (14.7)
n_2		132 (52.4)	104 (41.2)	23 (9.1)	41 (16.3)
n_3			102 (40.5)	98 (38.9)	76 (30.1)
n_4				103 (40.9)	58 (23.0)
n_5					40 (15.9)

LPA, Latent profile analysis; LC, latent class; Log-L (H0), log-likelihood of hypothesized model (H0); AIC, Akaike's Information Criterion (= −2 × model log-likelihood +2 × number of model parameters); BIC, Bayesian Information Criterion (= −2 × model log-likelihood + log(*n*) × number of model parameters); *p* value, the *p* value of Lo–Mendell–Rubin Likelihood Ratio Test (LRT) comparing k-1 and the k-class models.

Table 4. The Mean Profiles and Common Variances of the Clinical and Neuropsychological Assessment Variables According to the 3 Latent Classes of the Selected Latent Profile Analysis Model[a]

	Latent class means[b]			
Variable	*LC1 (n = 46)*	*LC2 (n = 104)*	*LC3 (n = 102)*	*Common variances*
BADL (lost functions)	**2.882**	0.420	0.125	1.359
IADL (lost functions)	**5.084**	0.798	0.376	1.515
NPI	**26.85**	11.73	9.470	124.7
FBI, A	**17.17**	6.555	4.003	34.83
FBI, B	**9.664**	2.315	2.394	20.69
Neuropsychological assessment				
MMSE	17.82	22.86	27.35	25.00
Short story (ES)	0.691	0.805	2.329	1.632
Colored progressive matrices (ES)	0.594	0.870	2.446	0.848
Rey figure, copy (ES)	0.152	0.490	2.362	1.81
Rey figure, recall (ES)	0.326	0.839	2.801	1.924
Fluency, letter (ES)	0.602	1.182	2.530	1.706
Fluency, category (ES)	0.323	0.949	2.854	1.261
Digit span (ES)	1.567	2.669	3.455	1.815
Token test (ES)	0.623	1.447	3.016	1.518
Trial-making. Test A (ES)	0.162	1.008	3.248	1.354
Trial-making. Test B (ES)	0.169	0.340	2.668	1.138

[a]All parameter estimates were statistically significant (i.e., different to zero using *t*-test, $p < 0.05$), excluding Rey Figure copy, Rey Figure recall, Trail Making A, and Trail Making B in LC1.

[b]Statistically significant ($p < 0.05$) means differences between LC1 versus (LC2, LC3) are bold and underlined, whereas between (LC1, LC2) versus LC are underlined.

LC, Latent class; BADL, Basic Activities of Daily Living; IADL, Instrumental Activities of Daily Living; NPI, Neuropsychiatry Inventory; FBI, Frontal Behavioral Inventory; ES, equivalent scores (according to Italian normative data, range 0–4; 0 = poor performance to 4 = better performance).

Latent profile analysis

LPA models were fitted with 16 variables that had from 1 to 5 latent classes (LCs) (see Table 3). The fit statistics suggested that the model with 5 LCs had the best fit, producing minimum AIC and BIC values; the model with 3 LCs had the highest separation of the LCs evaluated by entropy measure, and the improvement in goodness of fit between neighboring class models showed no statistically significant *p* values of Lo–Medell–Rubin test comparing 3 versus 4 LCs ($p = 0.089$) and 4 versus 5 LCs ($p = 0.273$). Thus, the model with 3 LCs was preferred because the estimated mean profiles were more interpretable than those with 5 LCs, and were in line with our previous study performed on 92 FTLD patients.[5]

Table 4 shows the parameter estimates for the 3 selected LCs. These parameters represent the LC prevalences, the LC-specific mean profiles, and the common variances of 16 variables considered in the LPA model. Of the total sample, 46 (18.3%) patients belonged to Latent Class 1 (LC1), 104 (41.2%) to Latent Class 2 (LC2), and 102 (40.5%) to Latent Class 3 (LC3). From cross-table frequencies displayed in Table 5 , no significant association between LCs and clinical diagnoses was found (χ^2 test = 11.99; degrees of freedom [df] = 8, $p = 0.15$). As shown in Fig. 1 , these three LCs were significantly separated from each other, with results comparable to previous analysis performed on 92 FTLD patients.[5] In particular, statistically significant pairwise mean differences, provided by multiple comparisons based on the Fisher LSD testing, suggested that the latent classes are described as follows: LC1 denoted subjects with high means on behavioral disturbances (FBI-A, FBI-B, and NPI) and daily living functional impairment (BADL, IADL) compared to the other two classes. LC3 was defined by subjects with fewer cognitive disturbances measured by this neuropsychological assessment compared to those in LC1 and LC2. Finally, LC2 represented the patients with fewer behavioral disturbances but an equal cognitive profile compared to LC1 patients. In addition, LC2 shared identical behavioral deficits, but have more pronounced cognitive impairment than LC3 patients.

In keeping with our previous study, we adopted the following clinical labels for the 3 LCs: "pseudomanic behavior" phenotype for LC1; and "pseudodepressed behavior" phe-

Table 5. FTLD Diagnosis Distribution According to Latent Classes

Diagnosis/LC	*LC1*	*LC2*	*LC3*
bvFTD	52.2 (24)	45.2 (47)	44.1 (45)
SD	2.2 (1)	3.8 (4)	2.9 (3)
PNFA	10.9 (5)	5.8 (6)	2.0 (2)
CBDS	10.9 (5)	22.1 (23)	31.4 (32)
PSP	23.9 (11)	23.1 (24)	19.6 (20)

Results are expressed as conditional latent classes percentage and number of patients between brackets. Chi-squared test = 11.99, df = 8, $p = 0.150$.

FTLD, Frontotemporal lobar degeneration; LC, Latent class; bvFTD, behavioral variant of frontotemporal dementia; SD, semantic dementia; PNFA, progressive non-fluent aphasia; CBDS, corticobasal degeneration syndrome; PSP, progressive supranuclear palsy.

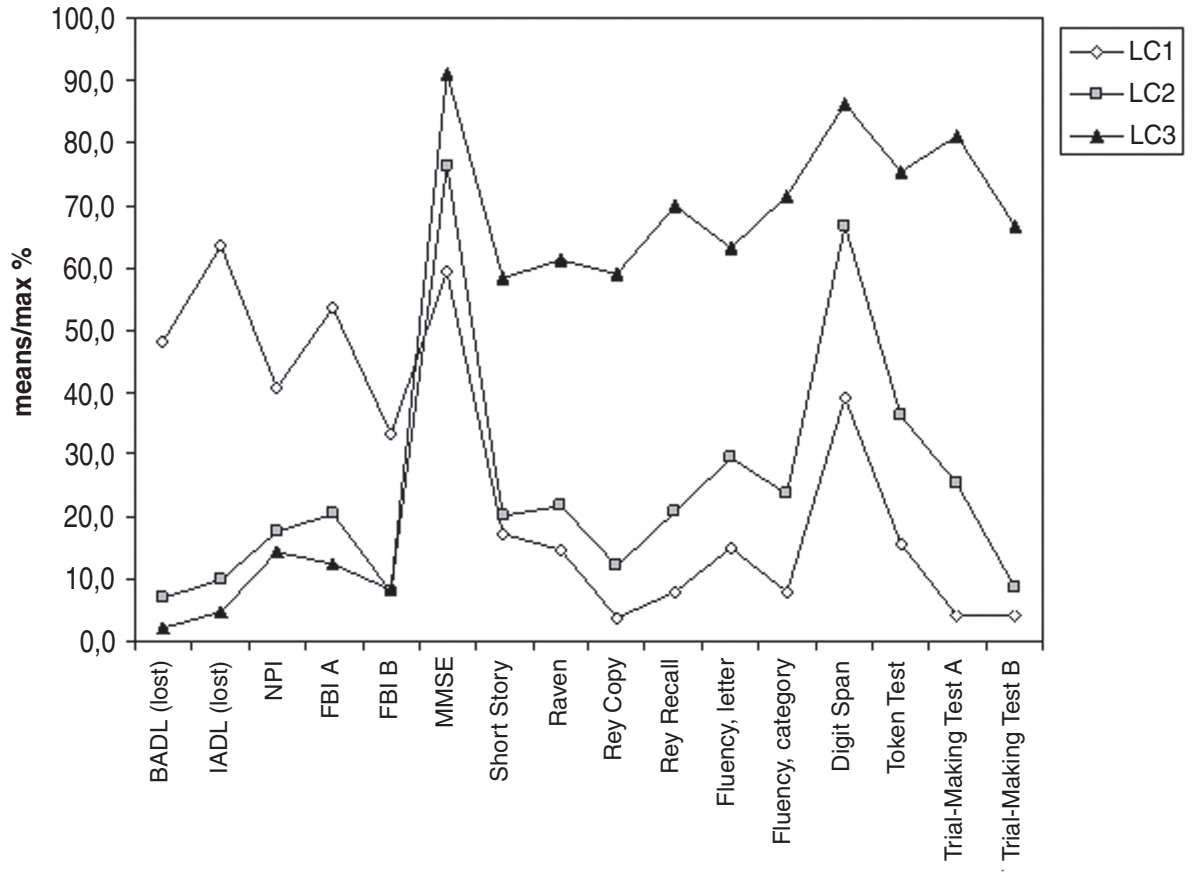

FIG. 1. FTLD patients labeled according to the generated three latent classes. Values of functional impairment (Basic and Instrumental Activities of Daily Living [BADL and IADL], behavioral disturbances (Neuropsychiatry Inventory [NPI] and Frontal Behavioral Inventory [FBI-A plus FBI-B]), and the scores of all the neuropsychological tests included in the assessment (see test for details) are reported as mean/max%. The higher the value, the worse the performance for functional and behavioral deficits; the higher the value the better the performance for neuropsychological assessment. LC1 had the worse functional and behavioral scores compared to LC2 and LC3 patients, whereas LC3 had the better cognitive scores compared to LC1 and LC2 patients. MMSE, Mini-Mental State Examination.

notype for LC3 (as the analysis of the subscores of the behavioral profile highlighted a greater prevalence of depressive symptoms); LC2 was named as the "cognitive" phenotype (see ref. 5).

Disease duration at time of evaluation did not differ among LC groups. The mean disease duration of the all sample was 5.3 years (SD = 2.7). Mean disease duration in LC1 was 6.1 (2.1), in LC2 was 5.1 (2.4), and in LC3 was 5.3 (3.0) ($p = 0.062$).

Survival analysis

Of 252 patients, 68 had been institutionalized ($n = 42$) or died ($n = 26$) throughout the 5-year observation. In the overall group, the failure rate was about 1 event per 100 person-months at risk, the average age at diagnosis was 70.1.3 ± 8.1 years, whereas the estimated age at onset of symptoms was 64.5 ± 8.1 years. The median survival time from the onset of symptoms was 102.0 months (SD = 38.3) in the overall group, whereas the median survival from diagnosis was 24.0 months (SD = 10.6).

The univariate and multivariate Cox proportional estimates using time at study enrollment/diagnosis are reported in Table 6. Age at onset of symptoms, gender, years of schooling, positive family history for dementia, and co-morbidities, i.e., hypertension, hypercholesterolemia, diabetes, and cardiomyopathy, did not significantly correlate with rate of survival, setting the significant level at $p < 0.01$, two sided. No significant differences in survival across clinical diagnoses were also observed (χ^2 test, $p = 0.151$).

Conversely, the role of LCs as a specific predictor of survival in FTLD was noteworthy. Compared to LC3, patients belonging to either LC1 (HR = 10.7, 95% CI = 5.45–20.9, $p < 0.001$ for univariate model, and HR = 15.8, 95% CI = 7.19–24.9, $p < 0.001$ for multivariate model) or patients belonging to LC2, even if not statistically significant (HR = 1.88, 95% CI = 0.93–3.85, $p = 0.08$ for univariate model, and HR = 2.07, 95% CI = 0.98– 4.37, $p = 0.06$ for multivariate model), had an increased risk of mortality/early institutionalization.

Figure 2 displays the corresponding Kaplan–Meier survival curves ($p < 0.001$ by log-rank testing): LC1 patients had the worse, LC2 the average, and LC3 the best prognosis with a median survival time of 20 months for LC1, and 60 months for LC1 and LC2. The survival probability at 5 years was 8.8%, 59.7%, and 74.7% for LC1, LC2, and LC3, respectively. Age at onset of symptoms, gender, years of schooling, positive family history for dementia, and co-morbidities did not significantly correlate with rate of survival when this was calculated from time of disease onset.

Table 6. Hazard Ratio Estimates of Prognostic Factors According to Univariate and Multivariate Cox Models

	Univariate model		*Multivariate model*[a]	
Prognostic factor	*Hazard ratio (95% CI)*	p *value*	*Hazard ratio (95% CI)*	p *value*
LC3	1 (reference)		1 (reference)	
LC2	1.89 (0.93 to 3.84)	0.079	2.07 (0.98 to 4.37)	0.056
LC1	10.7 (5.46 to 20.9)	**<0.001**	15.8 (7.19 to 34.9)	**<0.001**
bvFTD	1 (reference)		1 (reference)	
SD + PNFA	1.80 (0.88 to 3.68)	0.109	1.85 (0.80 to 4.28)	0.150
CBDS	0.57 (0.27 to 1.20)	0.140	0.98 (0.44 to 2.19)	0.967
PSP	1.13 (0.64 to 2.01)	0.678	1.36 (0.70 to 2.67)	0.364
Estimated age at onset, years[b]	1.02 (0.99 to 1.05)	0.186	1.00 (0.97 to 1.04)	0.901
Education, years	1.01 (0.95 to 1.08)	0.769	1.07 (0.99 to 1.14)	0.071
Gender (1 = male)	4.28 (0.79 to 2.08)	0.311	1.79 (0.99 to 3.24)	0.054
Family history (1 = yes)[c]	1.05 (0.64 to 1.72)	0.857	1.80 (1.04 to 3.13)	0.038
Hypertension (1 = yes)	0.77 (0.47 to 1.28)	0.312	0.94 (0.52 to 1.73)	0.850
Hyperchol (1 = yes)	0.66 (0.38 to 1.13)	0.126	0.88 (0.49 to 1.60)	0.677
Diabetes (1 = yes)	2.04 (1.04 to 3.99)	0.038	1.58 (0.72 to 3.46)	0.255
Cardiomyopathy (1 = yes)	0.83 (0.40 to 17.3)	0.616	0.93 (0.42 to 2.07)	0.859

[a]19 patients had missing values on the prognostic factors set.
[b]7 patients had missing age.
[c]17 patients had missing family history.
CI, Confidence interval; LC, latent class; bvFTD, behavioral variant of frontotemporal dementia; SD, semantic dementia; PNFA, progressive non-fluent aphasia; CBDS, corticobasal degeneration syndrome; PSP, progressive supranuclear palsy; *p* value, the *p* value of *t*-test = parameter/standard error (Wald test).

Brain functional correlates of latent classes

Finally, we sought to evaluate the brain SPECT correlates specifically associated with the worst prognosis—LC1 compared to the others. A total of 115 patients out of 252 underwent a SPECT scan. Nineteen patients belonging to LC1, 40 belonging to LC2, and 56 belonging to LC3 were compared to control subjects, respectively.

We first confirmed our previous work,[5] and a distinct functional pattern was found in LC1, LC2, and LC3 sub-

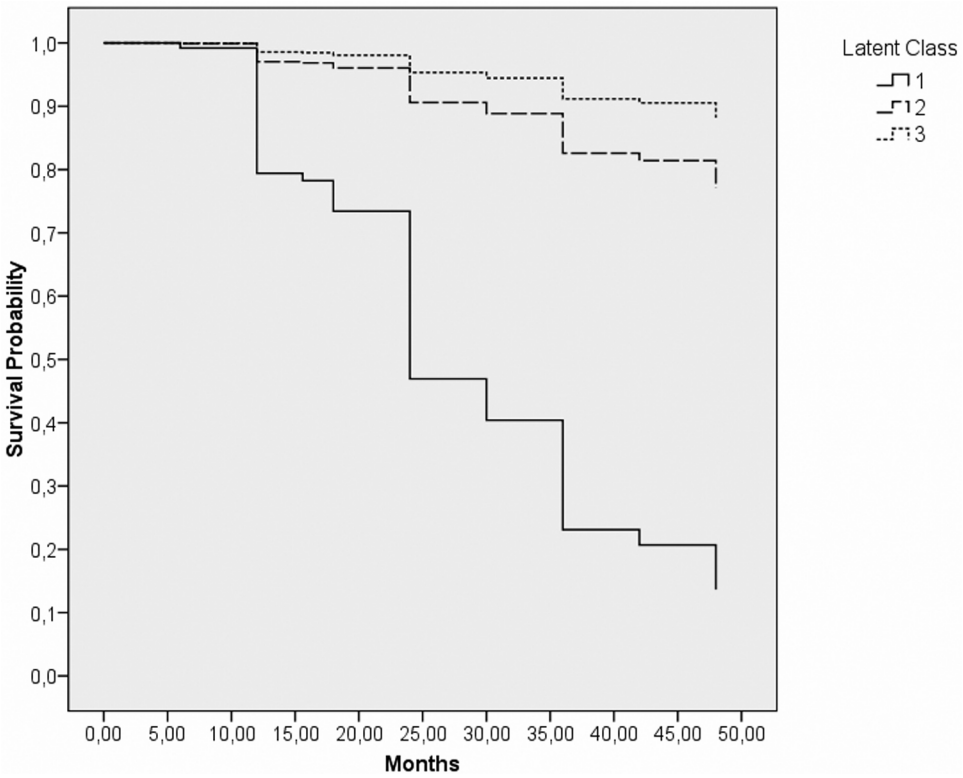

FIG. 2. Survival curves of multivariate Cox model for groups defined by latent classes.

groups. Comparisons of LC1 ("pseudomanic behavior" phenotype) versus controls showed significant hypoperfusion in medial frontal cortex ($x,y,z = -5,30,12$; T = 4.54, cluster size = 2835) and in the orbitobasal frontal cortex (−2,10,−18; T = 4.90, cluster size = 2835). LC2 ("cognitive" phenotype) versus controls showed significant hypoperfusion in the left temporal pole (−14,−40,−25; T = 2.80, cluster size = 204). LC3 ("pseudodepressed behavior" phenotype) showed comparable hypoperfusion in the left temporal pole (−14,14,−28; T = 3.10, cluster size = 318), and in the right dorsolateral frontal cortex (20,54,18; T = 3.31, cluster size = 138).

As shown in Fig. 3 , LC1 was specifically characterized by a greater hypoperfusion in the orbitomesial frontal cortex (−4,30,18; T = 5.15, cluster size = 12,088) compared to LC3; the right putamen (36,−6,6; T = 4.39, cluster size = 702), and the left superior temporal gyrus (−30,−40,18; T = 4.36) were more hypoperfused as well. The same pattern, to a lesser extent, was found when LC1 was compared to LC2, the former being characterized by hypoperfusion in the orbitomesial frontal cortex (−6,18,40; T = 5.11, cluster size = 2925) and in the right putamen (34,−10,4; T = 5.27, cluster size = 743).

The comparison between LC2 and LC3 did not yield significant differences; for completeness and according to an *a priori* hypothesis of a worse prognosis in LC2 compared to LC3 patients, the results were explored at $p < 0.005$ as well. At this threshold, LC2 showed a greater hypoperfusion in the left dorsolateral frontal cortex (−48,25,22; T = 3.34, cluster size = 508 and −28,32,42; T = 2.95, cluster size = 130) compared to LC3. The inverse comparisons, i.e., LC3 < LC1, LC3 < LC2, LC2 < LC1, did not show any voxel above the pre-established threshold.

Discussion

This study provides an estimate of the natural history in a large clinical Italian sample of 252 FTLD patients, with a median survival time for the entire group of 102 months at the time of symptom onset, and with a failure rate from the diagnosis of about 1 institutionalization/death in 100 patients-months for the entire group. We did not observe any correlation between survival and several demographic and clinical variables, including age at disease onset, education, gender, family history for dementia, and co-morbidities. When survival was analyzed according to FTLD phenotype attributed on the basis of the first symptom presentation, no significant differences were found. Conversely, the data-driven approach by LPA that identified three clinical syndromes allowed us to find clusters of patients with reduced survival.

Few longitudinal studies of disease progression have been reported in FTLD, with a total duration of about 7 years from symptom onset.[7,12,15,18] Overall, our results resemble these previous findings. Data in the literature on predictors of survival still have not identified strong associated factors at the time of diagnosis to be used in clinical practice. The available data on clinical phenotypes suggest that these did not significantly differ in term of survival over time.[7,12] Only when FTLD cases with motor neuron disease were considered was a striking effect on survival reported[12]; however, these patients are a minority of the FTLD patients, and they were excluded in the present sample. It has been demonstrated that the analysis of demographic characteristics and family history for dementia did not yield consistent results.[12,16]

In spite of these negative findings, a data-driven nosology suggested that FTLD can be summarized into three different clinical categories with a poor concordance with the current clinical classification, and these clusters fit well with different rates of survival.

LPA posits that a heterogeneous group can be reduced to several homogeneous subgroups through evaluating and then minimizing the pairwise correlations among responses

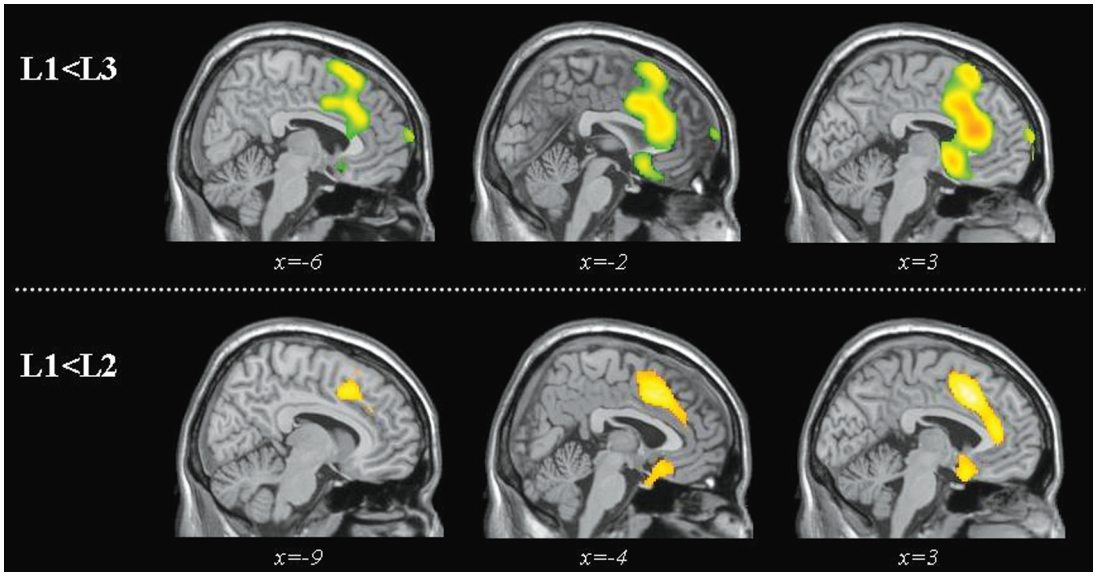

FIG. 3. Maps of significant voxels representing regions of hypoperfusion in FTLD patients belonging to LC1 (L1) compared with LC2 (L2) and LC3 (L3), superimposed on a reference T1-weighted MRI image. Statistical threshold, $p < 0.001$, T > 3.17, minimum cluster size = 50 voxels.

across multiple continuous variables. Thus, LPA is capable of determining the number and composition of unobserved latent classes that produce observed data. This is particularly useful when there is evidence that certain symptoms co-aggregate at above-normal levels (that is, symptoms that are beyond what is usually seen in patients who present certain syndrome patterns) to form distinct clusters.

Confirming our previous results in a larger sample of consecutively enrolled FTLD patients, in the present study cognitive performances, the severity of behavioral symptoms, and functional impairment defined three distinct clusters, named "pseudomanic behavior," "cognitive," and "pseudodepressed behavior." The first, i.e., LC1, was represented by greater behavioral disturbances, such as dishinibition and abnormal social conduct, as evidenced in FBI and NPI scores. The second LC2 profile was underscored by a "cognitive" phenotype, mainly characterized by executive dysfunction. The third LC3 showed better performances in neuropsychological test scores compared to the other two LCs and subtle behavioral abnormalities, represented mainly by depressive symptoms. We have also confirmed, as previously demonstrated, that the three clusters were underscored by specific functional correlates.[5]

The most relevant finding of this work was that the LPA data-driven approach was able to measure disease progression confidently in single-subject FTLD patients, as the "pseudomanic behavior" phenotype showed the worst, whereas the "pseudodepressed behavior" the best prognosis over time.

Several explanations may account for such a result. We can speculate that the worst prognosis in "pseudomanic behavior" could be likely attributed to poor coping, and health care–seeking behavior among the caregivers of patients may be a further issue influencing institutionalization. Conversely, we may hypothesize that the use of antidepressant drugs as selective serotonin reuptake inhibitors (SSRI) in "pseudodepressed patients" may favor a good prognosis by a neuroprotective mechanism. Future clinical trials will disentangle this issue.

Interestingly, SPECT analyses showed that the hypoperfusion of orbitomesial frontal regions, which are specific features of LC1 when compared to the others, are associated with a faster decline. Evidence from neuroimaging and neuropsychological studies helped to illuminate the functions of the orbitomesial frontal cortex, which is recognized to be of crucial importance in sensory integration, reward processing, decision making, reward prediction, and subjective hedonic processing, all functions that are deeply implicated in strategies for species survival.[25] Thus, deficits in this brain region are *per se* factors influencing strong outcomes linked to life expectancy, thus affecting survival through the patients' difficulties in executive functioning instead of overwhelming neurodegeneration.

The observations of the present study might have several implications in clinical practice. First, this classification stratifies patients according to risk of mortality, and thus is useful in testing therapeutic approaches on homogeneous patients. Because the effects of a disease-modifying drug must be measurable within a reasonable timeframe, LPA characterized clusters of defined survival risk for clinical trials. Second, as recently suggested,[17] the estimate of mortality risk might be of help in calculating the sample size needed to test future pharmacological and nonpharmacological interventions. In fact, the identification and enrollment of subjects at greater risk of disease progression, as in those belonging to the LC1 group, maximize power to detect a therapeutic effect and dramatically decrease the number of patients needed for power calculations. Third, this approach might provide some hints to clinicians for facing counseling and defining patients' prognosis with their care givers.

It is noteworthy that the results of this study should be replicated in other cross-sectional work to determine if the same clusters remain stable across studies and if the different related survival rates are confirmed. Moreover, we considered both institutionalization and death as outcome measures, and we acknowledge that institutionalization may be different between patients with significant behavioral disturbance and those with mostly extrapyramidal disease. Neuropathological confirmation would be necessary to understand further the relationship between clinical and neuropathological phenotypes. Indeed, we can not exclude that patients with a worse prognosis might be affected by FTD with subclinical motor neuron disease. In an era of treatment that targets disease mechanism, it would be desirable that latent class models will be used to further discriminate molecular/genetic determinants of FTLD pathology. Finally, we should further validate whether the genetic background, i.e., *APOE* status and H2 *MAPT*-Tau haplotype, influences long-term outcomes.

In conclusion, FTLD is a malignant disease but with a wide range of survival rates among patients. Latent classes might be employed in future clinical trials, and the identified clusters should be tested separately for pharmacological and nonpharmacological interventions to reduce the chance of including highly heterogeneous patients.

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Disclosure Statement

All authors have no actual or potential conflicts of interest, including any financial, personal, or other relationships with other people or organizations within 3 years of beginning the work submitted that could inappropriately influence the present work.

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Address reprint requests to:
Barbara Borroni, M.D.
Clinica Neurologica
Università degli Studi di Brescia
Pza Spedali Civili
1—25100 Brescia, Italy

E-mail: bborroni@inwind.it

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