**Cognitive correlates in amyotrophic lateral sclerosis: a population-based study in Italy.**

# Cognitive correlates in amyotrophic lateral sclerosis: a population-based study in Italy

Anna Montuschi, PsyD, PhD; Barbara Iazzolino, PsyD; Andrea Calvo, MD, PhD; Cristina Moglia, MD; Leonardo Lopiano, MD, PhD; Gabriella Restagno, MD; Maura Brunetti, BSc; Irene Ossola, BSc; Anna Lo Presti, PhD; Stefania Cammarosano, MD; Antonio Canosa, MD; Adriano Chiò, MD, FAAN

From: the ALS Center, 'Rita Levi Montalcini' Department of Neuroscience, University of Torino, Italy (Drs Montuschi, Iazzolino, Calvo, Moglia, Cammarosano, Canosa, and Chiò); the Neuroscience Institute of Torino (NIT) (Drs Calvo and Chiò); the Department of Neurology, Azienda Ospedaliera Città della Salute e della Scienza, Torino, Italy (Drs Calvo, Lopiano and Chiò); the Laboratory of Molecular Genetics, Azienda Ospedaliera Città della Salute e della Scienza, Torino, Italy (Dr Restagno and Mss Brunetti and Ossola); the 'Cognetti De Martiis' Department of Economical and Statistical Science, University of Torino, Italy (Ms Lo Presti)

**Correspondence to**: Adriano Chiò, MD, ALS Center, 'Rita Levi Montalcini' Department of Neuroscience, University of Torino, via Cherasco 15, 10126 Torino, Italy. achio@usa.net

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**Abstract**

**Background.** Very few data are available about the characteristics of cognitive impairment in ALS patients in population-based series.

**Methodology.** ALS patients incident in Piemonte, Italy, between 2009 and 2011 underwent an extensive neuropsychological battery. Cognitive status was classified as follows: normal cognition, frontotemporal dementia (ALS-FTD), executive cognitive impairment (ALS-ECI), non-executive cognitive impairment (ALS-NECI), behavioral impairment (ALS-Bi), non-classifiable cognitive impairment (ALS-NCCI). We assessed also 127 age- and gender-matched controls identified through patients' general practitioners.

**Results.** Out of the 281 incident patients, 207 (71.9%) underwent the neuropsychological testing; of these, 19 were excluded from the analysis due previous conditions affecting cognition. Ninety-one (49.7%) patients were cognitively normal, 23 (12.6%) had ALS-FTD, 36 (19.7%) ALS-ECI, 10 (5.5%) ALS-NECI, 11 (6.0%) ALS-Bi, and 11 (6.0%) ALS-NCCI, one had co-morbid Alzheimer's disease. ALS-FTD patients were older, had a lower education level, and had a shorter survival than any other cognitive group. Of the 9 cases with *C9ORF72* mutation, six had ALS-FTD, two ALS-ECI and one was cognitively normal; one of the 5 patients with *SOD1* mutations and one of the 5 patients with *TARBDP* mutations had ALS-Bi.

**Conclusions.** About 50% of Italian ALS patients had some degree of cognitive impairment, in keeping with a previous Irish study, despite the largely different genetic background of the two populations. The lower educational attainment in ALS-FTD patients indicated a possible role of cognitive reserve in ALS-related cognitive impairment. ALS-ECI and ALS-NECI may represent discrete cognitive syndromes in the continuum of ALS and FTD.

## Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by a progressive loss spinal, bulbar and cortical motor neurons, leading to voluntary muscles weakness and wasting and ultimately to death due to respiratory failure. While in about 90% of patients ALS occurs sporadically, in 10% it is genetically transmitted.[1,2] Extramotor features in ALS include cognitive changes, which have been described in 10 to 50% of patients.[3,4]

Frequency and clinical correlates of cognitive impairment in ALS are still poorly understood. With only one exception,[4] all studies have been performed on small clinic-based cohorts and did not use standardized methodologies for the evaluation of cognition. Recent consensus criteria proposed a classification of frontotemporal cognitive and behavioral syndromes in ALS[5] which includes ALS with frontotemporal dementia (ALS-FTD) and two milder forms of ALS with behavioral impairment (ALS-Bi) and ALS with cognitive impairment (ALS-Ci).

The aim of this study was to assess the frequency and the clinical pattern of cognitive impairment in a population-based series of ALS patients, identified through the Piemonte and Valle d'Aosta register for ALS (PARALS), fully characterized from the clinical and genetic point of view.

## Methods

We invited to participate to the study all ALS patients resident in the provinces of Torino and Cuneo of Piemonte region, Italy, (n=281), and diagnosed between January 1st 2009 and December 31st 2011, identified through the PARALS,[6] meeting El Escorial revised diagnostic criteria for definite, probable, and probable laboratory-supported ALS.[7] Disease severity was assessed with the ALSFRS-R scale.[8] All patients underwent pulmonary function tests within 4 weeks before or after the neuropsychological evaluation.

Patients with history of neurological disorders affecting cognition (major stroke, severe head injuries, mental retardation), alcohol- and drug-dependence, severe mental illness and use of high-dose psychoactive medications were tested but not included in data analysis. Patients resident in the area but who were not of Italian mother tongue were assessed only through an unstructured interview and therefore were excluded from the analysis. Patients were invited to participate to the study at the time of the diagnosis or during the first scheduled follow-up visit (~2 months later) and were interviewed at home or at the ALS clinic. In no case cognitive examination was performed more than 12 months after diagnosis. A total of 127 healthy age-, gender- and education-matched controls underwent the same neuropsychological battery. Controls were enrolled thought patients' general practitioners (GPs) and were interviewed at home, at the GP office or at the hospital. Only nine subjects asked to participate as controls denied their participation. Most GPs were willing to collaborate (~85%). When a GP did not collaborate, another GP practicing in the same area was contacted.

***Neuropsychological battery***. Patients and controls underwent a battery of neuropsychological tests encompassing executive function, memory, visuo-spatial function and language, selected according to Clinical Diagnostic Criteria for Frontotemporal Lobar Degeneration,[9] and ALS-FTD Consensus Criteria.[5] The neuropsychological battery included: Mini Mental State Examination (MMSE); Wisconsin Card Sorting Test (WCST); Trail Making A and B (TMT A-B); Stroop Colour-Word Interference Test (Stroop); letter and category fluency test; Wechsler Memory Scale II - revised (WMS-R-Form 2); Rey-Osterrieth Complex Figure Test (ROCF); Token test; Wechsler Adult Intelligence Scale revised (WAIS-R); Raven's Progressive Colored Matrices; Frontal Assessment Battery (FAB). In some cases supplementary tasks were administered for a comprehensive evaluation of language; the following tests were used: semantic systems tests (7 and 8) of the Battery for the Analysis of Aphasic Deficits (BADA)[10] (Miceli et al, 1994) and the Silhouette trial of the Visual Object and Space Perception (VOSP) battery.[11]

Neurobehavioral dysfunction was determined both on basis of direct observation and patient's history,[9,12] and with the Frontal Systems Behavior Scale (FrSBe),[13] using the Family-form evaluated by a close relative (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.[14] 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 not to refer to physical disability. Cognitive impairment was defined as impairment on two tests of executive or non-executive function that was below the fifth percentile of healthy controls.

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 ~2 hours, and was usually 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' and controls' $O_2$ saturation at the time of the neuropsychological testing was measured with a pulse oximetry; none of the patients and controls had evidence of hypoxemia (oxygen saturation <92 mm Hg).

***Cognitive classification***. Clinical diagnosis and cognitive classification were performed with the collaboration of two neurologists specialist in ALS and FTD and two neuropsychologists. Patients' cognitive status was classified as follows:

***a. ALS with normal cognition***.

***b. ALS with frontotemporal dementia (ALS-FTD)***. The diagnosis of frontemporal dementia was defined according to Clinical Diagnostic Criteria for Frontotemporal Lobar Degeneration.[9]

***c. ALS co-morbid with non-FTD dementias***. The diagnoses of non-FTD dementias were based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders-IV-TR[15] and those of the

National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA).[16]

***d. ALS with executive cognitive impairment (ALS-ECI)***. ALS patients who did not meet criteria for FTD or other types of dementia, but who had an impairment in two tests of executive dysfunction compared to healthy controls, i.e. had an executive dysfunction, were classified as ALS with executive cognitive dysfunction. A more conservative cut-off than that proposed by the ALS-FTD Consensus Criteria[5] was utilized (2.3$^{rd}$ percentile).[4]

***e. ALS with non-executive cognitive impairment (ALS-NECI)***. This group includes ALS patients with impairment in two non-executive domains, in particular visuo-praxic abilities, and no impairment in executive function.

***f. ALS with behavioral impairment (ALS-Bi)***.This group includes patients with predominant behavioral disturbances and with impairment in none or only one test of executive dysfunction and no impairment in non-executive domains.

***g. ALS with non-classifiable cognitive impairment (ALS-NCCI)***. This group includes ALS patients with impairment in one executive and/or one non-executive test, sometimes associated to smooth behavioral changes.

***Genetic analysis***. All coding exons and 50bp of the flanking intron-exon boundaries of *SOD1*, of exon 6 of *TARDBP*, and of exons 14 and 15 of *FUS* and exons 5, 9, 12 and 14 of *OPTN* and the single exon of *ANG* have been PCR amplified, sequenced using the Big-Dye Terminator v3.1 sequencing kit (Applied Biosystems Inc.), and run on an ABIPrism 3130 genetic analyzer. In patients with positive family history for ALS or FTD all coding exons of *VCP* have also been assessed. These exons were selected as the vast majority of known pathogenic variants are known to lie within these mutational hotspots. A repeat-primed PCR assay was used to screen for the

presence of the GGGGCC hexanucleotide expansion in the first intron of *C9ORF72*.[17] A cut-off of ≥30 repeats was considered pathological.

***Statistical methods.*** Comparisons between means were made with Student's *t*-test or analysis of variance (ANOVA); comparisons between categorical variables were made with $\chi^2$ test; for all comparisons, Levene's test was used to confirm the equality of variances.

Survival was calculated from onset to death/tracheostomy or censoring date (June 30$^{th}$, 2013), using the Kaplan-Meier method, and compared with the log-rank test. No patients were lost to follow-up. Multivariable analysis was performed with Cox proportional hazards model (stepwise backward) (for details, see Table 3). For the analysis of the relationship between cognitive status and disease progression, the progression rate for the ALSFRS-R score, its four sub-scores (bulbar, fine motor, gross motor and respiratory) and forced vital capacity percent of predicted (FVC%) was calculated as the mean monthly number of points loss from disease onset to the time of cognitive evaluation. For example, the progression rate for the ALSFRS-R score was calculated as follows: (48-ALSFRS-R at time of cognitive evaluation)/duration from onset to diagnosis (months). In the Cox model, these variable were dichotomized on basis of their median value. The list of all variables included in the Cox model is reported in Table 3.

A $p$ level <0.05 was considered significant. All tests were two-tailed. Statistical analyses were carried out using SPSS 20.0 (SPSS, Chicago, IL).

***Standard Protocol Approvals, Registrations, and Patient Consents***. The study design was approved by our institutional Ethical Committee. Patients and controls signed a written informed consent. The database was managed according to the Italian law for the protection of privacy.

**Results.** A flow chart of the sequence of participants selection is reported in Figure 1. Of the 281 patients diagnosed in the study area in the 2009-2011 period, 202 (71.9%) underwent the

neuropsychological battery. Of the 79 non-captured patients, 34 were not able to undergo the battery of tests due to their motor disability (7 patients were tracheostomized or used non-invasive ventilation for more than 16 hours; 18 patients had severe difficulties in both writing and speaking; 9 patients had a severe fatigue and, although willing to collaborate, could not adequately perform the whole battery), five were not of Italian mother tongue, 30 declined participation, and 10 died before being tested. Nineteen tested patients were excluded from the analysis due to previous neurological disorders affecting cognition (7 patients), severe mental illness (6), drug or alcohol abuse (2), use of high-dose psychoactive medications (1 due to bipolar disorder, 1 due to paranoid schizophrenia), analphabetism (1), mental retardation (1).

Non-captured patients did not differ demographically and clinically from those who underwent the examination (Table 1). The median time from diagnosis to the neuropsychological assessment was 1.9 months (interquartile range 1.2-3.8).

***Cognitive classification***. According to the classification criteria for patients' cognitive status, 23 (12.6%) had ALS-FTD, 36 (19.7%) ALS-ECI, 10 (5.5%) ALS-NECI, 11 (6.0%) ALS-Bi, and 11 (6.0%) ALS-NCCI; 91 (49.7%) patients were cognitively normal (E-Figure 1). One patient had co-morbid AD. Twenty-two out of the 23 patients with ALS-FTD presented with behavioral changes typical of behavioral variant FTLD (bv-FTD); one patient had semantic dementia. Mean scores of the performed tests for each cognitive group and controls are reported in E-Table 1. Box plots of selected test are reported in E-Figures 2 to 6.

Cognitive groups were clinically and demographically different (Table 2). Patients with ALS-FTD, ALS-ECI and ALS-Bi had a higher mean age (~70 years) than those with normal cognition and ALS-NECI. ALS-NCCI had the lowest age at onset. Patients with ALS-FTD and those with ALS-NECI had a higher frequency of bulbar onset than all other groups ($p=0.003$). The mean number of education years was significantly lower in patients with ALS-FTD than in all other groups.

ALSFRS-R score and FVC% at time of the cognitive examination did not show significant differences. However, the ALSFRS-R bulbar sub-score (items 1, 2 and 3 of the ALSFRS-R scale) was significantly lower in the group with ALS-FTD (data not shown). The rate of decline of ALSFRS-R, of its sub-scores, and of FVC% was similar in the various groups (E-Table 2).

***Patients' cognitive status and genetics***. Of the 9 cases carrying the GGGGCC hexanucleotide repeat expansion in the first intron of the *C9ORF72* gene, 6 had ALS-FTD, two ALS-ECI and one was cognitively normal. One of the 5 patients with *SOD1* mutations and one of the 5 patients with *TARBDP* mutation had ALS-Bi. Both patients with *FUS* and *OPTN* mutations were cognitively normal. Genetic status was significantly correlated to the presence/absence of cognitive impairment (p=0.0001).

***Survival analysis (Figure 2)***. The overall median survival time was 2.7 years (95% confidence interval [c.i.] 2.4 to 2.9). Patients with ALS-FTD had a significantly shorter survival (1.9, 95% c.i. 1.7 to 2.2) than any other group of patients with cognitive impairment, with the only exception of those with ALS-NECI (2.0, 95% c.i. 1.6 to 2.4). Patients with ALS-Bi (3.0, 95% c.i. 0.8 to 5-3) had a survival time similar to that of cognitively normal patients (3.1, 95% c.i. 2.7 to 3.4). Patients with ALS-ECI had an intermediate survival between the two groups (2.6, 95% c.i. 2.0 to 3.1). Cognitive status remained significant in Cox multivariable analysis (Table 3). The presence of FTD significantly increased the risk of death compared to non-demented patients; also ALS-NECI and ALS-ECI resulted to be independently related to a worse outcome.

**Discussion.** We have studied cognitive status in a population-based series of ALS patients in Italy using an extensive battery of tests evaluating multiple cognitive domains. In our series, 13% of patients had a co-morbid FTD, while 50% had normal cognition. The remaining patients showed

various degrees of cognitive impairment who did not meet the criteria for FTD, but that otherwise had some clinical significance, including a negative effect on disease outcome.

The frequency of cognitive impairment in our epidemiological series was similar to that described in Irish patients.[4] However, differently from that study, according to ALS-FTD Consensus Criteria[5] we identified a group of patients with cognitive impairment, i.e. patient with isolated behavioral impairment, accounting for 6% of cases. These patients did not show impairment in more than one executive or one non-executive test, but had a behavioral impairment at extensive clinical observation and at the FrSBe test. Interestingly, one control patient also meet the criteria for cognitive behavioral impairment.

We also identified a group of patients (6% of our series) (NCCI) with impairment in one executive and/or one non-executive test who did not fulfill the criteria for other cognitive groups. These patients largely differed both from cognitively normal patients and from all other cognitive subgroups, being younger, less frequently bulbar, and with a higher mean education level. It is possible that this group includes pre-morbid FTD cases, i.e. patients who did not meet the criteria for other cognitive impairments but who could have developed more severe impairment later in the course of the disease.

In our series, ALS-FTD patients with full-blown comorbid dementia had a significant lower educational level, in keeping with another population-based study.[4] The lower mean educational level in Italian patients and controls in this series compared to that of the Irish study[4] reflects the low level of education in the Italian population born before 1950.[18] Educational level, as well as higher occupation attainment, are considered proxies of cognitive reserve.[19] The role of cognitive reserve in protecting from AD is widely accepted,[19] although the underlying mechanisms are still unclear. Cognitive reserve is also involved as protective mechanism in several cognitive functions impaired in FTD, in particular speed of processing/executive functioning, visual spatial abilities and

verbal memory.[20-22] Our finding suggests either that a longstanding frontal dysfunction interferes with learning and might underline the future development of cognitive impairment or that low level education put patients at higher risk of developing FTD. Differently from patients with ALS-FTD, those with ALS-ECI, ALS-NECI and ALS-Bi did not differ from normal controls regarding educational level, and those with ALS-NCCI had a higher educational level than both other cognitive groups and controls. This finding may indicate that either cognitive reserve does not have a role in these variants of cognitive impairments in ALS, or that some patients develop cognitive impairment not meeting the full criteria for FTD because they are protected by their cognitive reserve.

ALS-FTD and ALS-ECI patients had an older age at onset than controls, ALS-Bi and ALS-NECI, in keeping with various papers,[3,23] but not all.[4,24] This difference may be due to the higher mean age of our patients compared to other series.[4,24]

In our series bulbar onset was significantly more frequent in ALS-FTD and ALS-NECI. Bulbar onset has been found to be more commonly related to FTD features in several series,[3,25,26] but not in all.[4,23] Supporting our findings, a $^{18}$FDG-PET study showed a significantly higher relative decrease in metabolism in large frontal and parietal regions in bulbar onset patients compared with spinal ones.[27]

In this study a genetic characterization of all ALS patients was performed. *C9ORF72* hexanucleotide repeat expansion was the more frequent mutation, and, as expected,[1,28] it was also the significantly associated with FTD compared to other gene mutations or no genetic mutations . However, FTD patients with *C9ORF72* mutation accounted only for one fourth of all cases with ALS-FTD, indicating that other genetic, epigenetic, or environmental mechanisms underlie the involvement of pre-frontal cortex in ALS. The role of still unknown genes is supported by the fact

that ALS-FTD was more commonly related to a positive family history of ALS than all other cognitive conditions.

Cognitive impairment has a strong negative impact on ALS outcome.[4,14,26,29,30] The survival of our patients with ALS-FTD and ALS-ECI was about one year shorter than that of cognitively normal, ALS-Bi and ALS-NECI patients. The reason of this finding is still not completely understood. The presence of neurobehavioral dysfunction or of isolate dysexecutive behavior in ALS at diagnosis has been found to be a strong predictor of a poor outcome, partially related to a reduced efficacy of life-prolonging therapies such as non-invasive ventilation and percutaneous endoscopic gastrostomy,[14] while the decline in cognitive function was faster in patients who were cognitively impaired at baseline.[31] However, we could not find any significant correlation between ALS progression, evaluated with ALSFRS-R at the time of the interview, and patients' cognitive status, indicating that the shorter survival of ALS patients with cognitive impairment is not completely explained by the progression rate of their motor impairment. Cox multivariable analysis confirmed that cognitive status was independently related to ALS outcome.

A limitation of this study is that it is based on a single observation shortly after the diagnosis of the disease. However, at least two series with a follow up cognitive assessment in ALS patients found that an onset of FTD or other forms of cognitive impairment is rare during the disease course.[31,32]

In this study of cognitive status of incident Italian ALS patients, the frequency of cognitive impairment was similar to that reported by a population-based study performed in Ireland,[4] despite the different genetic backgrounds of the two populations,[1,2] i.e. the higher frequency of *C9ORF72* mutations in Ireland, and of *SOD1* and *TARDBP* mutations in Italy. We found that ~15% of patients had ALS-FTD and another 35% had some degree of cognitive impairment. Co-morbid FTD was associated with higher age at onset, bulbar onset and lower educational level, likely to represent a proxy for a reduced cognitive reserve, and has a significantly reduced survival than any other

cognitive group. It remains to be understood whether ALS-ECI and ALS-NECI represent incomplete forms of cognitive impairment or discrete cognitive syndromes within the spectrum of ALS and FTD, with strong effect on the disease outcome.

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**Table 1**. Demographic and clinical characteristics of ALS patients and controls

| | **ALS patients enrolled for the study (n=183)*** | **Non-captured ALS patients (n=79)** | **Healthy controls (n=127)** |
|---|---|---|---|
| **Mean age at onset (years, SD)** | 67.0 (9.9) | 66.9 (10.3) | 66.5 (11.4) |
| **Gender (female, %)** | 76 (41.5%) | 35 (44.3%) | 54 (42.5%) |
| **Education (number of years, SD)** | 8.3 (4.1) | 8.5 (4.2) | 8.7 (4.3) |
| **Site of onset (bulbar, %)** | 62 (33.9%) | 26 (32.9%) | - |

All comparisons are non-significant

* 19 patients tested but not included in the study due to exclusion criteria (see text) are not shown in the table

**Table 2.** Demographic and clinical characteristics of ALS patients according to cognitive status

| | **Cognitively normal (n=91)** | **ALS-FTD (n=23)** | **ALS-ECI (n=36)** | **ALS-NECI (n=10)** | **ALS-Bi (n=11)** | **ALS-NCCI (n=11)** | **p** |
|---|---|---|---|---|---|---|---|
| **Mean age at onset (yrs, SD)** | 65.9 (10.6) | 69.1 (7.7) | 70.0 (7.4) | 64.9 (12.8) | 68.1 (9.9) | 61.9 (9.5) | 0.04 |
| **Gender (female, %)** | 40 (43.5%) | 11 (47.8%) | 14 (38.9%) | 4 (40.0%) | 4 (36.8%) | 4 (36.8%) | 0.97 |
| **Disease duration at time of interview (years, SD)** | 1.23 (1.11) | 1.28 (0.60) | 1.18 (0.76) | 1.03 (0.63) | 1.19 (1.17) | 1.20 (0.62) | 0.99 |
| **Site of onset** | 28 (30.4%) | 10 (60.9%) | 10 (27.8%) | 6 (60.0%) | 2 (18.2%) | 2 (18.2%) | 0.015 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **(bulbar, %)** | | | | | | | |
| **Time lapse between diagnosis and interview (years, SD)** | 0.25 (0.23) | 0.35 (0.31) | 0.26 (0.26) | 0.12 (0.05) | 0.18 (0.12) | 0.31 (0.32) | 0.12 |
| **Mean education (yrs, SD)** | 8.6 (3.7) | 4.7 (1.9) | 7.8 (4.0) | 9.5 (5.1) | 9.9 (5.2) | 12.4 (4.4) | 0.0001 |
| **FALS (%)** | 11 (12.1%) | 7 (30.4%) | 2 (5.6%) | 0 | 0 | 0 | 0.015 |
| **Mean ALSFRS-R score at time of interview (SD)** | 38.8 (7.6) | 34.9 (7.3) | 36.4 (7.6) | 40.9 (6.4) | 34.5 (12.8) | 39.7 (6.3) | 0.086 |
| **Mean FVC% at time of interview** | 91.2 (25.5) | 80.7 (25.0) | 88.4 (28.7) | 83.2 (22.3) | 83.7 (26.6) | 92.3 (23.1) | 0.181 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **(SD)** | | | | | | | |

One patient with co-morbid Alzheimer's disease is not included in the Table. FALS, familial ALS; FTD, frontotemporal dementia; ECI, executive cognitive impairment; NECI, non-executive cognitive impairment; Bi, behavioural impairment; NCCI, non-classifiable cognitive impairment. p value is calculated with ANOVA (age, education, time lapse, ALSFRS-R, FVC) or $\chi^2$ (gender, site of onset, FALS status).

**Table 3.** Cox' multivariable analysis

| Variable | | OR (95% c.i.) | p value |
|---|---|---|---|
| ALS-FTD | No<br>Yes | 1<br>3.7 (2.1-6.6) | 0.0001 |
| ALSFRS total score | <0.7 points/month<br>≥0.7 points/month | 1<br>1.9 (1.3-2.9) | 0.003 |
| ALS-NECI | No<br>Yes | 1<br>3.6 (1.5-8.7) | 0.004 |
| ALS-ECI | No<br>Yes | 1<br>1.8 (1.1-3.1) | 0.025 |
| Type of onset | Spinal<br>Bulbar | 1<br>1.7 (1.1-2.7) | 0.03 |

The following variables were included in the Cox model: age (18-59, 60-69, 70-79, 80-99 years), gender, FALS status (FALS *vs.* SALS), gene mutation (*C9ORF72, SOD1, TARDBP, FUS, OPTN*, no mutation identified), years of education (≤5, 6-8, 9-13, ≥14), progression rate of ALSFRS-R total score (<0.7 *vs.* ≥0.7 point/months), ALSFRS-R bulbar score (<0.15 *vs.* ≥0,15 points/month), ALSFRS-R fine motor score (<0.2 *vs.* ≥0.2

points/month), ALSFRS-R gross motor score (<0.22 *vs.* ≥0.22 points/month), ALSFRS-R respiratory score (<0.1 *vs.* ≥0.1points/month), FVC% (<0.50 *vs.* ≥0.50 months). Cognitive status was included as ALS-FTD (yes *vs.* no), ALS-ECI (yes *vs.* no), ALS-NECI (yes *vs.* no) ALS-Bi (yes *vs.* no) and ALS-NCCI (yes *vs.* no). Enteral nutrition and non-invasive ventilation were included as time-dependent variables.

## Figure legends

**Figure 1**. Flow chart showing capture rate and the sequence of participant selection. ALS, amyotrophic lateral sclerosis.

**Figure 2**. Survival curves from disease onset to death/tracheostomy of the incident ALS cohort according to their cognitive classification; p=0.004.Ticks are censored patients. Red, ALS patients with normal cognition; green, ALS patients with co-morbid frontotemporal dementia (ALS-FTD); yellow, ALS patients with executive cognitive impairment (ALS-ECI); violet, ALS patients with non-executive cognitive impairment (ALS-NECI); blue, ALS patients with behavioural impairment (ALS-Bi); black, ALS patients with non-classifiable cognitive impairment (ALS-NCCI). The single patient with ALS with comorbid dementia of Alzheimer's type is not included.

Figure 1

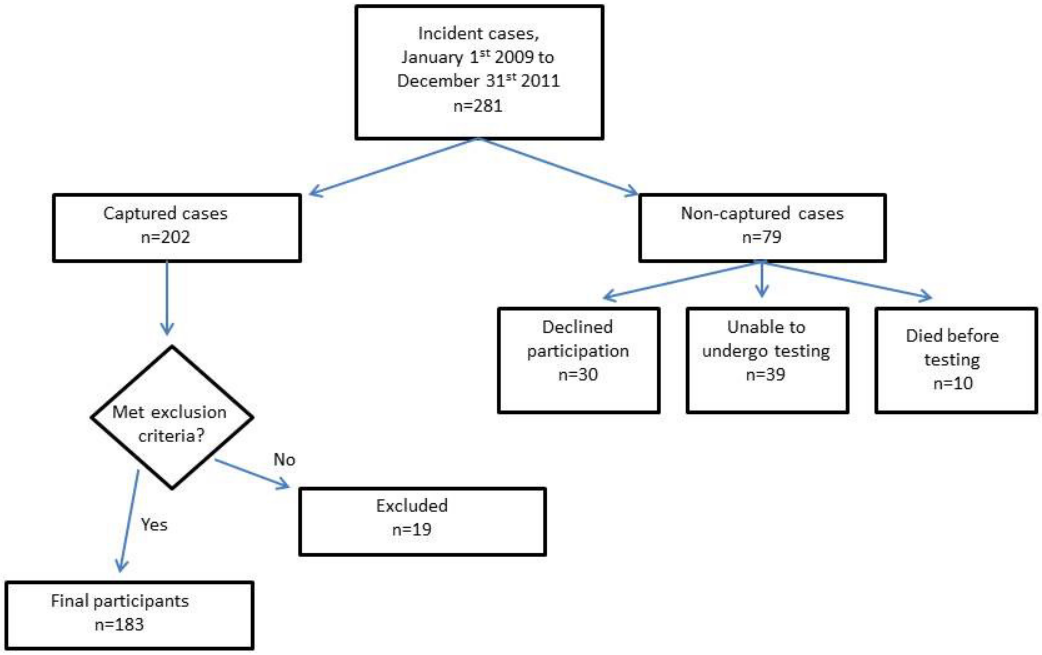
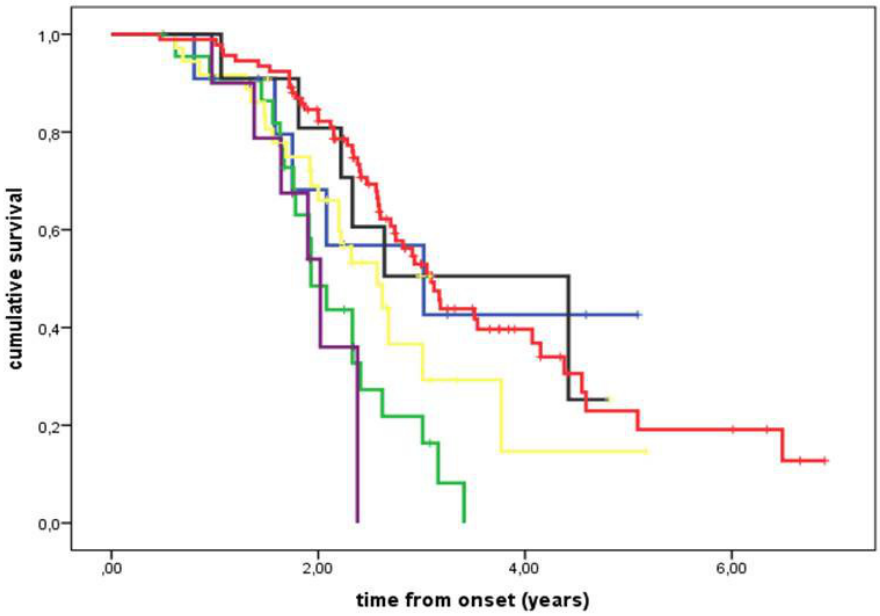

Incident cases, January 1st 2009 to December 31st 2011 n=281
Captured cases n=202
Non-captured cases n=79
Declined participation n=30
Unable to undergo testing n=39
Died before testing n=10
Met exclusion criteria?
No
Yes
Excluded n=19
Final participants n=183

Figure 2


1,0
0,8
0,6
0,4
0,2
0,0
cumulative survival
,00
2,00
4,00
6,00
time from onset (years)