

Age-adjusted Serum Reference Ranges for Lumipulse® G NfL Blood: Results from a Clinical Performance Study

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Background

Neurofilament light chain (NfL) is emerging as a key blood biomarker for neuro-axonal injury across a spectrum of neurological diseases. Its clinical utility depends on accurate interpretation within standardized reference frameworks, including robust age-related reference ranges, given the biomarker's sensitivity to age and comorbidities.

Study Objective

This study aimed to establish serum reference ranges for the Lumipulse G NfL Blood assay <CE>, supporting its clinical utility and regulatory validation. The assay is intended to detect NfL as a biomarker of neuro-axonal damage irrespective of the cause and can contribute to the monitoring of disease activity in patients with neurological diseases.

Method

Serum samples from a well-characterized hospital-based control cohort (n=651, 18-86 years of age, 56.8% females) were analyzed using the Lumipulse G NfL Blood assay (Fujirebio Europe N.V.). Strict in- and exclusion criteria were applied, using all available medical information (brain/spinal MRI, cerebrospinal fluid analysis, routine blood work, EEG/EMG, medical history) including information obtained at follow-up visits.

Inclusion criteria

- Clinical and paraclinical data indicates absence of disease associated with neuro-axonal damage
- Basic CSF examination shows no pathological results:
 - No intrathecal immunoglobulin synthesis or blood-CSF-barrier dysfunction
 - Absence of oligoclonal bands to exclude chronic inflammatory CNS disease / preclinical disease stage
- No evidence of peripheral nervous system disease

Exclusion criteria

- Body mass index (BMI) <18 kg/m² or >35 kg/m²; if not available: exclusion was also based on clinical signs from medical history of clinically relevant malnutrition or other conditions that can lead to extreme BMI)
- Known chronic kidney diseases or renal insufficiency (defined as an abnormal eGFR < 60 ml/min/1.73 m² but adjusted for age and gender and including documented medical history)
- Suspected Creutzfeldt-Jakob's disease
- Stroke or myocardial infarction
- Traumatic brain injury
- Diagnosis of diabetic polyneuropathy or possible diabetic polyneuropathy (determined by HbA1c levels or medical history) with impact on neuro-axonal damage
- Known damage to, or disease of, the central or peripheral nervous system

Reference limits were derived in accordance with CLSI guideline EP28-A3c using Generalized Additive Models for Location, Scale and Shape (GAMLSS), enabling age-dependent modelling of the distribution of NfL concentrations. Additional samples from patients with Alzheimer's disease (AD; n=50), amyotrophic lateral sclerosis (ALS; n=43), frontotemporal dementia (FTD; n=48), and multiple sclerosis (MS; n=66), each comprising different subtypes, disease stages and treatment status, were included for illustrative comparison.

Results

NfL concentrations in controls showed a clear age-dependent increase, with the 50th percentile rising from 4.69 pg/mL in individuals under 30 years of age to 18.03 pg/mL in those aged 70 and above (Table 1).

Table 1: NfL reference ranges for the Lumipulse G NfL Blood assay expressed as percentiles and z-scores (per age decade) according to the GAMLSS model.

Age clades (years)	NfL values in pg/mL						
	[*] = 95% confidence interval						
	50th percentile	80th percentile	84.1th percentile	90th percentile	93.3th percentile	95th percentile	97.7 th percentile
	(z-score 0.00)	(z-score 0.84)	(z-score 1.00)	(z-score 1.28)	(z-score 1.50)	(z-score 1.64)	(z-score 2.00)
≤29 (n=134)	4.69	5.88	6.16	6.70	7.19	7.54	8.59
	[4.48, 4.93]	[5.56, 6.24]	[5.80, 6.56]	[6.26, 7.20]	[6.65, 7.79]	[6.92, 8.22]	[7.69, 9.61]
30-39 (n=141)	5.52	7.22	7.63	8.44	9.19	9.73	11.42
	[5.23, 5.84]	[6.70, 7.80]	[7.05, 8.30]	[7.71, 9.29]	[8.30, 10.23]	[8.72, 10.92]	[9.91, 13.20]
40-49 (n=130)	6.76	8.36	8.73	9.45	10.09	10.55	11.93
	[6.46, 7.06]	[7.93, 8.84]	[8.24, 9.27]	[8.84, 10.17]	[9.35, 10.98]	[9.69, 11.60]	[10.64, 13.53]
50-59 (n=125)	8.43	10.51	10.99	11.94	12.80	13.40	15.24
	[8.03, 8.82]	[9.95, 11.10]	[10.37, 11.65]	[11.16, 12.75]	[11.86, 13.77]	[12.33, 14.51]	[13.70, 16.88]
60-69 (n=55)	12.28	16.68	17.77	19.97	22.03	23.53	28.30
	[11.15, 13.62]	[14.66, 19.03]	[15.46, 20.45]	[17.03, 23.36]	[18.43, 26.21]	[19.38, 28.33]	[22.31, 35.76]
≥70 (n=66)	18.03	23.42	24.72	27.29	29.64	31.33	36.58
	[16.59, 19.42]	[21.58, 25.16]	[22.67, 26.64]	[24.76, 29.70]	[26.55, 32.67]	[27.77, 34.90]	[31.32, 42.41]

Age-specific percentiles and z-score figures and tables were generated to facilitate clinical interpretation (Figure 1).

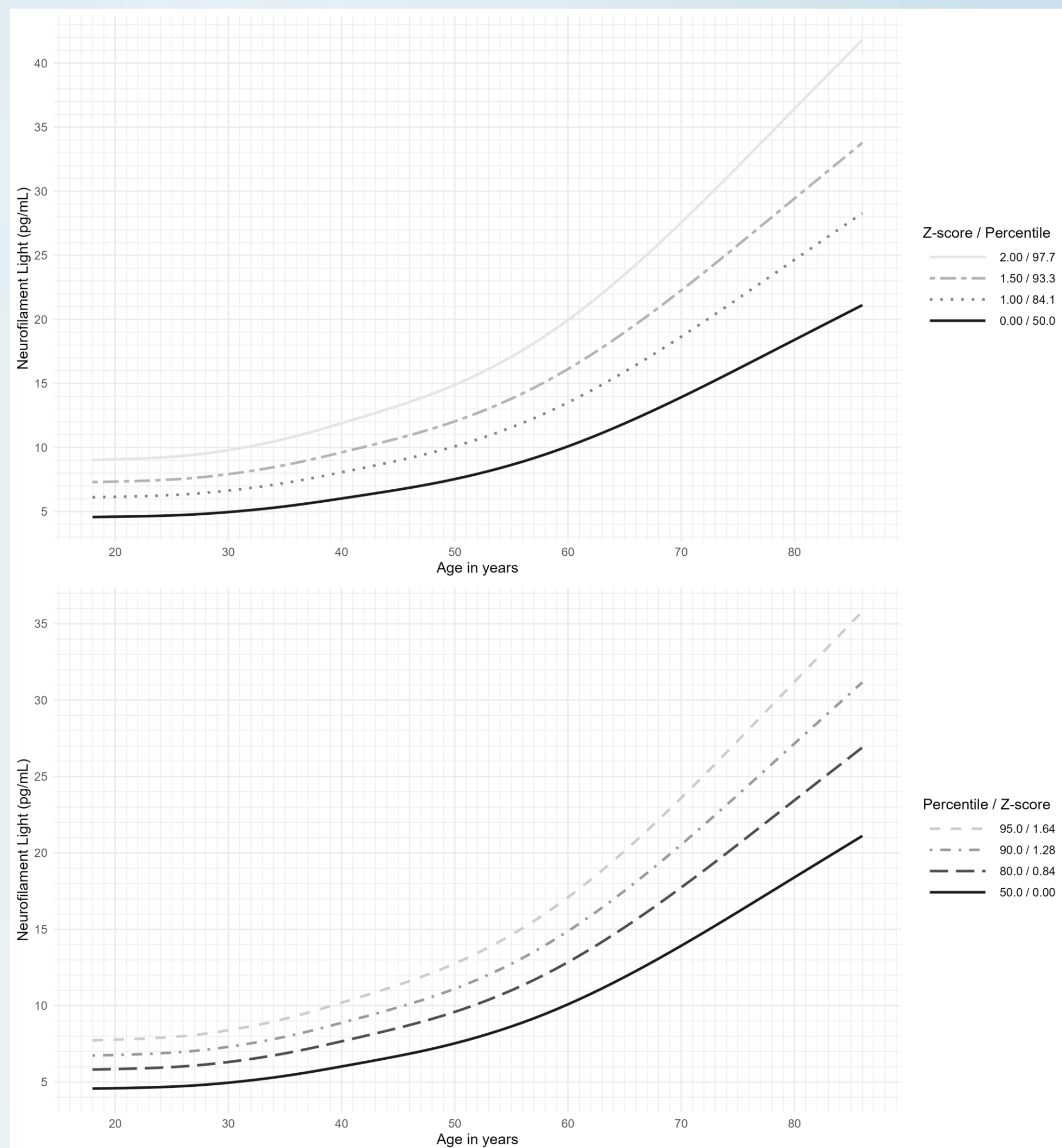


Figure 1: Visualization of the NfL reference ranges for the Lumipulse G NfL Blood assay expressed as age-related z-scores (0.00, 1.00, 1.50, 2.00; top panel) and percentiles (95th, 90th, 80th, 50th Pct, bottom panel).

Extreme BMI (<18 kg/m² or >35 kg/m²) have been shown to influence NfL values. In our study, these extreme BMI were excluded (apart from one value), and no association was found between BMI and the NfL concentration (Figure 2). Further stratification according to BMI was therefore not considered.

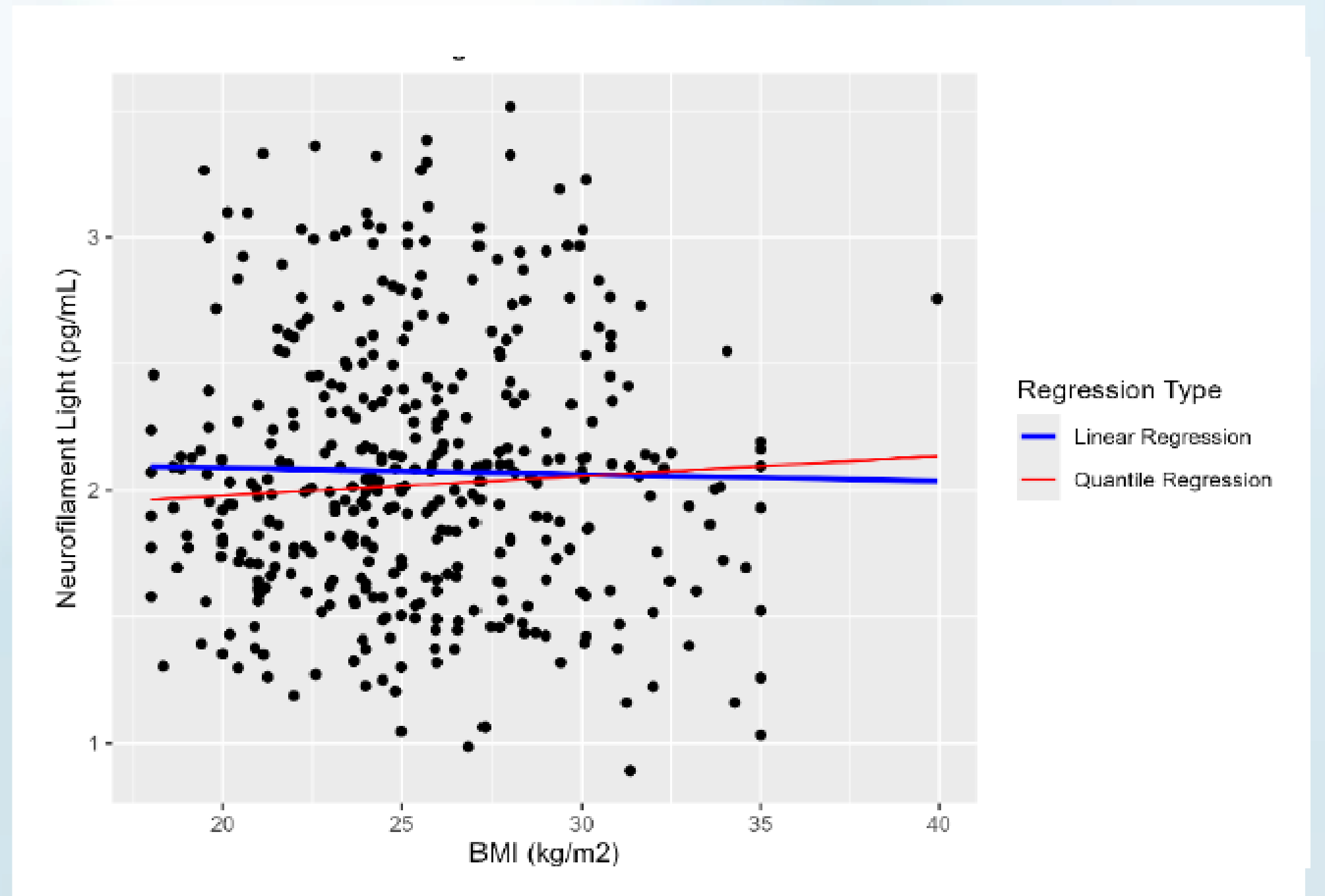


Figure 2: Association between NfL concentration and BMI in the reference range population using linear and quantile regression analysis.

The disease cohorts demonstrated significantly higher NfL levels compared to controls (Kruskal-Wallis and Steel tests, p<0.0001), with ALS showing the greatest elevations, followed by FTD, AD, and MS (Figure 3). Overlap between groups was observed, reflecting the non-specific nature of NfL and disease heterogeneity.

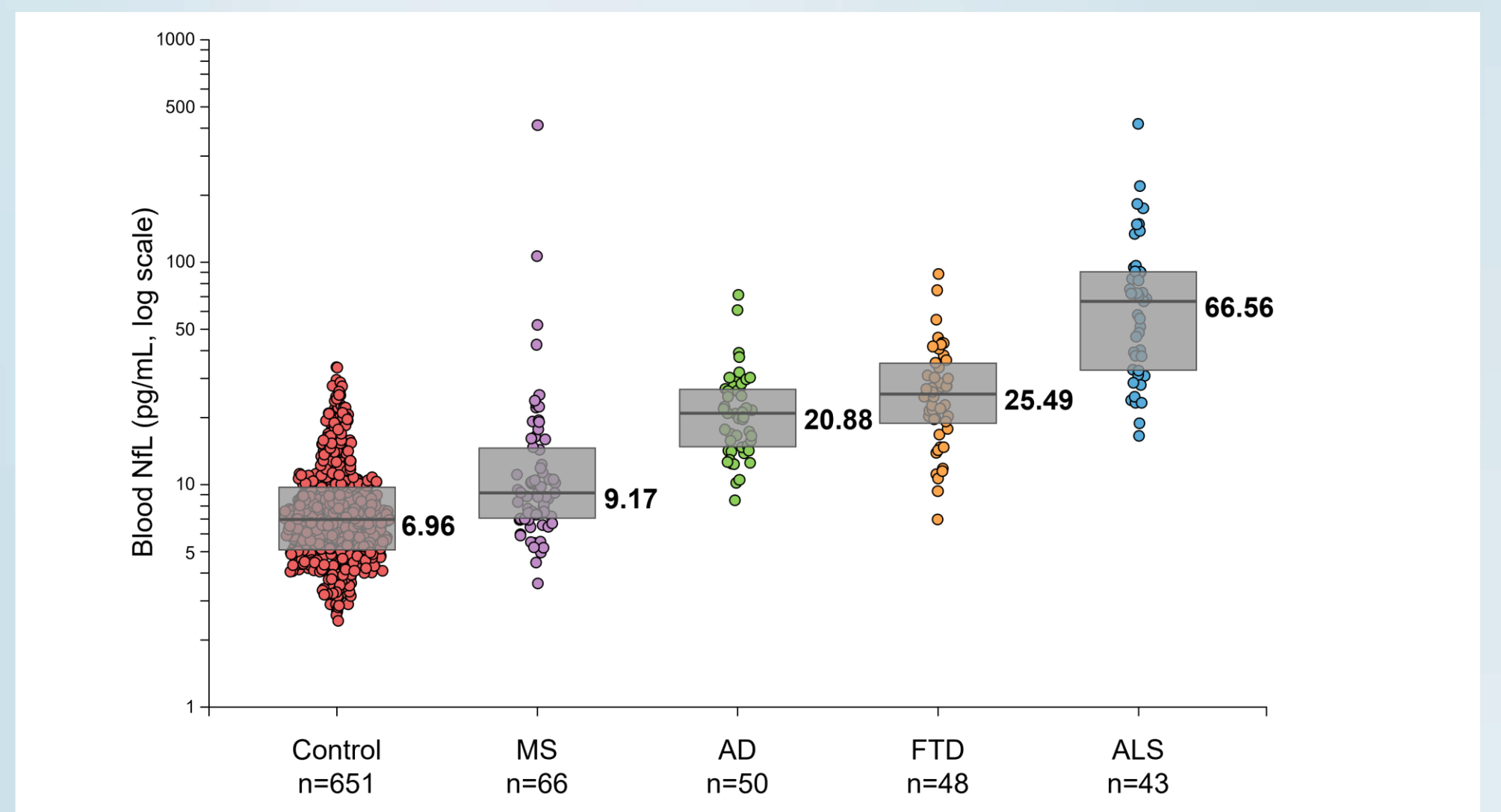


Figure 3: Box plot with median and inter-quartile range and minimum and maximum for the control (reference range) population and each of the different disease cohorts.

Conclusion

This study provides comprehensive, age-adjusted reference ranges for serum NfL using the Lumipulse G NfL Blood assay, enabling more precise interpretation of results in clinical and research settings. NfL is a sensitive marker for neuro-axonal injury, but its non-specificity and biological variability underscore the importance of contextual interpretation alongside clinical findings. These reference ranges support routine monitoring of disease activity and pave the way for future studies to refine diagnostic and prognostic thresholds, particularly in ALS and related disorders.

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