# Diagnostic and prognostic usefulness of serum neurofilament light chain in amyotrophic lateral sclerosis

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## Introduction

Neurofilaments (NFs), constituents of the axonal cytoskeleton released by degenerating motor neurons, are elevated in the CSF of ALS patients compared to controls and other neurological diseases.
CSF NF light chain and phosphorylated heavy chain (NFL and pNFH, respectively) discriminate between ALS and other neurological conditions, including ALS mimics (diseases mimicking ALS) with diagnostic sensitivity and specificity around 80%.
Moreover, CSF NFL and pNFH levels correlate with disease progression rate and survival in ALS, with higher levels associated with more rapid disease progression and shorter survival.
In our work we measured serum NFL in patients with ALS, patients with ALS-mimic conditions, non-neurodegenerative controls, and patients with other neurodegenerative diseases, in order to evaluate its diagnostic performance, its role as prognostic marker, and its stability over time.

## Patients and methods

**Patients**. 124 ALS patients (74 (59.7%) males and 50 (41.3%) females; site of onset in 39 (31.5%) bulbar, in 83 (66.9%) spinal, and in 2 (1.6%) unclear; median age of onset 60 y, range 26-74 y), 44 patients with ALS-mimic syndromes, 50 non-neurodegenerative controls, and 65 patients with other neurodegenerative diseases (Alzheimer's disease (AD, N = 20), frontotemporal dementia (FTD, N = 20), Parkinson's disease (PD, N = 19), and Creutzfeldt-Jakob disease (CJD, N = 6)). Patients were sampled in the Department of Neurology of Ulm University between 2009 and 2016.
**Methods**. NFL was measured in serum by single-molecule enzyme-linked immunosorbent assay (digital ELISA), using the Simoa HD-1 Analyzer and the NF-L Beta kit from Quanterix (Lexington, MA).

## Results

Serum NFL levels were significantly higher in ALS relative to non-neurodegenerative controls ($p < 0.0001$), AD ($p = 0.0006$), FTD ($p = 0.0063$), PD ($p < 0.0001$), and, most importantly, ALS mimics ($p < 0.0001$) (**Figure 1**). NFL levels did not differ between ALS and CJD ($p > 0.9999$). At a cut-off of 62 pg/mL, serum NFL discriminated between ALS and ALS mimics with 85.5% sensitivity (95% CI, 78% to 91.2%) and 73.3% specificity (95% CI, 62.2% to 88.5%). The same cut-off enabled discrimination between ALS and non-neurodegenerative controls with 85.5% sensitivity (95% CI, 78% to 91.2%) and 96% specificity (95% CI, 86.3% to 99.5%). For the discrimination between ALS and all other diagnostic categories together, sensitivity and specificity were 85.5% (95% CI, 78% to 91.2%) and of 77.3% (95% CI, 62.2% to 88.5%), respectively (**Figure 2**).
Within the ALS cohort, serum NFL levels correlated positively with progression rate ($r_s = 0.3359$, $p = 0.0008$) (**Figure 3**). Moreover, patients with serum NFL levels above the median (125 pg/mL) had a shorter survival than those with NFL ≤ 125 pg/mL ($p = 0.0054$) (**Figure 4**).
Finally, in the 29 ALS patients who underwent a second blood draw later in the disease course (after a median of 8.1 months, range 4-54.9 months), we could demonstrate relative stability of serum NFL levels (**Figure 5**, representing variations of NFL levels in patients re-sampled at different time points after the first blood draw).

**Figure 1**

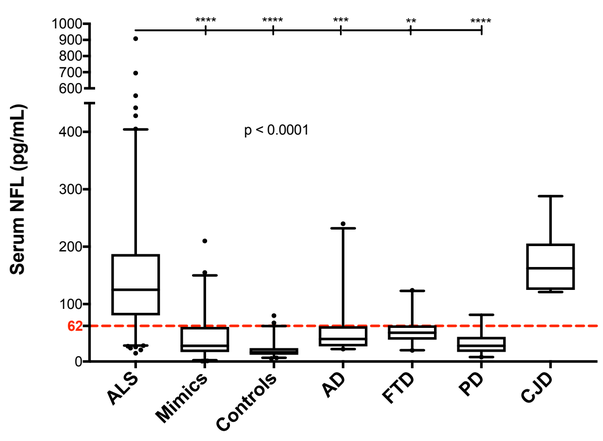



**Figure 2**

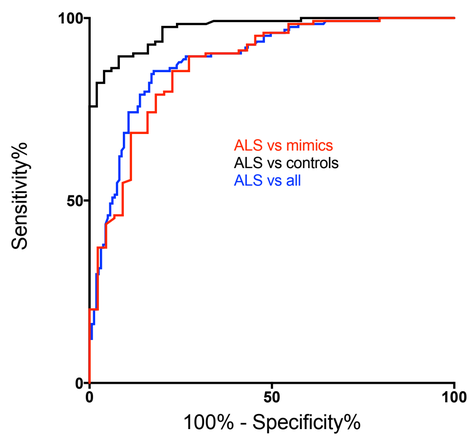



**Figure 3**

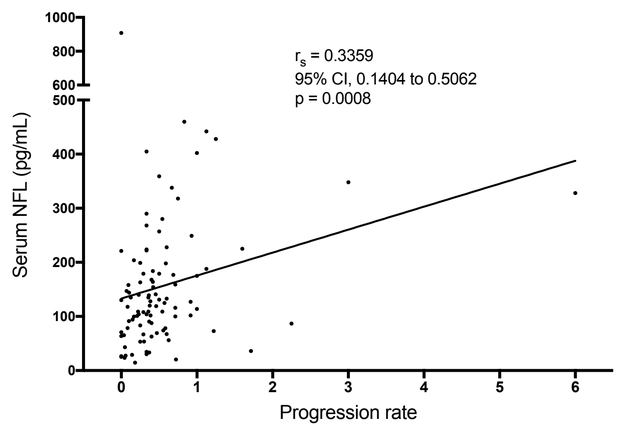



**Figure 4**

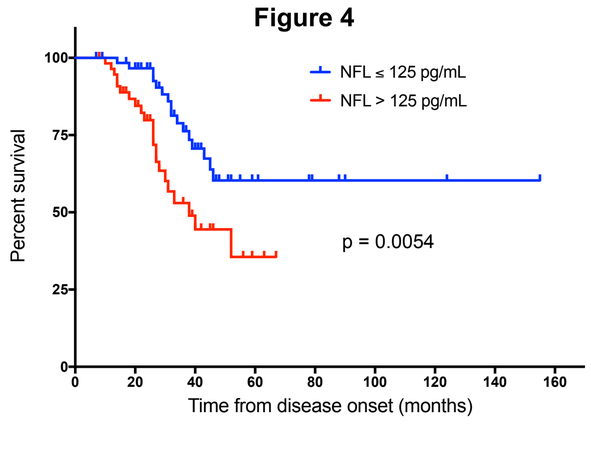
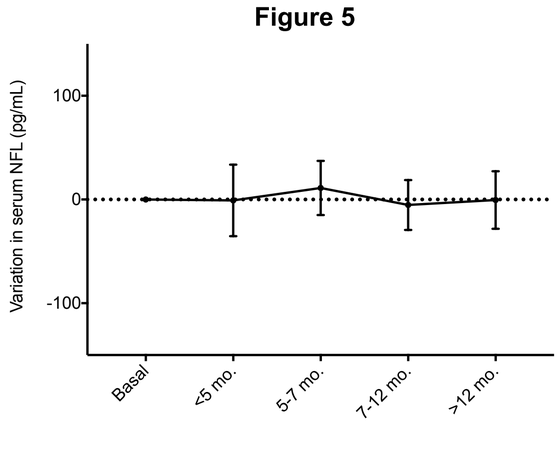



**Figure 5**




## Conclusions

The good diagnostic performance of serum NFL in ALS is comparable to that of NFL and pNFH measured in CSF. Serum NFL has also prognostic significance. In light of the easy accessibility of blood and of the relative stability of serum NFL levels over the disease course, this is a strong candidate biomarker not only for diagnosis but also for prognosis, patient stratification and detection of drug effects in clinical trials, and hopefully in a near future, monitoring of drug response in routine clinical context.

## References

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