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Validation of the revised classification of cognitive and behavioural impairment in ALS

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Abstract

Objective. In 2017, the diagnostic criteria for cognitive and behavioural impairment in ALS (ALSFTD-1) have been modified (ALSFTD-2) with the inclusion of a novel category (ALS with combined cognitive and behavioural impairment, ALScbi) and with changes of operational criteria of the other categories (ALS with cognitive impairment, ALSci, ALS with behavioural impairment, ALSbi, and ALS with frontotemporal dementia, ALS-FTD). We compared the two sets of criteria to assess the effect of the revised criteria on the cognitive classification of ALS patients.

Methods. Two cohorts of ALS patients were included in this study: a population-based cohort including patients identified through the Piemonte/Valle d'Aosta register for ALS in the 2014-2017 period (n=321), and a referral cohort recruited at the Turin ALS centre and at the ALS centre of the Maugeri Institute in Milan in the same period (n=205). Cognitive function was classified in blind by two neuropsychologists expert in ALS.

Results. ALSFTD-2 criteria determined a shift of about 15% of patients from their original category to a new one. In both cohorts about 9% of patients were re-classified to the novel category ALScbi. Among patients previously classified as cognitively normal, 14 (4.3%, population-based cohort) and 19 (9.3%, referral cohort) were re-classified as ALSbi or ALSci. The median survival of the different categories was significantly different with both with sets of criteria.

Conclusions. The new ALSFTD-2 criteria, compared to the old ones, have positive effects on the clinical practice being more sensitive to the early cognitive impairment and having a better prognostic yield.

Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease, characterized by loss of motor neurons at cortical, bulbar and spinal levels causing a progressive paresis of voluntary muscles, being fatal within 2 to 5 years from onset usually due to respiratory failure. The motor symptomatology of ALS is associated in about 50% of cases to a cognitive impairment ranging from isolate executive or behavioural deficits to frontotemporal dementia (FTD), a co-morbidity which has profound effects on ALS prognosis.[1,2] Until recently, the diagnosis of cognitive impairment in ALS has been based on the consensus criteria proposed in 2009 (ALSFTD consensus criteria, ALSFTD-1) which classified patients in ALS with co-morbid FTD (ALS-FTD), ALS with behavioural impairment (ALSbi), ALS with cognitive impairment (ALSci), and ALS with normal cognition (ALS-CN).[3] In 2017, the diagnostic criteria have been partially modified (ALSFTD-2) with the inclusion of a novel category (ALS with combined cognitive and behavioural impairment, ALScbi) and with changes of the operational criteria of the other categories.[4] The frequency and characteristics of the new cognitive subgroups in comparison to those based on the original criteria remain to be described.

The aim of this paper is to compare the ALSFTD-1 and ALSFTD-2 criteria in a population-based cohort of ALS patients and in two clinical series enrolled in referral (tertiary) ALS centres in Italy in order to assess (a) the effect of the revised criteria on the cognitive classification of ALS patients and (b) their prognostic value.

Methods

Patients. Two cohorts of patients were included in this study: (1) a population-based cohort including patients identified through the Piemonte and Valle d'Aosta register for ALS (PARALS) in the 2014-2017 period. The PARALS is a prospective epidemiological register established in 1995, whose characteristics have been already published.[5] All patients of this cohort were evaluated

at the Turin ALS centre. (2) Two referral cohorts, one enrolled at the ALS centre at the Maugeri Institute in Milan between 2014 and 2017, and the second including the patients not resident in Piemonte evaluated at the ALS centre in Turin in the same period. For the purpose of this study, the two referral cohorts have been combined.

Neuropsychological battery. In both centres ALS patients underwent a battery of neuropsychological tests encompassing executive function, memory, visuospatial function, social cognition and language, selected according to the Diagnostic Criteria for the Behavioural variant of Frontotemporal Dementia[6], and ALS-FTD Consensus Criteria[3,4]. All patients underwent the following neuropsychological battery (E-Table 1): Mini Mental State Examination (MMSE); Edinburgh Cognitive and Behavioural ALS Screen (ECAS)[7]; Wisconsin Card Sorting Test (WCST); Trail Making Test A and B (TMT A-B); Digit Span Forward and Backward; Letter and Category fluency test; Boston Naming Test (BNT); Rey Auditory Verbal Learning Test (RAVLT); Babcock Story Recall Test (BSRT); Rey-Osterrieth Complex Figure Test (ROCF); Raven's Colored Progressive Matrices (CPM47); Frontal Assessment Battery (FAB).

Neurobehavioral dysfunction was determined both with the direct observation by the neuropsychologist and patient's history,[6,8] with the behavioural screening section of the ECAS, and with the Frontal Systems Behaviour Scale (FrSBe),[9] using the Family-form evaluated by a close relative/caregiver (scores: normal ≤59, borderline 60-64; pathological ≥65). If a subject had scores reflecting a frontal systems abnormality both in the premorbid and in the post-illness forms, he/she was considered pathological only if there was an increase of ≥10 points at the T-score between the two forms [2]. Anxiety and depression were assessed with the Hospital Anxiety and Depression Scale (HADS); the item "I feel slowed down" was discussed with patients in order to have him/her not to refer to physical disability.[10]

The battery was administered following the same sequence in order to avoid the possible differential interference of the answers of one test over the others. The administration of the battery

required a median of 105 minutes (IQR 84-140), and was generally performed in the morning. If the subject felt too tired, a further session was scheduled to complete the battery, within two weeks after the first one. Patients' O_2 saturation at the time of the neuropsychological testing was measured with a pulse oximeter; none of the patients had evidence of hypoxemia (oxygen saturation <92 mm Hg). Patients underwent a neurological examination at the time of neuropsychological testing.

Cognitive classification. The original criteria (ALSFTD-1)[3] classified the patients in three main categories, besides those with normal cognition: (a) ALS patients with a FTD syndrome (ALS-FTD), who met either the Neary criteria or the Hodges criteria for FTD;[8,11] (b) patients who showed some degree of cognitive impairment, but did not meet the criteria for FTD were classified either as ALS with behavioural impairment (ALSbi) meeting at least two non-overlapping supportive diagnostic features from either the Neary criteria or Hodges criteria for FTD, or as ALS with cognitive impairment (ALSci), with evidence of cognitive impairment at or below the 5th percentile on at the least two distinct tests of cognition that are sensitive for executive functioning.

The 2017 revised criteria (ALSFTD-2)[4] made several modifications of the classification: first, it has established the novel category of ALS with combined cognitive and behavioural impairment (ALScbi), which includes patients who fulfils criteria for both ALSci and ALSbi; second, it has to some extent modified the criteria for the other three original cognitive categories. A comparison of the two sets of criteria is reported in Table 1. All patients were classified in blind by two neuropsychologists expert in ALS. When there was disagreement, the case was discussed until a final diagnosis was agreed.

Statistical methods. Comparisons between means were made with Student's t-test or analysis of variance (ANOVA); comparisons between categorical variables were made with χ^2 test. All tests were two-tailed. Rater agreement was calculated via the k statistic, which is the rate of observed agreement between all possible pairs of ratings adjusted for the proportion of agreement expected to

occur by chance.[12] Survival was calculated from onset to death/tracheostomy or censoring date (December 31st, 2017) using the Kaplan-Meier method, and compared with the log-rank test. No patients were lost to follow-up. Multivariable analysis for survival was performed with the Cox proportional hazards model (stepwise backward) with a retention criterion of $p<0.1$. A p level <0.05 was considered significant. Statistical analyses were carried out using the SPSS 25.0 statistical package (SPSS, Chicago, IL, USA).

Ethical considerations. The study was approved by the local Ethical Committees (Comitato Etico Azienda Ospedaliero-Universitaria Città della Salute e della Scienza and Comitato Etico Istituti Clinici Scientifici Maugeri). All patients provided written informed consent before enrolment. The databases were anonymized according to the Italian law for the protection of privacy.

Results

The population-based cohort included 321 patients and the referral cohort included 205 patients (Maugeri ALS centre, 109 patients, Turin ALS centre 96 patients). A comparison of the characteristics of the two series is reported in Table 2. As expected, the cases of the population-based (epidemiological) cohort are significantly older, more frequently male and with bulbar onset and have a shorter survival than those of the referral cohort. The median time from diagnosis to testing in the population-based cohort was 58 days (IQR 26-142) and in the referral cohort was 189 days (IQR 101-326).

Interrater agreement between the two blinded raters was very high. In the population based-cohort the two raters gave the same diagnosis in 303 cases and were discordant in 18, corresponding to a *k* value of 0.91 (95% c.i. 0.87-0.95). In the referral cohort it was concordant in 190 cases and discordant in 15, corresponding to a *k* value 0.87 (95% c.i. 0.81-0.94). A very good agreement was also obtained for each diagnosis (E-Tables 2 and 3).

According to the ALSFTD-1 criteria in the population-based cohort 45 patients (14.0%) were classified as ALS-FTD, 75 (23.4%) as ALSci, 19 (5.9%) as ALSbi, and 182 (56.7%) as cognitively normal. With the ALSFTD-2 criteria, 31 patients (9.7%) were re-classified to the novel category of ALScbi: of these, 28 had been previously classified as ALSci and 3 as ALSbi. Among patients previously classified as cognitively normal, 14 (4.3%) were re-classified: 8 moved to the ALSbi category and 6 to the ALSci category. Finally, 2 patients who has been previously classified as ALSci were re-classified as ALS-FTD. Overall, 47 patients (14.6%) had their cognitive category changed (Figure 1).

The reclassification of patients from ALS-CN to ALSbi was determined by the major emphasis of the ALSFTD-2 criteria on the presence of apathy as a sufficient criterion to make diagnosis of ALSbi compared to ALSFTD-1, which required two non-overlapping diagnostic features according to Neary's criteria. According to the revised ALSFTS-2 criteria for the diagnosis of ALSci, the reclassification of six patients formerly diagnosed as ALS-CN was due in five of them to the presence of impaired verbal fluency (letter), and in one to the impairment in two non overlapping tests, in which language impairment is not solely explained by verbal fluency deficits. The reclassification of ALSci and ALSbi patients to the novel ALScbi category included patients who met criteria for both categories, and was also influenced by the modification of criteria either for ALSci (impaired verbal fluency) or ALSbi (apathy). Lastly, two patients with ALSci were reclassified as ALS-FTD because of the presence of loss of insight and hallucinations, not included in the ALSFTD-1 criteria.

In the clinical-based cohort, according to the ALSFTD-1 criteria, 8 patients (3.9%) were classified as ALS-FTD, 37 (18.0%) as ALSci, 12 (5.9%) as ALSbi and 148 (72.2%) as cognitively normal. According to the ALSFTD-2 criteria, 17 (8.3%) patients were included in the novel category ALScbi: of these 14 had been previously classified as ALSci and 3 as ALSbi. Moreover, among patients who were previously classified as cognitively normal, 19 (9.3%) were re-classified as

ALSci and 1 as ALSbi. No patients were re-classified as ALS-FTD. Overall, 37 patients (18.0%) had their cognitive category changed. The change of category was due to the same reasons reported for the population-based cohort.

The shift of some patients from the previous categories to the novel ones has had some implications on the clinical characteristics of the cognitive categories (Table 3). In particular, the new ALScbi category is characterized by a higher age at onset (72.1 years, SD 6.6) than all other cognitive categories, and has a median survival (2.6 years, 95% CI 2.1-3.3) which is intermediate between that of ALS-FTD (2.1 years, CI 1.7-2.4) and ALSci (3.1, CI 2.3-3.8) (Figure 1A and 1B). Overall, the median survival of the different categories remains significantly different both with the ALSFTD-1 and ALSFTD-2 criteria (Figure 2). The other characteristics of cognitive subgroups did not modify significantly. p values of post-hoc paired comparisons are reported in E-Table 4.

Patients with non-executive impairment. The presence of non-executive impairment was searched for in the population-based cohort. A total of 11 patients showed an impairment in memory and visuospatial domains. Four of them had also an executive and/or behavioural impairment (2 ALSci and 2 ALScbi), while 7 were classified as cognitively normal according to the ALSFTD-2. These non-executive impaired patients were slightly older (70.1 years, SD 8.3) and had more frequently a bulbar onset (6 cases, 54.5%). Finally their median survival was similar to the ALScbi group (2.4 years, CI 1.8-3.1).

Discussion

Since 2009 cognitive impairment in ALS has been diagnosed according to the ALSFTD-1 criteria.[3] The revised ALSFTD-2 criteria, published in 2017, were deemed necessary due to the considerable improvement in the understanding of the cognitive profile of ALS patients, in particular, but not exclusively, the recognition of the extent of the deficits in social cognition and language[4] ALSFTD-2 criteria are more operational than the former ones and have the aim of delineating more

homogenous cognitive groups. To evaluate how the new classification of cognitive impairment in ALS impacts on the characteristics of the cognitive subgroups and their distribution, we applied the ALSFTD-2 criteria to a large population-based cohort and to two series of patients seen in referral ALS centres. Overall, the revised criteria determined the re-classification of 14.6% of patients of the population-based cohort and of 18.0% of those of the referral cohort.

The change of classification of these patients was mainly due to three modifications of the ALSFTD-2 criteria compared to the previous ones: first, the increased emphasis for language impairment, which can be diagnosed in presence of isolated impaired verbal fluency (letter) or of two non-overlapping tests, in which language impairment is not solely explained by verbal fluency deficits; second, the greater emphasis on apathy, whose presence is sufficient to make a diagnosis of ALSbi; third, the inclusion in the criteria for ALS-FTD of loss of insight and/or psychotic symptoms.

As a consequence of these changes in the classification criteria, patients who were previously categorized as ALS-CN were re-classified either as ALSci or as ALSbi. This change was particularly marked in the referral cohort (20 out of 148 patients, 13.5%) but was also present to a minor extent in the epidemiological-based cohort (14 out of 182 patients, 7.7%).

Inter-rater agreement of the classification of cognitive impairment in ALS was very high (*k* value 0.91 in the population-based series and 0.87 in the referral cohort),[13] indicating that the revised ALSFTD-2 criteria are highly reliable and that experienced professionals can accurately and consistently apply these criteria in the clinical setting. These observation holds also for each cognitive category, with a *k* statistics varying between 0.76 and 1, the complete concordance being observed for the diagnosis of ALS-FTD.

We found that the re-classification of patients from ALSFTD-1 to ALSFTD-2 has a substantial impact on the characteristics of the groups of patients. In particular, the newly proposed ALScbi group originates mainly from patients previously included in the ALSci group and is characterized

by the oldest age at onset compared to all other groups and a survival intermediate between ALSci and ALS-FTD. Moreover, patients re-classified as ALScbi have an educational level higher than that of ALS-FTD and ALSci, but lower than that of ALS-CN and ALSbi.

Patients with mixed cognitive and behavioural impairment but not meeting the criteria for FTD have been previously reported. A previous epidemiological-based study performed by our group found that 11 (6%) out of the 183 patients of the cohort had an impairment in one executive and/or one non-executive test associated with behavioural changes; these patients were labelled as ALS with non-classifiable cognitive impairment (ALS-NCCI).[2] Similarly, another paper based on a clinical series found that 1 out of 23 ALS patients showed both a cognitive and a behavioural impairment.[14] It remains to be clarified whether the ALScbi category represents a transitional stage to FTD similar to mild cognitive impairment in Alzheimer's disease.

With both classification, patients categorized at different cognitive diagnoses showed several clinical differences. In particular, patients with more severe cognitive impairment (ALS-FTD and ALScbi) were older than patients with normal cognition and had a lower education. Similar findings have been reported in other clinical[1,2,15] and epidemiological studies.[16,17] The higher frequency of bulbar onset in patients with cognitive impairment has been also reported.[18.19] Finally, the marked predominance of females in the ALS-FTD group is likely related to their higher frequency of bulbar impairment.

A relatively small percentage of ALS patients in the population-based cohort showed an impairment in non-executive domains, mainly memory and visuospatial domains, in isolation (7 cases, 2.2%), or associated (4 cases, 1.2%) to executive and behavioural impairment. The codification of these cases, who accounted for about 5% of cases in two previous population-based studies[1,2] remains uncertain. Similarly, a clinical-based series, on basis of a principal component analysis, showed that 24% of patients did not meet ALSFRS-1 criteria and were characterized by preeminent deficit in social cognition, language, and episodic memory.[20] A recent study did not find any difference in the

ALS-nonspecific functions (memory, visuospatial) evaluated with the ECAS, across disease stages classified according to King's staging.[19] In the ALSFTD-2 original paper it has been suggested that non-executive impairment is rare in isolation and it occurs at a comparable rate in controls, making questionable the introduction of a specific category in the classification.[4]

An interesting observation of our study is that the cognitive classification of patients was quite different in the two cohorts. Besides the well-known differences of epidemiological and referral cohorts in ALS,[21-22] i.e. younger age at onset, lower number of bulbar onset patients, and better survival in the referral cohort, we also found that referral cohort was characterize by a lower frequency of ALS-FTD patients (3.9% vs 14.6% with the ALSFTD-2) and, correspondingly, a higher percentage of ALS-CN (62.4% vs. 52.3%) ($p<0.0001$). This difference is likely to be related to the poorer propensity of patients with cognitive dysfunction and their caregiver to seek advice to referral ALS centres, but are usually followed by the local neurological departments.

We have found that the revised classification of frontotemporal dementia in ALS causes a shift of some 15% of patients from their original category to a new one. Most changes are due to the establishment of the novel category of ALScbi, which accounts for 10% of patients; this category is intermediate between ALSci and ALS-FTD in term of prognosis and includes older and more educated patients. Additionally, ~10% of cases who were previously classified as non-cognitively impaired were re-classified to the ALSci and, to lesser extent, to the ALSbi categories with the novel classification. Finally some patients previously classified as ALSci were diagnosed as FTD with the revised classification. These latter modifications were due to the increased role attributed to the impairment in verbal fluency (letter) and social cognition in the diagnosis of cognitive impairment in ALS by the ALSFTD-2 criteria.

It is possible that the higher sensitivity of ALSFTD-2 criteria compared to ALSFTD-1 leads to the inclusion of some false positive diagnoses of cognitive and/or behavioural impairment. For example, the relevance given to apathy in the diagnosis of ALSbi could indeed reduce the

specificity of the criteria, considering the complexity of the theoretical construct of this particular behaviour[23] and of its neuroanatomical and cognitive substrates.[24] However, it should be noted that in a study based on ECAS, apathy was the most common behavioural symptoms detected in ALS patients compared to FTD patients, in whom disinhibition predominated.[25] Longitudinal studies evaluating the progression over time of such patients are necessary to rule out this possibility.

However, despite this risk, we think that the higher sensitivity of ALSFTD-2 criteria for detecting early cognitive and behavioural signs entail several clinical advantages: first, they allow to identify and classify earlier the cognitive-behavioural impairment, also alerting caregivers for subtle modifications of cognition and/or behaviour; second, they have a better prognostic yield; third, they permit the clinician to timely discuss patients' directives on future therapies. Moreover, more sensitive diagnostic criteria for cognitive and behavioural impairment will improve the clinical and biological studies on the effects of cognitive damage in ALS patients and, in perspective, will be useful for detecting the early signs of cognitive impairment when specific treatment for FTD will be developed.

Authors' contributions: *Study concept and design:* Iazzolino, Pain, Moglia, Calvo, Mora, Chiò. *Analysis and interpretation of data:* Iazzolino, Pain, Mora, Chiò. *Drafting of the manuscript:* Mora, Chiò. *Critical revision of the manuscript for important intellectual content:* Iazzolino, Pain, Peotta, Calvo, Moglia, Canosa, Manera, Ilardi, Bombaci, Zucchetti, Mora, Chiò. *Obtained funding:* Chiò. *Administrative, technical, and material support:* Peotta, Calvo, Moglia, Canosa, Manera, Ilardi, Bombaci, Zucchetti. *Study supervision:* Mora, Chiò. Adriano Chiò has full access to data. The corresponding author confirm that all authors have read and approved the final draft of the manuscript and given written permission to include their names in the manuscript.

Conflict of interest: Adriano Chiò serves on scientific advisory boards for Mitsubishi Tanabe, Roche, and Cytokinetics and has received a research grant from Italfarmaco. Andrea Calvo has received research grant from Cytokinetics.

Barbara Iazzolino, Debora Pain, Laura Peotta, Cristina Moglia, Antonio Canosa, Umberto Manera, Antonio Ilardi, Alessandro Bombaci, Jean Pierre Zucchetti and Gabriele Mora, report no conflicts of interest.

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Table 1. Comparison of the two sets of criteria for the diagnosis of cognitive and behavioral impairment in ALS

ALSFTD-1[3]	**ALSFTD-2[4]**
ALSbi A diagnosis of ALSbi requires meeting at least two non-overlapping supportive diagnostic features from either the Neary criteria or Hodges criteria for FTD	**ALSbi** A diagnosis of ALSbi requires: 1. The identification of apathy with or without other behavior change OR 2. meeting at least two non-overlapping supportive diagnostic features from the Rascovsky criteria
ALSci A diagnosis of ALSci depends on evidence of cognitive impairment at or below the 5th percentile on at the least two distinct tests of cognition that are sensitive executive functioning	**ALSci** A diagnosis of ALSci depends on evidence of either executive dysfunction (including social cognition) or language dysfunction or a combination of the two. Executive impairment is defined as: 1. Impaired verbal fluency (letter). OR 2. Impairment on two other non-overlapping measures of executive functions (which may include social cognition) Language impairment is defined as: 1. Impairment on two non-overlapping tests and in which language impairment is not solely

	explained by verbal fluency deficits.
	ALScbi Patients who meet the criteria for both ALSci and ALSbi
ALS-FTD ALS-bvFTD ALS-dementia (ALS-D)*, FTD-MND All patient meeting either the Neary criteria or Hodges criteria for FTD	**ALS-FTD, ALS-dementia (ALS-D)*, FTD-MND** A diagnosis of ALS-FTD requires: 1. Evidence of progressive deterioration of behavior and/or cognition by observation or history AND 2. The presence of at least 3 of the behavioral/cognitive symptoms outlined by Rascovsky et al 2011 OR 3. The presence of at least 2 of those behavioral/cognitive symptoms, together with loss of insight and/or psychotic symptoms OR 4. The presence of language impairment meeting criteria for semantic dementia/ semantic variant PPA or non-fluent variant PPA. This may co-exist with behavioral/ cognitive symptoms as outlined above.

ALSbi: ALs with behavioural impairment; ALScbi, ALS with cognitive and behavioural impairment; ALSci, ALS with cognitive impairment; ALS-FTD, ALS with frontotemporal dementia; FTD, frontotemporal dementia; FTD-MND, frontotemporal dementia and motor neuron disease; ALS-D, ALS with dementia; PPA, primary progressive aphasia;

Table 2. Characteristics of the population-based and the referral cohorts.

	Population-based cohort (n=321)	**Referral cohort (n=205)**	**p**
Male (%)	181 (55.0%)	120 (58.3%)	0.65
Bulbar onset (%)	98 (29.8%)	45 (22.0%)	0.03
Mean age at onset (years, SD)	66.4 (10.1)	59.9 (11.7)	<0.0001
Median survival (years, IQR)	3.15 (1.95-7.10)	5.13 (3.12-8.21)	<0.0001

Table 3. Clinical characteristics of patients according to the two cognitive classifications in the population-based cohort.

	ALSFTD-1					**ALSFTD-2**					
	ALS-CN (n=182)	**ALSbi (n=19)**	**ALSci (n=75)**	**ALS-FTD (n=45)**	**p**	**ALS-CN (n=168)**	**ALSbi (n=24)**	**ALSci (n=51)**	**ALScbi (n=31)**	**ALS-FTD (n=47)**	**p**
Mean age at onset (years, SD)	64.3 (10.4)	67.1 (8.2)	69.7 (8.2)	69.7 (8.5)	0.001	64.7 (10.1)	64.8 (12.7)	66.8 (10.2)	72.1 (6.7)	69.9 (8.4)	0.001
Gender (female, %)	75 (41.2%)	7 (36.8%)	32 (42.7%)	30 (66.7%)	0.016	71 (42.3%)	8 (33.3%)	24 (47.1%)	11 (35.5%)	30 (63.8%)	0.04
Onset (bulbar, %)	37 (20.3%)	10 (52.6%)	21 (28.0%)	25 (55.6%)	0.0001	33 (19.6%)	10 (41.7%)	16 (31.4%)	8 (25.8%)	26 (55.3%)	0.0001
Mean education (years, SD)	10.1 (4.0)	9.6 (4.4)	7.5 (3.4)	7.8 (3.4)	0.0001	10.0 (4.1)	10.5 (4.3)	7.2 (3.2)	8.7 (3.5)	7.8 (4.8)	0.0001
Median	4.0	3.4	2.9	2.0	0.0001	4.0	5.4	3.1	2.7	2.1	0.0001

survival (years, IQR) *	(3.1-4.8)	(2.1-4.7)	(2.3-3.4)	(1.5-2.4)		(3.2-4.8)	(1.4-9.4)	(2.3-3.8)	(2.1-3.3)	(1.7-2.4)	

P values refer to comparisons across the groups. P values of post-hoc paired comparisons are reported in E-Table 4.

Figure legends

Figure 1. Category change between the ALSFTD-1 and ALSFTD-2 criteria in the population-based cohort.

Figure 2. Survival of population-based cohort according to cognitive classification. **A.** ALSFTD-1 criteria ($p<0.0001$). **B.** ALSFTD-2 criteria ($p<0.0001$). Orange, cognitively normal; blue, ALSbi; red, ALSci; green, ALS-FTD; violet, ALScbi.