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RESEARCH ARTICLE

Serum neurofilament levels and patient-reported outcomes in multiple sclerosis

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Abstract

Objective: Serum neurofilament light (sNfL) is a promising new biomarker in multiple sclerosis (MS). We explored the relationship between sNfL and health outcomes and resource use in MS patients. **Methods**: MS patients with serum samples and health-outcome measurements collected longitudinally between 2011 and 2016 were analyzed. sNfL values were evaluated across age and gender. Data were analyzed using correlation with log-transformed sNfL values. **Results**: A total of 304 MS patients with a mean age of 32.9 years, average EDSS of 1.6 (SD = 1.5) and baseline sNfL of 8.8 (range 1.23–78.3) pg/mL were studied. Baseline sNFL values increased with age and were higher in females. Baseline sNfL correlated with baseline Multiple Sclerosis Quality of Life physical composite (mean = 49.4 (9.1), $P = 0.035$) and baseline EDSS ($P = 0.002$). Other PRO measures at baseline did not show a significant relationship with baseline sNfL. Average of baseline and follow-up sNfL correlated with MSQoL physical-role limitations (mean = 48.9 (10.8), $P = 0.043$) and social-functioning (mean = 52.3 (7), $P = 0.034$) at 24-month follow-up. We found a trend for numerically higher sNfL levels in nonpersistent patients compared to those who were persistent to treatment (11.13 vs. 8.53 pg/mL, $P = 0.093$) measured as average of baseline and 24-month values. Baseline NfL was associated with number of intravenous steroid infusions (mean = 0.2; SD = 3.0, $P = 0.013$), whereas the average of baseline and 12 months NfL values related to inpatient stays at 12 months (mean = 0.2; SD = 3.0 $P = 0.053$). **Conclusion**: Serum NfL is a patient-centric biomarker that correlated with MS patient health-outcomes and healthcare utilization measures in a real-world cohort.

Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating and neurodegenerative disease of the central nervous system. The development of a simple direct biomarker is critical to improving the monitoring of disease activity and treatment response. Serum neurofilament light (sNfL) has emerged as a promising candidate biomarker. NfL is a neuro-specific protein which helps provide structural support in axons. Initial studies showed that NfL in cerebrospinal fluid (CSF) was elevated in relapsing and progressive patients with MS and other neurodegenerative conditions.[1–5] More recently a serum assay using single molecular array immunoassay techniques has become available, and it correlates with CSF level with great sensitivity.[6]

NfL has already been shown in multiple studies to be associated with gadolinium-enhanced MRI lesion activity, relapse, EDSS, use of disease-modifying treatment (DMT), and brain atrophy development in the future.[6–10] However, the relationship between NfL and real-world health outcomes (quality of life, persistence of treatment, healthcare utilization) is not well characterized. Further understanding of sNfL to capture these patient-specific

outcomes is important to help support the potential of sNfL as a biomarker.

Previous cross-sectional studies have suggested there may be a correlation between sNfL and some patient-reported outcome (PRO) measures including quality of life using the MS Quality of Life 54 (MSQoL54) and EQ5D.[11,12] We sought to further characterize the longitudinal relationship between sNfL and other patient-reported outcomes, treatment persistence, and health care resource use measures. We additionally investigated the longitudinal relationship of sNfL and these measures.

Patients and Methods

Data source

The Comprehensive Longitudinal Investigation of Multiple Sclerosis at Brigham and Women's Hospital and Brigham MS Center (CLIMB) is a longitudinal study of over 2,100 MS patients initiated in the year 2000. This study and the CLIMB Study were conducted with the approval of the Institutional Review Board of the Partners Human Research Committee. Written informed consent was obtained from the participants for the CLIMB study and included retrospective analyses of collected data.

The current evaluation focusing on the relationship of sNFL and health outcomes is performed on a selected cohort (based on inclusion criteria below) as a retrospective analysis.

Inclusion of subjects

Patients included in this analysis were MS patients enrolled in CLIMB between April 2011 and April 2016. All patients with baseline sNfL and patient-reported outcome measures during this time were included.

Furthermore, patients with baseline and follow-up measurements (at 12 and 24 months) for patient-reported outcomes, medication use, and healthcare utilization (inpatient visits, steroid use) were included in the analysis. Only visits with concurrent PROs and sNfL measurements were included in the analysis. Since PRO administration changed from annually to biennially during this period, many patients had two measurements with the second measurement at month 12 or month 24 and only a few had three measurements.

Data collection

Demographic information was collected and entered onto an iPad or paper intake form by patients at their enrollment visit and updated at each subsequent visit as part of the CLIMB study. Intake items include age, race, education, education, employment status, occupation, and ethnicity were also collected at this time as part of the CLIMB study. Physicians obtained visit data at clinic visits including relapse information, EDSS and MRI information. Demographic, clinical, and PRO data were stored in an Oracle database. Demographic data are reviewed and updated by study staff. Clinical assessments are recorded at each visit and auto-checked for gross errors. A trained study staff reviews EDSS scores to ensure consistency with neurological examination. QOL data are reviewed for data completeness by CLIMB study staff to reduce measurement bias. Health care utilization measures including, the number of outpatient visits, days of inpatient stays, number of IV steroid infusions were collected retrospectively using linked electronic medical records (EMR) for the purposes of this study. For each patient, the date of the baseline sNfL measurement was determined, and the chart was reviewed for number of steroid infusions, number of outpatient visits and inpatient stays during the subsequent 12 months were recorded. Disease-modifying therapy start and stop dates were obtained from the database and analyzed further to subgroup patients as persistent versus nonpersistent DMT users for the purposes of this retrospective study. Nonpersistent DMT users were defined as not persistently remaining on the same therapy for 12 or 24 months, respectively, from the time of date of first entry included in the study to follow-up at 24 months.

PRO measurements

A series of PRO measures were administered to CLIMB patients including the CES-D, MFIS, MSQoL-54, and WPAI. The CES-D [8] scale is a 20-item self-reported assessment measuring the major facets of depression. Response options range from 1 to 4 for each item (1 = Rarely or None of the Time, 2 = Some or Little of the Time, 3 = Moderately or Much of the time, 4 = Most or Almost All the Time). Scores range from 20 to 80, with high scores indicating greater depressive symptoms. The CES-D also provides cutoff scores (e.g., 36 or greater) that aid in identifying individuals at risk for clinical depression. The MFIS [9] is an instrument that assesses three facets of fatigue including physical, mental, and psychosocial fatigue. Overall score ranges from 0 to 84 with higher scores indicating a greater impact of fatigue on a person's activities. The MSQoL54 [10] is a 54 item-questionnaire that combines the MOS Short Health Survey Form with 18 additional MS-specific health-related issues. In this paper, we have used the SF-36 subscores due to inconsistent reporting of some of the MS-specific health-related issues. It consists of eight subscales and two summary scores – physical health and mental health. The

WPAI [11] is widely used to measure the self-reported effect of health conditions and symptom severity on work productivity and regular activities during the past 7 days. It measures absenteeism, presenteeism as well as the impairments in work and activity because of health problem during the past seven days. Correlation of patient-reported outcome measures at 24 months with baseline sNfL was also assessed given possible lag to observe the consequences or translation of low or elevated sNfL levels on the QoL of patients.

NfL measurements

Serum samples were collected annually as part of the CLIMB study at the time of patient visits and stored at −80°C. Using these collected samples, the sNfL analysis was performed retrospectively using single-molecule array (SIMOA) assay (Quanterix Corp, Boston, MA, US) for the purposes of this study. The date of first sNfL assessment (at enrollment) was defined as the index date (baseline). Serum was also obtained at year one (approximately 12 months from baseline) and at year two (approximately 24 months from baseline) and sNfL was analyzed retrospectively for this study. Log-transformed sNfL levels were used for our analysis. Subjects missing NfL levels at the timepoint were removed from the analysis for that time point. sNfL at baseline was averaged with sNfL at year one, with sNfL at year two and sNfL at year one, two, and three were averaged. Analyses were performed with these different averaged values.

Data availability statement

We adhere to the Neurology data-sharing policy. De-identified limited datasets from this study can be made available to qualified investigators with appropriate Ethics/IRB approval. Data are stored for up to 5 years postpublication.

Statistical analysis

Baseline characteristics of subjects were estimated using the mean and standard deviation for continuous variables and proportions for dichotomous variables. The baseline values for sNfL across different age groups and gender were also evaluated. The association between baseline log-transformed sNfL and mean baseline age was estimated using Pearson's correlation coefficient, and the association between log-transformed sNfL and baseline EDSS and ARR over the subsequent 2 years was estimated using Spearman's correlation coefficient. Furthermore, the association between the 24-month EDSS and the average of the baseline log-transformed sNfL and month 24 log-transformed sNfL was estimated using Spearman's correlation coefficient. Baseline sNfL levels and the average of baseline and month 12 sNfL levels were correlated with the number of outpatient visits, days of inpatient stays, and number of steroid infusions in the subsequent year.

To estimate the association between sNfL and PROs, Pearson's correlations coefficients were estimated between PRO measurements and log-transformed baseline sNfL measures. In addition, partial Pearson's correlations coefficients were estimated between PRO measurements and log-transformed sNfL values adjusting for age and EDSS score.

Additionally, the association between 24-month PRO measurement and the average of log-transformed sNfL baseline and log-transformed 24-month sNfL was estimated using Pearson's correlation coefficient.

As an exploratory analysis, partial Pearson's correlation coefficient was used to adjust this association for age and EDSS score. Furthermore, given we completed 17 comparisons for each outcome correlations with PRO measures in the main analysis, the Bonferroni corrected alpha level was 0.0029 (0.05/17) so that p-values for all analyses were explored and then compared to at 0.05 and 0.0029 given the multiple comparisons. Finally, the subject who were treated with the same disease-modifying treatment (DMT persistent) were compared to subjects who changed treatment (DMT nonpersistent) using a Wilcoxon rank sum test. All analyses were performed by researchers at the Partners MS Center at the Brigham and Women's Hospital using the statistical package R version 3.6.3 (www.r-project.org).

Results

Subject characteristics

The baseline characteristics of our MS patient cohort, including disease subtype at baseline, are shown in Table 1. There were 304 subjects with a baseline sNfL levels and PRO measures, 104 subjects with a follow-up visit at year one with PROs measured and 107 with a follow-up visit at year two with PROs measured. A summary of sNfL characteristics of the patients is also shown. There was a notable range in sNfL scores at baseline and in year one (7.85 pg/mL to 78.3 pg/mL and 8.7 pg/mL to 68.4 pg/mL, respectively) (Table 1).

Baseline sNfL values across age and gender

The threshold baseline NfL values increased linearly across higher age (Table 2). The mean baseline sNfL value for age group of 25–35 years was 6.97 (3.83) and increased to 10.7 (3.45) for patients >55 years of age.

Table 1. Baseline characteristics and sNfL values.

Demographics	
N	304
Age of disease onset	32.9 (9.3) years
Age when PROs were first evaluated	46.0 (9.5) years
Disease duration at first PROs administration	13.0 (7.9) years
Sex % female	*N* = 231 (76%)
Race % white	*N* = 288 (94.7%)
Ethnicity % Hispanic	*N* = 11 (3.62%)
EDSS at first sNFL	1.6 (1.5)
Patients with clinically isolated syndrome	17
Patients with primary progressive MS	9
Patients with primary relapsing	1
Patients with relapsing remitting	257
Patients with secondary progressive	20
sNFL at baseline	8.8 pg/mL (7.885/1.23/78.3); *n* = 304
sNFL at year 1	10.3 pg/mL (8.775/3.35/68.4); *n* = 104
sNFL at year 2	8.8 pg/mL (7.92/3.02/19.6); *n* = 107
Average sNFL at baseline-y1	9.5 pg/mL (8.5525/3.325/39.5); *n* = 104
Average sNFL at baseline-y2	9.2 pg/mL (8.235/3.025/45.2); *n* = 107

In this table, we present the mean (median/minimum/maximum) and number of subjects.
EDSS, Expanded Disability Status Scale.

Table 2. Baseline sNfL levels in RMS patients by Age group and gender.

	Baseline sNfL values (N)	p-value
Age groups		
18–25	4.91 (0.35) *n* = 3	<0.001
25–35	6.97 (3.83) *n* = 40	
35–45	7.84 (4.54) *n* = 87	
45–55	9.46 (6.92) *n* = 124	
≥55	10.7 (3.45) *n* = 50	
Gender		
Female	9.20 (6.05) *n* = 231	0.006
Males	7.65 (3.30) *n* = 73	

Moreover, baseline sNfL value for females was higher at 9.20 (6.05) compared to males [7.65 (3.30)].

Correlations with clinical outcomes and healthcare resource use

Baseline sNfL levels showed a moderate correlation with age ($r = 0.39$; $P < 0.001$). In terms of correlation with clinical measures, the correlation between sNfL and the EDSS was mild but statistically significant ($r_s = 0.15$; $P = 0.009$), and there was a limited correlation with ARR during the 2 years following baseline assessment was ($r_s = 0.010$; $P = 0.870$).

When baseline sNfL was compared with health care utilization over the subsequent 12 months, baseline NfL was associated with the number of intravenous steroid infusions over the subsequent 12 months ($r_s = 0.144$; $P = 0.013$). There was a mean of 0.9 (SD 2.3) steroid infusions given. Correlation with other healthcare resource measures showed limited correlations (see Table 3 for detailed results).

Correlation with PRO measures

In the univariate analyses, baseline sNfL levels had the largest correlations with the physical functioning subscale of the SF-36 and the physical composite score of the SF-36, and higher sNfL values were associated with lower quality of life (Table 3). For the measures of fatigue, depression, and work productivity, there were limited correlations between sNfL and each PRO. After adjusting for age and EDSS, the correlation between the SF-36 scores and sNfL was attenuated (Table 3).

When the average of the baseline sNfL score and the month 24 sNfL score were correlated with the month 24 PROs, an association was observed between role physical functioning and social functioning (Table 4). There were limited associations between fatigue, depression, and work productivity in this analysis as well. All analyses were also fit removing subjects who had a relapse within 3 months of the sNfL serum sample and the results were largely unchanged (data not shown).

Correlation with DMT persistence

We found a trend for numerically higher sNfL levels in patients on nonpersistent DMT compared to those who were on persistent treatment (11.13 vs. 8.53 pg/mL, $P = 0.12$) measured as average of baseline and 24-month log-transformed sNfL. There were 42 patients in this cohort who switched DMT during the study period. The reasons included drug reaction intolerance (12 patients), JCV antibody status positivity (3 patients), pregnancy (1 patient), injection fatigue (6 patients), worsening EDSS (2 patients), worsening inflammatory disease activity (12 patients), and unclearly documented (6 patients).

Discussion

This study investigates the longitudinal relationship between sNfL and quality of life as well as sNfL and

Table 3. Correlation of baseline sNfL levels with patient-reported outcome measures.

	Score	Pearson's correlation with log-transformed baseline sNfL	Partial Pearson's correlation with log-transformed baseline sNfL
Physical functioning (SF-36)	50 (9.9); n = 302	**−0.17; P = 0.0035**	−0.04; P = 0.479
Role physical (SF-36)	47.8 (11.1); n = 304	−0.06; P = 0.306	0; P = 0.975
Bodily pain (SF-36)	51.9 (8.7); n = 304	−0.05; P = 0.398	0.02; P = 0.718
General health (SF-36)	48.5 (9.1); n = 304	−0.01; P = 0.874	0.02; P = 0.798
Vitality (SF-36)	48.4 (10.2); n = 302	0.01; P = 0.906	0.04; P = 0.539
Social functioning (SF-36)	51.4 (8.1); n = 304	−0.02; P = 0.728	0.04; P = 0.51
Role emotional (SF-36)	48.8 (10.8); n = 304	0; P = 0.957	0.07; P = 0.216
Mental Health (SF-36)	51.3 (7.9); n = 304	0; P = 0.937	0.03; P = 0.638
Physical composite (SF-36)	49.4 (9.1); n = 300	**−0.12; P = 0.035**	−0.03; P = 0.666
Mental composite (SF-36)	50.1 (8.4); n = 300	0.06; P = 0.329	0.07; P = 0.219
Total fatigue (MFIS)	22.2 (15.3); n = 299	0; P = 0.98	−0.08; P = 0.167
Physical fatigue (MFIS)	10.5 (7.9); n = 299	0.05; P = 0.358	−0.05; P = 0.44
Mental fatigue (MFIS)	10.1 (7.6); n = 299	−0.05; P = 0.36	−0.09; P = 0.11
Psychological fatigue (MFIS)	1.7 (1.7); n = 299	0; P = 0.955	−0.08; P = 0.165
CESD	28 (7.1); n = 298	−0.03; P = 0.653	−0.05; P = 0.398
Overall work impairment (WPAI)	16.3 (22.7); n = 295	0.01; P = 0.929	−0.01; P = 0.815
Activity impairment (WPAI)	17.3 (23.2); n = 301	0.06; P = 0.314	−0.01; P = 0.926

Partial Pearson's correlation coefficient calculated adjusting for age and EDSS score. Given the 17 comparisons between NfL and PROs, the Bonferroni corrected type I error rate is 0.05/17 = 0.0029. Statistically significant values have been bolded.

health care utilization measures amongst MS patients in a real-world setting. We found an association between longitudinal sNfL levels and follow-up patient-reported outcome measures including physical functioning, social functioning, and the mental composite. We also found the relationship between baseline sNfL and baseline patient physical function. sNFL levels were associated with the health care utilization measures of the number of steroid infusions, but not with the number of outpatient visits or inpatient stays. We also found sNfL baseline levels vary across age groups and increase with age. Moreover, baseline sNfL levels were found to be higher among females.

Patient-reported outcome measures have been shown to correlate with neuroaxonal loss as measured by brain atrophy and lesion burden.[13] Additionally, both patient-reported outcome measures and NfL are known to correlate with disease progression as measured by EDSS change[14] as well as brain atrophy.[15] By accounting for disability and age, we sought to explore the relationship between NfL and quality of life. The effect was attenuated at baseline. Another smaller study of MS patients in a phase II nonrandomized study in Canada prior to undergoing hematopoietic stem cell transplant, found that sNfL correlated with physical but not mental scores at baseline on MSQoL54.[11] However, age nor EDSS was accounted for by their models. Prior to accounting for age and disability, we had similar findings. This suggests there are many complex factors that contributed to patient quality of life and direct assessment remains the best way to capture them.

However, since we did find a relationship between the sNfL and some quality of life measures at follow-up it is possible that subtle early neuroaxonal damage as measured by sNfL has longer term future consequences to overall patient well-being that is not captured by EDSS alone. Given the current lack of standardization, particularly in clinical trials, of administering patient-reported outcome measures, if a simple direct biomarker like sNfL could be used as a proxy, this would be extremely useful.

In this cohort of patients, we did not find a significant relationship between fatigue and sNfL at baseline. In previously published work from our group, we found average sNfL levels during year 1–3 correlated with baseline and 10-year MFIS scores but otherwise annual and averaged yearly NfL did not correlate with 10-year NfL.[15] Serum NfL has not been found to correlate with fatigue by other groups.[11,16] Taken together, the relationship between fatigue and sNfL may be complex due to a number of factors. First, fatigue is a symptom with notable variability. In one study of MS patients over a 2-year period, 54% of patients fluctuated between "fatigued" and "nonfatigued" states and only 27% were persistently fatigued.[17] It is hypothesized that there may be inflammatory factors contributing to fluctuating fatigue. There may be a difference in underlying pathology between patients that are fatigued, have fluctuating fatigue and those that are persistently fatigued. In fact, recent work has suggested that patients that have persistent fatigue have more gray and white matter changes than those with fluctuating fatigue or no fatigue.[18] In this study, patients who had relapsing fatigue as compared to nonfatigued, also showed

Table 4. Average sNFL (baseline and 24-month follow-up) as compared to 24-month PROs.

	Summary statistics for change	Pearson's correlation with log-transformed sNfL	Partial Pearson's correlation with log-transformed sNfL
Physical functioning (SF-36)	50.6 (9.4); n = 107	−0.11; P = 0.276	−0.05; P = 0.645
Role physical (SF-36)	48.9 (10.8); n = 105	**−0.2; P = 0.043**	−0.2; P = 0.049
Bodily pain (SF-36)	52.5 (8.4); n = 107	−0.13; P = 0.189	−0.11; P = 0.278
General health (SF-36)	49.3 (8.9); n = 106	0.01; P = 0.885	0; P = 0.99
Vitality (SF-36)	47.6 (9.8); n = 107	−0.11; P = 0.277	−0.08; P = 0.439
Social functioning (SF-36)	52.3 (7); n = 107	**−0.21; P = 0.034**	−0.23; P = 0.022
Role emotional (SF-36)	50.7 (9.1); n = 107	−0.15; P = 0.127	−0.15; P = 0.12
Mental Health (SF-36)	51.1 (7.7); n = 106	−0.12; P = 0.219	−0.14; P = 0.15
Physical composite (SF-36)	50.3 (9.4); n = 103	−0.11; P = 0.263	−0.08; P = 0.435
Mental composite (SF-36)	50.4 (7.6); n = 103	−0.17; P = 0.083	−0.2; P = 0.052
Total fatigue (MFIS)	19.9 (13.7); n = 107	0.06; P = 0.512	0.01; P = 0.883
Physical fatigue (MFIS)	9.5 (7.3); n = 107	0.07; P = 0.485	0.01; P = 0.893
Mental fatigue (MFIS)	9 (7); n = 107	0.04; P = 0.698	0.01; P = 0.92
Psychological fatigue (MFIS)	1.4 (1.4); n = 107	0.08; P = 0.41	0.02; P = 0.809
CESD	27.5 (6); n = 107	0.14; P = 0.162	0.15; P = 0.125
Overall work impairment (WPAI)	14.2 (18.9); n = 104	−0.06; P = 0.558	−0.05; P = 0.626
Activity impairment (WPAI)	14.1 (16.8); n = 106	0.05; P = 0.581	0.02; P = 0.836

Partial Pearson's correlation coefficient calculated adjusting for age and EDSS score. Given the 17 comparisons between NfL and PROs, the Bonferroni corrected type I error rate is 0.05/17 = 0.0029. Statistically significant values have been bolded.

differences in the bilateral frontal lobes. This may suggest that there is some component of fatigue may be regionally specific in the brain.

We did not find a significant relationship between sNfL and depression as measured by the CES-D. Notably, the positive predictive value of CES-D using the DSM diagnosis for major depressive disorder amongst a cohort of patient's with MS in one study was 59.6%, suggesting this may not be the most sensitive measure of depression in this cohort.[19] Recent works have found sNfL of patients with neurodegenerative conditions was significantly elevated than those with psychiatric disorders[20] and have also looked at the possibility of sNfL even being a discriminative marker between the two[21] suggesting depression and neuro-degeneration may be independent processes and thus not biologically linked by a biomarker like sNfL. In a subcohort analysis, we also found a trend toward patients who remained on the same DMT persistently for 24 months having lower mean sNfL as compared to those who did not. This may be a function of underlying disease therapy as those that needed to switch medications may have had more severe disease and thus more elevated sNfL or simply that persistent use is associated with lower sNfL. Previous work has shown that NfL levels are decreased when patients are treated with DMT agents[8,22,23] and also decreased when switching to more efficacious agents,[24] but more work needs to be done to better understand the relationship between switching between different agents of relatively equal efficacy as it may allow us to use sNfL to inform our decisions to switch treatments. We did not account for switching disease-modifying treatment within the main analyses given the disparate reasons for switch, but future work could investigate this.

We also found a relationship between baseline sNfL and the use of steroids in the following year. SNfL has been associated with new gadolinium-enhancing lesions,[6,14,25] and thus the use of steroids likely corresponds to clinician response to overall increased disease activity. Importantly, this demonstrates the ability of sNfL to capture clinically, and not just radiographic) disease activity as it translates into treatment decision making. Given the cost associated with administrating the relationship between sNfL and these measures suggests sNfL may be a good, clinically relevant marker of secondarily health care utilization.

The strengths of this study include a large deeply phenotyped MS cohort with multiple patient-reported outcomes and sNfL values as well as adjustment for both age and EDSS. The challenges include additional longitudinal follow-up, as well as correlative MRI studies which will be the topic of future work. In addition, blood was only collected once a year, and thus sNfL was only analyzed annually. This may have missed intermediate changes between yearly assessments. Additionally, we were unable to adjust for body mass index.

In summary, while there may be a correlation between sNfL and some longitudinal quality of life values especially physical functioning, sNfL may not be immediately sensitive to many potentially distant aspects of quality of

life including depression as measured by the CES-D, fatigue as measured by the MFIS or most measures included in the SF-36 in 2-year follow-up.

SNfL does show promise as a marker of secondary health care utilization given the association of values with IV steroid use. The ability of sNfL to correlate with these key patient-centric measures strengthens sNfL's future use as a biomarker that captures patient-perceived physical and functional aspects of MS and secondary healthcare utilization.

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References

1. Zetterberg H, Skillback T, Mattsson N, et al. Association of Cerebrospinal Fluid Neurofilament Light Concentration With Alzheimer Disease Progression. JAMA Neurol 2016;73:60–67.
2. Teunissen CE, Khalil M. Neurofilaments as biomarkers in multiple sclerosis. Mult Scler 2012;18:552–556.
3. Norgren N, Sundström P, Svenningsson A, et al. Neurofilament and glial fibrillary acidic protein in multiple sclerosis. Neurology 2004;63:1586–1590.
4. Rosengren LE, Karlsson JE, Karlsson JO, et al. Patients with amyotrophic lateral sclerosis and other neurodegenerative diseases have increased levels of neurofilament protein in CSF. J Neurochem 1996;67:2013–2018.
5. Silber E, Semra YK, Gregson NA, Sharief MK. Patients with progressive multiple sclerosis have elevated antibodies to neurofilament subunit. Neurology 2002;58:1372–1381.
6. Disanto G, Barro C, Benkert P, et al. Serum Neurofilament light: a biomarker of neuronal damage in multiple sclerosis. Ann Neurol 2017;81:857–870.
7. Disanto G, Adiutori R, Dobson R, et al. Serum neurofilament light chain levels are increased in patients with a clinically isolated syndrome. J Neurol Neurosurg Psychiatry 2016;87:126–129.
8. Kuhle J, Disanto G, Lorscheider J, et al. Fingolimod and CSF neurofilament light chain levels in relapsing-remitting multiple sclerosis. Neurology 2015;84:1639–1643.
9. Lycke JN, Karlsson JE, Andersen O, Rosengren LE. Neurofilament protein in cerebrospinal fluid: a potential marker of activity in multiple sclerosis. J Neurol Neurosurg Psychiatry 1998;64:402–404.
10. Rosso M, Gonzalez CT, Healy BC, et al. Temporal association of sNfL and gad-enhancing lesions in multiple sclerosis. Ann Clin Transl Neurol 2020;7(6):945–955.
11. Thebault S, R. Tessier D, Lee H, et al. High serum neurofilament light chain normalizes after hematopoietic stem cell transplantation for MS. Neurol Neuroimmunol Neuroinflamm 2019;6(5):e598.
12. Kaufmann M.Higher serum neurofilament light chain levels are associated with lower self-reported quality of life in the Swiss MS registry and the Swiss MS cohort-study. In: Salmen A, ed.
13. Mowry EM, Beheshtian A, Waubant E, et al. Quality of life in multiple sclerosis is associated with lesion burden and brain volume measures. Neurology 2009;72:1760–1765.
14. Kuhle J, Nourbakhsh B, Grant D, et al. Serum neurofilament is associated with progression of brain atrophy and disability in early MS. Neurology 2017;88:826–831.
15. Chitnis T, Gonzalez C, Healy BC, et al. Neurofilament light chain serum levels correlate with 10-year MRI outcomes in multiple sclerosis. Ann Clin Transl Neurol 2018;5:1478–1491.
16. Hakansson I, Johansson L, Dahle C, et al. Fatigue scores correlate with other self-assessment data, but not with clinical and biomarker parameters, in CIS and RRMS. Mult Scler Relat Disord 2019;36:101424.
17. Johansson S, Ytterberg C, Hillert J, et al. A longitudinal study of variations in and predictors of fatigue in multiple sclerosis. J Neurol Neurosurg Psychiatry 2008;79:454–457.
18. Palotai M, Nazeri A, Cavallari M, et al. History of fatigue in multiple sclerosis is associated with grey matter atrophy. Sci Rep 2019;9:14781.

19. Pandya R, Metz L, Patten SB. Predictive value of the CES-D in detecting depression among candidates for disease-modifying multiple sclerosis treatment. Psychosomatics 2005;46:131–134.
20. Eratne D, Loi SM, Walia N, et al. A pilot study of the utility of cerebrospinal fluid neurofilament light chain in differentiating neurodegenerative from psychiatric disorders: a 'C-reactive protein' for psychiatrists and neurologists? Aust N Z J Psychiatry 2020;54(1):57–67.
21. Katisko K, Cajanus A, Jaaskelainen O, et al. Serum neurofilament light chain is a discriminative biomarker between frontotemporal lobar degeneration and primary psychiatric disorders. J Neurol 2020;267 (1):162–167.
22. Sejbaek T, Nielsen HH, Penner N, et al. Dimethyl fumarate decreases neurofilament light chain in CSF and blood of treatment naive relapsing MS patients. J Neurol Neurosurg Psychiatry 2019;90:1324–1330.
23. Gunnarsson M, Malmestrom C, Axelsson M, et al. Axonal damage in relapsing multiple sclerosis is markedly reduced by natalizumab. Ann Neurol 2011;69:83–89.
24. Piehl F, Kockum I, Khademi M, et al. Plasma neurofilament light chain levels in patients with MS switching from injectable therapies to fingolimod. Mult Scler 2018;24:1046–1054.
25. Varhaug KN, Barro C, Bjørnevik K, et al. Neurofilament light chain predicts disease activity in relapsing-remitting MS. Neurol Neuroimmunol Neuroinflamm 2018;5:e422.

