Serum neurofilament light: a biomarker of neuronal damage in multiple sclerosis

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Supplementary table 1

Multivariable GEE model testing associations between several demographic and clinical variables including EDSS*Disease course interaction and sNfL in the SMSC cohort.

Variables / Interactions (*)		Multivariable		
		β	95%CI	*p*
Age (years)		1.011	1.004-1.018	0.001
EDSS		1.133	1.081-1.187	<0.001
Disease course	CIS/RRMS	-	-	-
	PPMS/SPMS	1.459	0.948-2.244	0.086
Recent relapse (<60 days)	No	-	-	-
	Yes	1.408	1.140-1.740	0.002
Recent EDSS worsening	No	-	-	-
	Yes	1.131	0.970-1.317	0.115
DMT	Untreated	-	-	-
	Treated	0.813	0.711-0.929	0.002
EDSS * Disease course		0.904	0.829-0.985	0.021

GEE: Generalized Estimated Equations model. sNfL: serum NfL; EDSS: Expanded Disability Status Scale; CIS: clinically isolated syndrome; RRMS: relapsing remitting MS; SPMS: secondary progressive MS; PPMS: primary progressive MS; DMT: Disease modifying treatment.

Supplementary table 2

Multivariable GEE model testing associations between several demographic and clinical variables and sNfL in the SMSC cohort *after* start of new DMT.

Variables		Multivariable		
		β	95%CI	*p*
Time under DMT (years)		0.900	0.830-0.976	0.011
sNfL at baseline		1.003	1.001-1.004	0.001
Age (years)		1.015	1.008-1.021	<0.001
Gender	F	-	-	-
	M	0.952	0.832-1.090	0.478
EDSS		1.096	1.054-1.139	<0.001
Disease course	CIS/RRMS	-	-	-
	PPMS/SPMS	0.980	0.764-1.257	0.875
Recent relapse (<60 days)	No	-	-	-
	Yes	1.422	1.024-1.973	0.035
Recent EDSS worsening	No	-	-	-
	Yes	1.203	0.964-1.501	0.102

GEE: Generalized Estimated Equations model. sNfL: serum NfL; DMT: Disease modifying treatment; F: female; M: male; EDSS: Expanded Disability Status Scale; CIS: clinically isolated syndrome; RRMS: relapsing remitting MS; SPMS: secondary progressive MS; PPMS: primary progressive MS.

Supplementary table 3

Model-predicted means (marginal means) and model estimates including 95% confidence intervals from GEE models: Probability of a relapse within 60 days before sampling, ARR one and two years before sampling and probability of EDSS worsening before sampling according to different sNfL percentile categories.

Percentiles	samples n (%) with sNfL > percentile	Relapses <60 days before sampling					ARR 1 year before sampling*				
		Above (%)	Below (%)	OR	95%CI	*p*	Above	Below	IRR	95%CI	*p*
80th	287 (49.4)	18.7 (14.2-24.1)	7.1 (4.6-10.6)	3.02	1.72-5.28	<0.001	0.77 (0.66-0.90)	0.41 (0.34-0.50)	1.86	1.46-2.38	<0.001
90th	228 (39.2)	21.0 (16.0-27.0)	7.5 (5.2-10.8)	3.26	1.98-5.38	<0.001	0.85 (0.72-1.01)	0.42 (0.35-0.50	2.03	1.60-2.59	<0.001
95th	171 (29.4)	23.8 (17.9-30.9)	8.1 (5.7-11.4)	3.56	2.16-5.88	<0.001	0.92 (0.76-1.10)	0.44 (0.38-0.52)	2.06	1.62-2.62	<0.001
97.5th	135 (23.2)	26.6 (19.5-35.1)	8.5 (6.1-11.8)	3.89	2.30-6.58	<0.001	0.97 (0.80-1.18)	0.47 (0.40-0.55)	2.08	1.64-2.63	<0.001
99th	105 (18.1)	29.8 (21.2-40.2)	9.0 (6.6-12.3)	4.28	2.46-7.44	<0.001	1.06 (0.84-1.33)	0.48 (0.42-0.56)	2.19	1.70-2.81	<0.001

Percentiles	samples n (%) with sNfL > percentile	ARR 2 years before sampling*					EDSS worsening since visit before sampling*				
		Above	Below	IRR	95%CI	*p*	Above (%)	Below (%)	OR	95%CI	*p*
80th	287 (49.4)	0.64 (0.57-0.73)	0.53 (0.46-0.60)	1.23	1.06-1.42	0.007	9.1 (6.1-13.4)	3.6 (1.9-6.6)	2.72	1.23-6.02	0.014
90th	228 (39.2)	0.68 (0.59-0.77)	0.53 (0.46-0.60)	1.28	1.11-1.49	0.001	10.7 (7.0-15.9)	3.6 (2.0-6.4)	3.23	1.48-7.04	0.003
95th	171 (29.4)	0.70 (0.61-0.80)	0.53 (0.47-0.61)	1.31	1.13-1.51	<0.001	12.9 (8.4-19.2)	3.6 (2.1-6.3)	3.93	1.85-8.33	<0.001
97.5th	135 (23.2)	0.74 (0.64-0.87)	0.53 (0.47-0.60)	1.39	1.18-1.64	<0.001	14.8 (9.4-22.5)	3.8 (2.3-6.3)	4.36	2.09-9.09	<0.001
99th	105 (18.1)	0.78 (0.66-0.92)	0.54 (0.48-0.61)	1.45	1.22-1.73	<0.001	17.0 (10.4-26.5)	4.0 (2.5-6.5)	4.86	2.30-10.25	<0.001

OR: odds ratios; ARR: annualized relapse rate; IRR: incidence rate ratios; 95%CI=95% confidence intervals. * Samples from patients with a relapse within 30 days excluded.

Supplementary table 4

Model-predicted means (marginal means) and model estimates including 95% confidence intervals from GEE models: ARR one and two years after sampling and EDSS worsening within 1 year after sampling according to different sNfL percentiles.

Percentiles	samples n (%) with sNfL > percentile	ARR 1 year after sampling*					ARR 2 years after sampling*				
		Above	Below	IRR	95%CI	*p*	Above	Below	IRR	95%CI	*p*
80th	287 (49.4)	0.28 (0.21-0.37)	0.17 (0.12-0.24)	1.62	1.08-2.44	0.021	0.24 (0.18-0.32)	0.14 (0.10-0.19)	1.69	1.19-2.39	0.003
90th	228 (39.2)	0.30 (0.22-0.41)	0.18 (0.13-0.24)	1.71	1.12-2.64	0.014	0.26 (0.19-0.35)	0.14 (0.11-0.19)	1.80	1.23-2.65	0.003
95th	171 (29.4)	0.32 (0.22-0.46)	0.18 (0.14-0.24)	1.75	1.10-2.76	0.017	0.27 (0.18-0.39)	0.16 (0.12-0.21)	1.69	1.03-2.79	0.038
97.5th	135 (23.2)	0.36 (0.24-0.52)	0.18 (0.14-0.24)	1.94	1.21-3.10	0.006	0.30 (0.21-0.45)	0.15 (0.12-0.21)	1.96	1.22-3.15	0.005
99th	105 (18.1)	0.40 (0.26-0.62)	0.19 (0.14-0.24)	2.15	1.29-3.60	0.003	0.33 (0.21-0.50)	0.16 (0.12-0.21)	2.03	1.26-3.27	0.004

Percentiles	samples n (%) with sNfL > percentile	EDSS worsening within 1 year after sampling*				
		Above (%)	Below (%)	OR	95%CI	*p*
80th	287 (49.4)	11.0 (7.3-16.3)	6.7 (3.8-11.5)	1.72	0.84-3.50	0.135
90th	228 (39.2)	12.7 (8.1-19.3)	6.5 (3.9-10.6)	2.10	1.03-4.29	0.042
95th	171 (29.4)	15.1 (9.4-23.4)	6.3 (3.8-10.3)	2.63	1.25-5.54	0.011
97.5th	135 (23.2)	15.3 (8.8-25.4)	7.0 (4.4-10.9)	2.41	1.07-5.42	0.034
99th	105 (18.1)	14.6 (7.5-26.4)	7.7 (5.0-11.6)	2.06	0.85-4.98	0.110

OR: odds ratios; ARR: annualized relapse rate; IRR: incidence rate ratios; 95%CI=95% confidence intervals. *Samples from patients with a relapse within 30 days excluded.