

Prognostic Value Of Blood-based Phosphorylated Tau Biomarkers And NfL By Amyotrophic Lateral Sclerosis Clinical Phenotype

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Background

- Amyotrophic lateral sclerosis (ALS) is a **progressive neurodegenerative disease** characterized by degeneration of upper and lower motor neurons, leading to gradual muscle weakness, disability, respiratory failure and death typically within 2 to 5 years from symptom onset. It exhibits substantial clinical heterogeneity in motor neuron involvement, site of onset, progression rate and survival.^[1,2,3]
- In ALS, **neurofilament light chain (NfL)** has established diagnostic and prognostic value, however, it provides limited information on cross-sectional disease severity and the relative contribution of upper vs lower motor neuron pathology.^[4-11] In contrast, Alzheimer's disease (AD)-related biomarkers, including **phosphorylated tau (p-tau)** and **brain-derived tau (BD-tau)**, are elevated in ALS, yet their biological and clinical relevance remains unclear.^[12-14]

Aim

To determine whether blood-based tau biomarkers (p-tau181, p-tau217, p-tau231, BD-tau), NfL and GFAP are differentially associated with disease severity, LMN and muscle involvement, disease progression and survival in ALS.

Results

Table 1. Demographic and clinical characteristics of the ALS cohort

Characteristic	N	ALS cohort
Demographics and general characteristics		
Age, years	119	64 (53, 74)
Sex	119	
Female		67 (56%)
Male		52 (44%)
BMI, kg/m ²	119	23.1 (19.8, 26.7)
eGFR, mL/min/1.73 m ²	117	104 (94, 114)
Clinical phenotype		
ALS onset form	119	
Bulbar		39 (33%)
Spinal		80 (67%)
Riluzole treatment	119	73 (61%)
Disease severity		
King's stage	119	
Kings 1/2/3		53 (45%)
Kings 4		66 (55%)
ALSFRS-R, points	119	32 (24, 40)
SVC, % predicted	81	74 (59, 90)
Disease progression and survival		
ALSFRS-R slope, points lost/month	119	0.86 (0.48, 1.50)
Survival time from symptom onset, months	119	32 (20, 45)
Death during follow-up	119	71 (60%)
Lower motor neuron and muscle involvement		
EMG	119	
Available		67 (56%)
Not available		52 (44%)
% Affected muscles	63	76 (57, 88)
Number LMN-affected regions	67	3 (2, 3)
CK, U/L	90	126 (65, 254)
hs-cTnT, ng/L	113	23 (14, 35)

Data are presented as median (IQR) for continuous variables and n (%) for categorical variables.

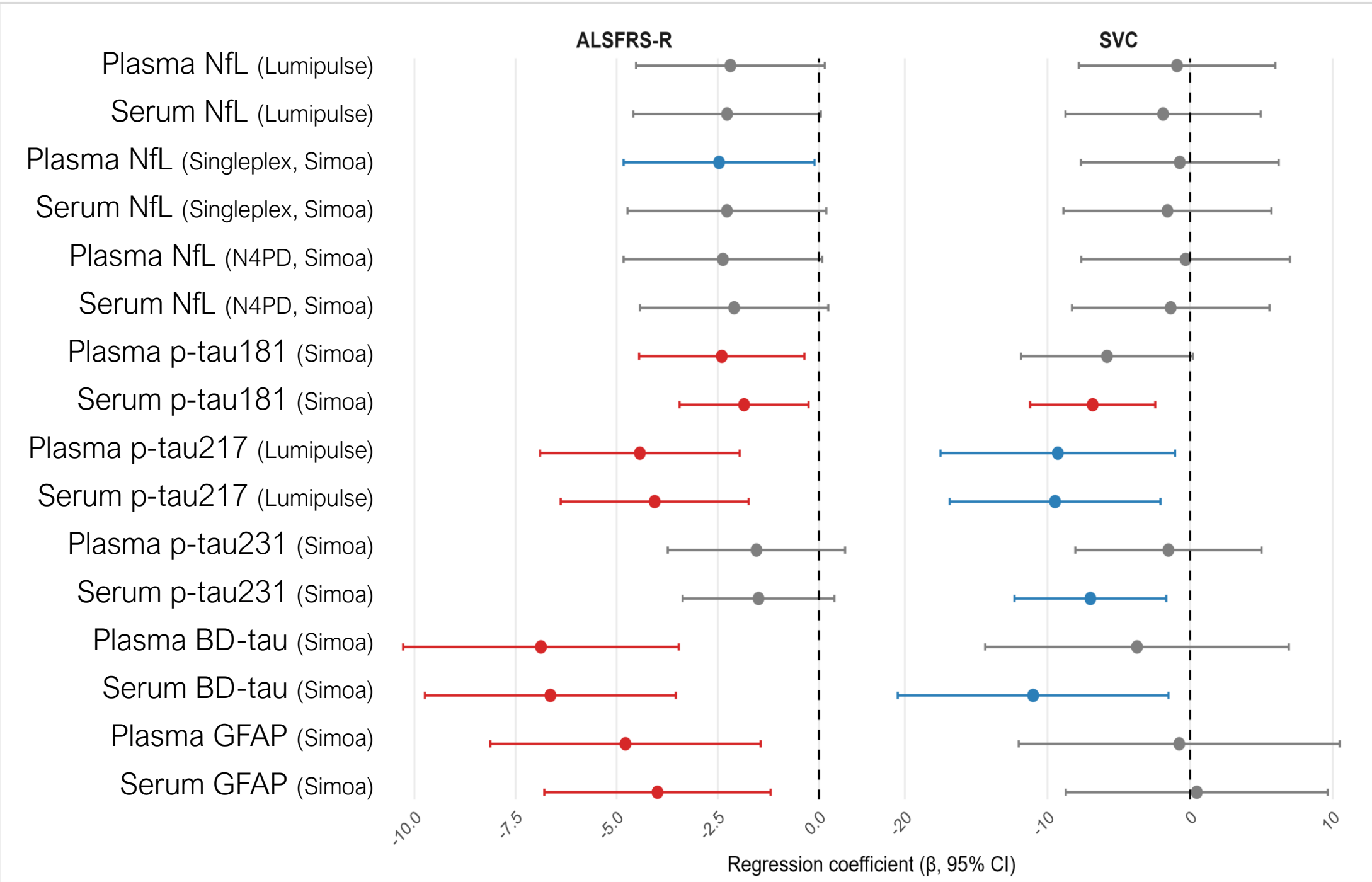


Figure 1. Associations between blood-based biomarkers and cross-sectional disease severity measures in ALS

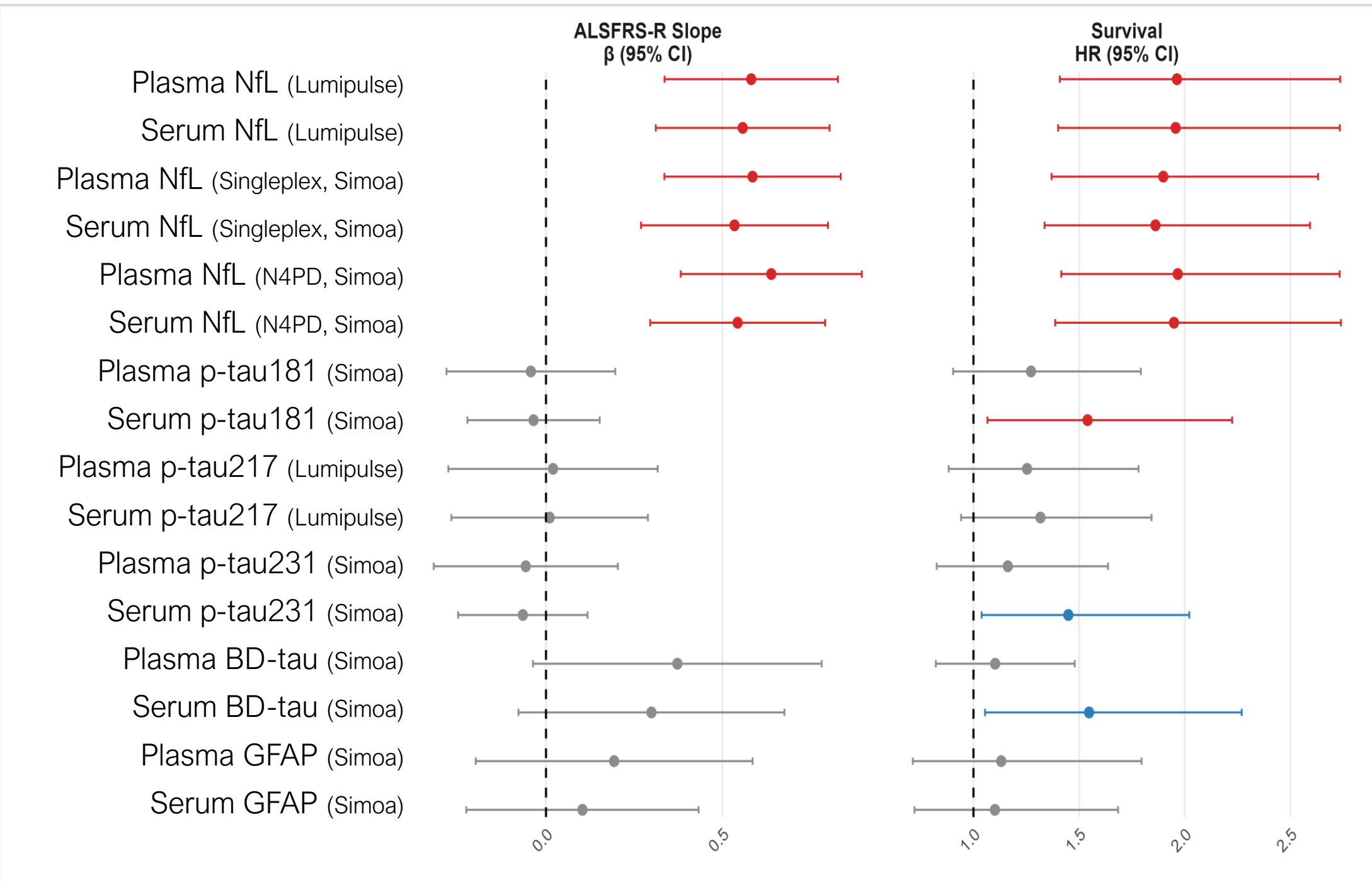
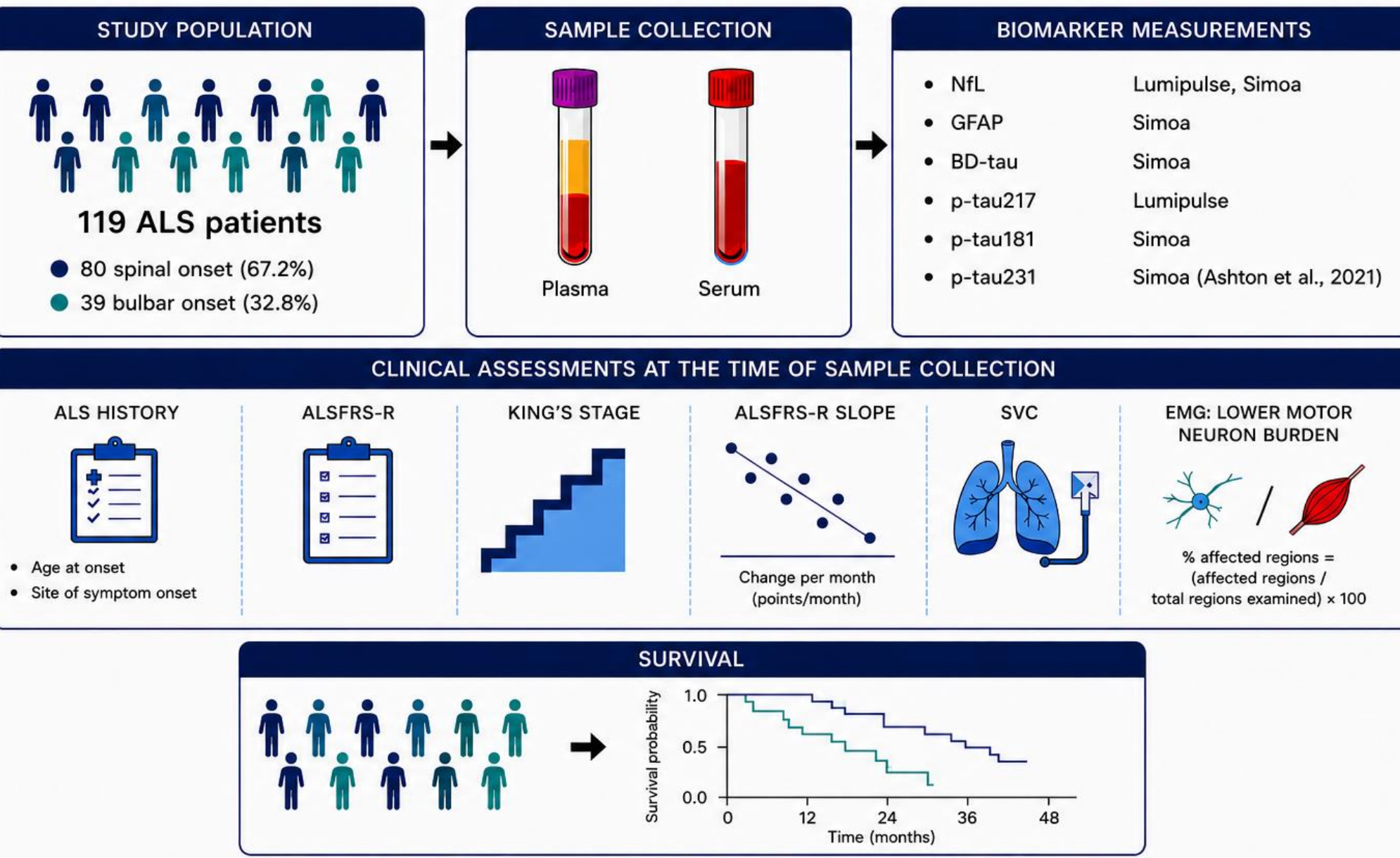


Figure 2. Associations between blood-based biomarkers and disease progression and survival in ALS

Methods

This is a retrospective, longitudinal cohort study. We included consecutive subjects who met the revised El Escorial criteria for definite or probable ALS between 10 February 2020 and 15 July 2025 at Hospital del Mar (Barcelona, Spain).



Biomarker levels were log-transformed. Group comparisons were performed using adjusted ANCOVA models. Associations between biomarker levels and variables of interest were examined using adjusted linear regression models and residualized Spearman correlations. Survival was assessed using multivariable Cox regression. Multiple testing was controlled using the Benjamini-Hochberg false discovery rate (FDR).

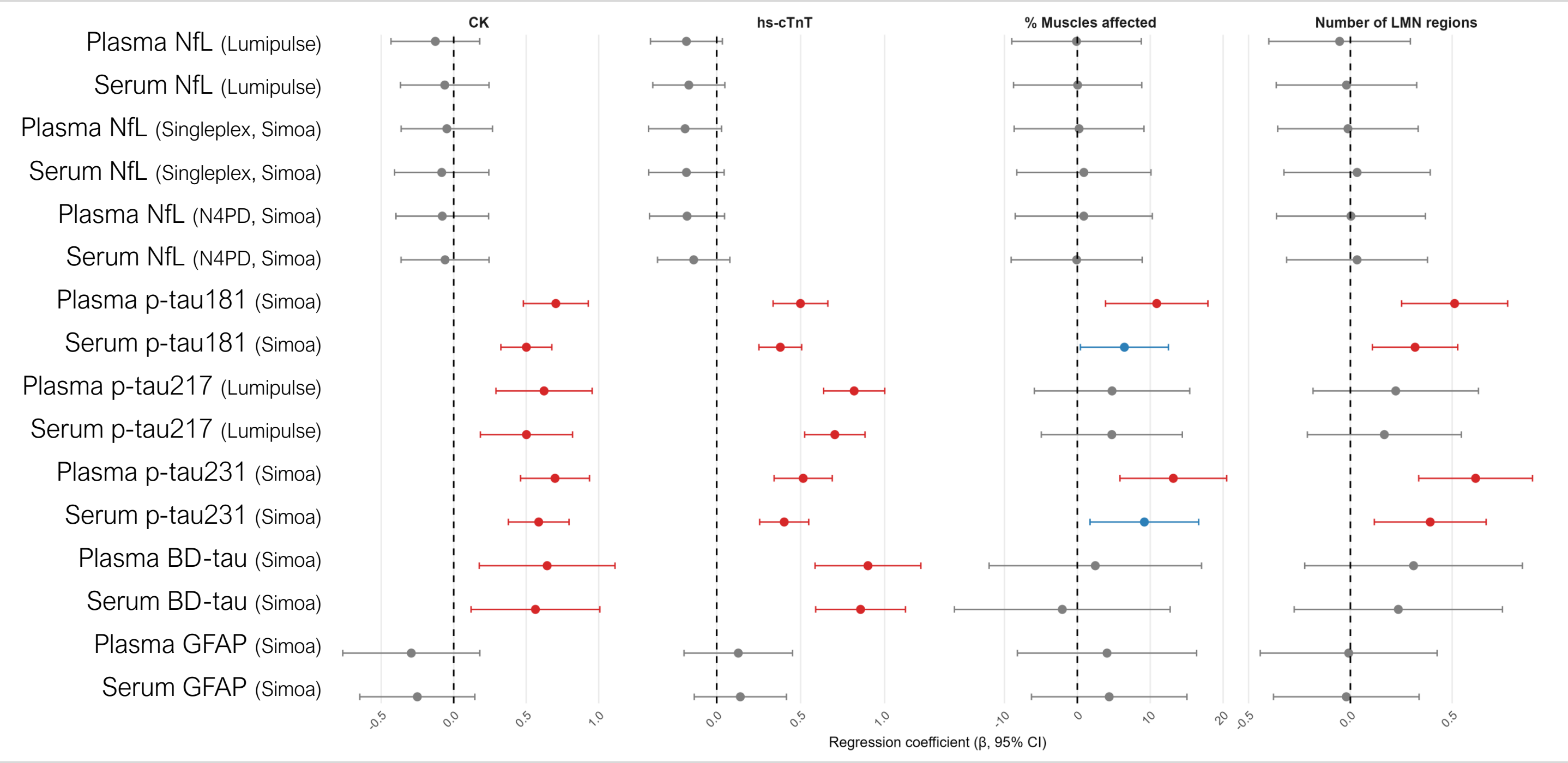


Figure 3. Associations between blood-based biomarkers and muscle/LMN involvement

Conclusions

Different blood-based biomarkers capture distinct biological and clinical aspects of ALS:

→ p-tau217 and BD-tau reflect cross-sectional disease severity

→ Tau-related biomarkers, particularly p-tau181 and p-tau231, reflect LMN and muscle-related disease burden

→ NfL captures disease aggressiveness and prognosis

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