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REVIEW

The role of serum neurofilament light (sNfL) as a biomarker in multiple sclerosis: insights from a systematic review

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Abstract

Objective This systematic literature review (SLR) was conducted to explore the role of serum neurofilament light chain (sNfL) as a biomarker in multiple sclerosis (MS) disease management.

Methods The review was conducted in accordance with the recommendation laid by the Cochrane Handbook for Systematic Reviews. A comprehensive literature search was performed in key biomedical databases (EMBASE®, MEDLINE®, MEDLINE®-In-Process, and all Evidence-Based Medicine [EBM] Reviews databases) to retrieve studies reporting the association between sNfL and disease activity in patients with MS. Additional evidence was also identified through hand searching of key conference proceedings and gray literature.

Results Following review of 1831 records, 75 studies from 180 publications were included in the review. The studies included in the SLR consistently demonstrated an association between higher sNfL levels and an increased risk of future relapses within 2 years and MS disease progression. Higher levels of sNfL were also linked to an increased likelihood of experiencing gadolinium-enhancing T1 and T2 lesions. Patients with lower sNfL levels had a higher likelihood of achieving no evidence of disease activity status. Furthermore, an inverse correlation was observed between sNfL levels and cognitive impairment as assessed via the Symbol Digit Modalities Test performance and Timed 25-Foot Walk scores.

Conclusion This SLR demonstrates the significance of sNfL as a sensitive biomarker for monitoring MS progression. Convenient and reliable sNfL measurement could benefit routine clinical practice, providing clinicians with a simple and effective tool to monitor disease and treatment response.

Keywords Multiple sclerosis · Serum neurofilament light chain (sNfL) · Systematic review · Biomarker · Relapse · Disease progression

Introduction

Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system characterized by inflammation, neurodegeneration, and disability accumulation [1, 2]. MS affects 2.9 million people globally and approximately 1 million in the United States [3, 4]. It imposes a considerable burden on patients, healthcare providers, and society and creates economic challenges for the healthcare system [5–8]. The management of MS necessitates continuously tracking

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disease activity and optimizing treatments. However, diagnostic approaches based on traditional clinical assessment and magnetic resonance imaging (MRI) techniques have limitations in accurately capturing (subclinical) disease activity, assessing treatment response, and predicting short- and long-term outcomes [9, 10]. Consequently, the availability of a sensitive and minimally invasive biomarker is imperative, particularly for the early identification of patients at high risk for progression (early progression).

Neurofilament light chain (NfL), a cytoplasmic protein found in neurons, is released in response to neuroaxonal pathology and can be detected at elevated levels in both the cerebrospinal fluid (CSF) and blood [11, 12]. Elevated NfL levels are markers of neuroaxonal injury and are significantly higher in the CSF and blood of patients with neurological conditions like MS, traumatic brain injury, amyotrophic lateral sclerosis, and other neurodegenerative conditions compared with age-matched controls [13]. Monitoring changes in blood NfL (plasma or serum [sNfL]) or CSF NfL (cNfL) from baseline provides valuable insights into disease progression, prognosis, and efficacy of disease-modifying therapies (DMT) [14–16]. It also correlates with MRI metrics of inflammation and tissue loss, retinal nerve fiber layer (RNFL) thickness, and macular ganglion cell layer/inner plexiform layer thickness, independent of acute episodes of optic neuritis [17]. NfL offers a real-time measurement of neuronal injury as levels change in relation to neuronal injury and remain elevated for approximately 3 months. Other conventional/nonconventional metrics such as MRI provide only a retrospective view.

Despite the potential of elevated cNfL levels as an MS biomarker, its practical application is hindered by the invasive nature of lumbar puncture and the need for frequent longitudinal measurements. In comparison, sNfL measurements present distinct advantages such as being minimally invasive, cost-effective, and more feasible for periodic monitoring requirements [18]. However, it is critical to realize that sNfL does not serve as a substitute for MRI, which is essential for determining spatial localization and is, therefore, a critical part of the diagnostic workup [13]. The single-molecule array (Simoa) assay is widely used to quantify low concentrations of sNfL [19]. A plethora of clinical trials and real-world evidence studies provide evidence for the association of high sNfL levels with adverse clinical outcomes, such as development of new T2 lesions and relapses, in patients with MS. Nonetheless, effectively incorporating sNfL into clinical practice warrants caution and further exploration in different clinical settings [20]. The key considerations include the timing and frequency of measurements as well as proper interpretation of values. Addressing these aspects remains an important unmet need [15, 21–23]. Notably, discrepancies observed in the reported utility of measuring sNfL are potentially due to differences in study design, sample size, assays deployed, and the specific outcomes measured. To support evidence-based clinical decision-making, a systematic literature review (SLR) was performed to collect and assess existing evidence concerning the relationship between sNfL and MS disease activity, progression, and response to DMT. The specific objectives of the SLR were to (1) provide evidence on the use of sNfL as a prognostic and monitoring marker in MS, (2) provide guidance on the interpretation of sNfL assay results with respect to association with disease outcomes/treatment response, (3) examine the correlation of changes in sNfL with different disease outcomes, and (4) substantiate sNfL values as a marker of treatment response.

Methods

An SLR was performed in accordance with the guidelines recommended by the National Institute of Health and Care Excellence (NICE) [24] and Cochrane Collaboration [25, 26] and reported in alignment with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [27].

A comprehensive literature search was conducted in Excerpta Medica (EMBASE®), Medical Literature Analysis and Retrieval System Online (MEDLINE®), MEDLINE®-In-Process, and all Evidence-Based Medicine (EBM) Reviews databases for original research articles (up to September 14, 2023) reporting the association of sNfL with MS disease progression/treatment outcomes. The list of search terms (Table S1; Online Resource) included multiple sclerosis, neurofilament, neurofilament light chain, sNfL, and pNfL among others. Additionally, conference proceedings from the American Academy of Neurology (AAN), Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS), Consortium of Multiple Sclerosis Centers (CMSC), European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), and European Academy of Neurology (EAN) were searched (from January 1, 2021, to December 31, 2023) to identify abstracts not yet indexed in the aforementioned biomedical databases at the time of the search. Furthermore, the ClinicalTrials.gov database, gray literature, and bibliographies of relevant SLRs were searched to retrieve potentially eligible studies. This article relies on previously conducted research and does not present results of any novel studies involving human participants or animals conducted by the authors.

Eligibility criteria and article selection

The SLR included English language articles of original research studies in adult patients with MS that reported the relationship between sNfL levels and disease activity/treatment response. The studies pertaining to plasma NfL levels have been treated as equivalent to sNfL levels in terms of their implications and interpretations. A

Table 1 Review eligibility criteria

Criteria	Inclusion	Exclusion
Patient population	Adults (aged ≥ 18 years) with MS	Children/adolescents (aged < 18 years)
		Patients without MS
		Studies conducted exclusively in patients with CIS
		Non-human studies
Interventions	No restrictions (All DMTs)	None
Comparator (if any)	No restrictions	None
Key outcomes	NfL levels (serum, plasma)	Studies that do not measure NfL (serum, plasma) as an outcome
	Measures of association of NfL (serum, plasma) with	Studies that do not have any information on association of NfL with outcomes of interest
	Disease activity	
	T2 and T1 gadolinium-enhancing lesions	
	Disability	
	EDSS	
	Relapses	
	CDW	
	NEDA	
	Brain volume	
	PIRA	
	RAW	
	Silent progression (worsening of disability in the absence of signs of inflammation)	
	Cognition	
	Disease progression or disease worsening	
	Optical coherence tomography including peripapillary retinal nerve fiber layer thickness, ganglion cell layer and inner plexiform layer thickness, and macular cube volume	
Study designs	Clinical trials (Phase 2, 3, or 4 RCTs or non-RCTs), RWE, retrospective and prospective studies	Phase 1 studies
	SLR or meta-analysis (to be used for bibliographic searching)	Reviews/editorials
		Economic studies
		Study protocols
		Letters
		Opinions
		Case reports
		News/notes
		Model-based studies/simulations
Language	Studies published in English language	Non–English language studies
Search timeframe	Database searches: No restriction	–
	Conference abstracts: Last 3 years (2021–2023)	
	Hand searching (i.e., desktop searches, ClinicalTrials.gov searches, bibliographic searches of relevant studies/SLRs)	

CDW, confirmed disability worsening; *CIS*, clinically isolated syndrome; *DMT*, disease-modifying therapy; *EDSS*, Expanded Disability Status Scale; *MS*, multiple sclerosis; *NEDA*, no evidence of disease activity; *NfL*, neurofilament light chain; *PIRA*, progression independent of relapse activity; *RAW*, relapse-associated worsening; *RCT*, randomized controlled trial; *RWE*, real-world evidence, *SLR*, systematic literature review

predefined list of inclusion and exclusion criteria are described in Table 1. Two reviewers (SM and SH) screened the abstracts of all the records retrieved from the literature search, as well as potential full-text publications, against the predetermined inclusion criteria. Any disagreements between the two reviewers at both stages were resolved by a third independent reviewer (MKB).

Data extraction and quality assessment

Two reviewers from a pool of three (SM, SH, or MKB) extracted and validated data from the final list of included publications. In the event of discrepancies, a third independent reviewer was engaged to resolve any conflicts. Multiple publications from the same study/cohort were linked and extracted as a single reference. The extracted details encompassed the publication details, study design, total study population, research objective, inclusion/exclusion criteria for the study population, baseline patient data, and conclusions drawn by the authors. The baseline patient data captured included age, gender, disease duration, previous therapies, Expanded Disability Status Scale (EDSS) score, and sNfL levels (including the measurement technique used). The extracted outcomes included sNfL levels at different time points (including the change from baseline) as well as associations of sNfL with disease activity, T2 and T1 gadolinium-enhancing (Gd +) lesions, disability, EDSS score, relapses, confirmed disability worsening (CDW), no evidence of disease activity (NEDA), brain volume, progression independent of relapse activity (PIRA), relapse-associated worsening (RAW), silent progression (characterized by worsening disability without signs of inflammation), cognition, disease progression or worsening, and optical coherence tomography parameters such as peripapillary RNFL (pRNFL) thickness, ganglion cell layer and inner plexiform layer (GCIPL) thickness, and macular cube volume.

The quality assessment of the randomized controlled trials (RCTs) and non-RCTs included in the SLR was conducted using the modified Cochrane risk of bias assessment tool (RoB 2.0) for RCTs [28] and the modified Downs and Black checklist for non-RCTs [29]. The RoB 2.0 is a validated instrument that identifies and evaluates five potential biases in studies, including biases related to the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of reported results. The tool classifies the risk of these biases as high, low, or unclear [28]. Similarly, the Downs and Black checklist consists of 27 questions across five subscales, assessing study aspects such as reporting, external validity, internal validity bias, internal validity confounding (selection bias), and power. Based on the total score, studies are categorized as poor (≤ 14), fair (15–19), good (20–25), and excellent (26–28) [29]. Two independent reviewers evaluated the studies as part of the appraisal process. At instances where there were inconsistencies, a third reviewer was consulted to achieve consensus.

Results

A comprehensive search of key biomedical databases resulted in the identification of 1771 potential records, with an additional 60 records obtained from other sources such as conference proceedings and bibliographic searching. After screening the titles and abstracts based on predefined eligibility criteria (Table 1), 1299 records were excluded. The subsequent detailed assessment of 532 full-text publications resulted in the inclusion of 75 pertinent studies from 180 publications. Data extraction followed a predetermined template and the PRISMA flow chart demonstrating the literature screening and study selection process is depicted in Fig. 1.

Study characteristics

Among the studies included in the review ($n = 75$), 24 were identified as RCTs or their respective post hoc analyses/long-term extensions. The remaining 51 studies were grouped as non-RCTs, comprising a range of study types, including prospective and retrospective studies, case–control studies, open-label extensions of multiple RCTs, and noncomparative clinical studies. Most studies primarily focused on patients with relapsing MS (RMS), comprising over 80% of the study population ($n = 52$), followed by studies that included patients with all MS subtypes ($n = 16$) and those with progressive multiple sclerosis (PMS; $n = 7$). Most studies ($n = 54$) employed the original or revised McDonald criteria for the diagnosis of MS [30–33], while criteria were not reported in 13 studies. Notably, the McDonald criteria for MS diagnosis are being revised and the publication is expected by the first quarter of 2025 [34]. Additionally, the McDonald criteria were used alongside the Lublin/Poser criteria in four studies [15, 16, 35, 36]. One study each utilized the Schumacher criteria [37], the 2013 revised Lublin criteria [38], the Poser criteria [39], and physician-confirmed criteria [40]. Most of the studies ($n = 47$) were multicenter investigations, demonstrating a collaborative effort among multiple institutions. There were 22 single-center studies providing focused data from a specific institution. Information regarding the number of centers was not reported in six studies. All RCTs included in the analysis were determined to have a low risk of bias based on the assessment using the RoB 2.0 tool. Additionally, a majority of the non-RCTs ($n = 43$) were identified as being of fair quality when evaluated using the modified Downs and Black checklist (Table S2; Online Resource).

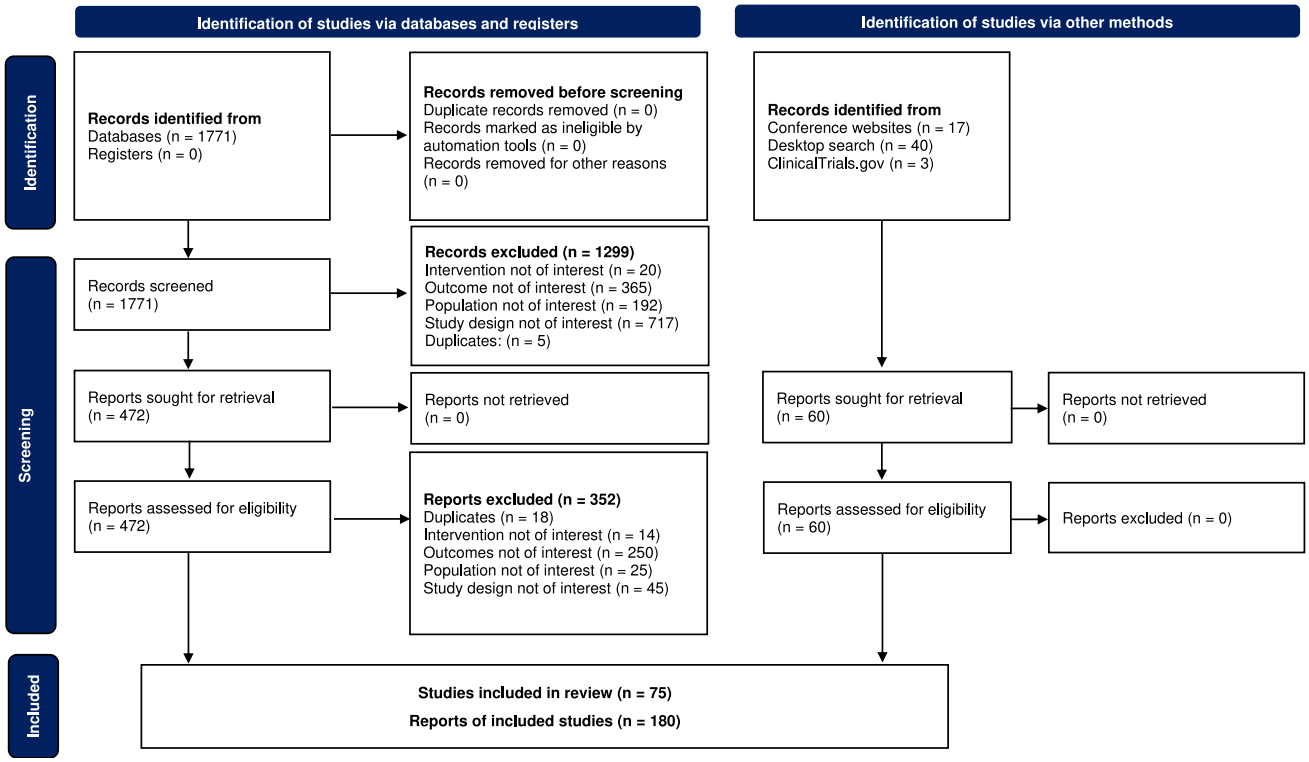

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram [27]

sNfL measurement methods

Most studies ($n = 65$) used SIngle MOlecule Array (Simoa) assay for measuring sNfL levels, with HD-1 analyzer ($n = 15$), SR-X analyzer ($n = 7$), HD-X analyzer ($n = 3$), and no further details ($n = 40$) on the specific analyzer variants used. Two studies measured sNfL using an assay that involves the use of capture monoclonal antibody 47:3 and the biotinylated detector monoclonal antibody 2:1 from UmanDiagnostics, and the assay was run on a Simoa HD-1 instrument (Quanterix) using a 2-step Assay Neat 2.0 protocol [41, 42]. The acridinium-ester immunoassay [40], ADVIA® Centaur NfL assay (Siemens) [21], and Atellica® immunoassay [43] were employed in one study each. The sNfL assay used was not specified in seven studies.

The patients with MS were reported to have higher sNfL levels compared with healthy controls [16, 44, 45]. The sNfL levels were generally higher in PMS compared with RMS [16]. As outlined in Table 2, in studies that employed the Simoa assay to measure sNfL levels, the reported median baseline levels varied among patients with RMS and PMS (RMS 5.7 to 35.8 pg/mL [46, 47]; PMS 2.4 to 26.9 pg/mL [48, 49]). These variations could be attributed to the substantial heterogeneity across the included patient population such as number of prior therapies, age, disease duration, and gender. The levels of sNfL reported in studies using the Atellica® immunoassay analyzer and ADVIA® Centaur NfL assay were comparable to those reported in studies using the Simoa assay. In the study by Kuhle et al., sNfL levels measured using capture antibody 47:3 and detector antibody 2:1 from UmanDiagnostics were markedly higher than those obtained with the commercially available Simoa assay or Siemens assays (Table 2) [41, 42].

The patients with MS who received DMTs demonstrated clinical benefits compared with untreated patients. The therapeutic effects of DMTs were accompanied by a reduction in sNfL levels compared with the baseline measurements. In general, monoclonal antibodies (i.e., ofatumumab, ocrelizumab, alemtuzumab, natalizumab, and rituximab), which exhibit higher clinical benefits compared with oral therapies (i.e., dimethyl fumarate, fingolimod, siponimod, and teriflunomide) and platform therapies (interferons and glatiramer acetate), were associated with greater decreases in sNfL levels relative to the baseline measurements (Table S3; Online Resource).

Table 2 Baseline sNfL levels reported across included studies

Author year	Intervention	*N*	Assay	Mean (SD)/median (range) in pg/mL
All multiple sclerosis subtypes (RRMS, SPMS, PPMS, CIS)				
Sotirchos 2023 [40]	DMTs	6974	Atellica® solution platform using acridinium-ester immunoassay (Siemens)	11.1 (IQR: 8.4–14.8)
Pauwels 2022 [67]	DMTs	115	Simoa® NF-light™ Advantage Kit (Quanterix) using HD-1 analyzer	12.12 ± IQR: 7.5[a]
Sotirchos 2022 [17]	NR	403	Simoa assay (Quanterix) using HD-1 analyzer	8.3 (IQR: 6.3–12.4)
Disanto 2021 [68]	Rituximab	59	Simoa® NF-light™ Kit (Quanterix) using HD-X analyzer	7.9 (IQR: 5.9–45.2)
Lin 2021 [56]	NR	78	Simoa assay (Quanterix)	19.7 (IQR: 15.2–28.8)
Jakimovski 2020 [49]	DMTs	127	Simoa assay	21.1 (IQR: 13.9–31.7)
Sehr 2019 [69]	Fingolimod	15	Simoa® NF-light™ Kit (Quanterix) using HD-1 analyzer	8.42[b] (NR)
Barro 2018 [16]	DMTs	257	Simoa assay (Quanterix)	32.9 (IQR: 23.2–46.6)
Relapsing multiple sclerosis (studies with ≥ 80% RRMS)				
Bar-Or 2023 [44] (OPERA I and II)	Ocrelizumab	720	Simoa® NF-light™ Kit (Quanterix) using HD-X analyzer	10.7 (2.7–230.7)
	IFNβ−1a	701	Simoa® NF-light™ Kit (Quanterix) using HD-X analyzer	10.4 (2.7–339)
Bar-Or 2023 [21]	Ofatumumab	284	ADVIA® Centaur NfL assay (Siemens)	9.1 (IQR/range: NR)
Bove 2023 [70]	Ofatumumab	278	NR	9.4 (NR)
Cutter 2023 [50]	IFNβ−1a	159	Simoa Human Neurology 4-Plex A assay (Quanterix) using HD-1 analyzer	17 (16.4)
	Glatiramer acetate	172	Simoa Human Neurology 4-Plex A assay (Quanterix) using HD-1 analyzer	20.5 (30.5)
	IM IFNβ−1a + glatiramer acetate	344	Simoa Human Neurology 4-Plex A assay (Quanterix) using HD-1 analyzer	19.6 (20.6)
Gimenez 2023 [71]	Pooled (dimethyl fumarate/natalizumab)	49	Simoa assay	9 (5.3)
Hauser 2023 [43] Alvarez 2023 [66]	Ofatumumab/ofatumumab[c]	690	Atellica® Immunoassay Analyzer part of Antelleca solution (Siemens)	8.26 (IQR/range: NR)
	Teriflunomide/ofatumumab[c]	677	Atellica® Immunoassay Analyzer part of Antelleca solution (Siemens)	10.42 (IQR/range: NR)
Seiberl 2023 [72]	Cladribine	14	Simoa® NF-light™ Advantage Kit (Quanterix) using SR-X analyzer	24.7 (23.8)
Wessels 2023 [73]	Natalizumab	89	NR	14.61 (IQR/range: NR)
	Ocrelizumab	266	NR	9.45 (IQR/range: NR)
Brune 2022 [45]	DMTs	257	Simoa assay (Quanterix)	6.7 (2.2–93.2)
Harris 2022 [74]	Placebo	79	Simoa® NF-light™ Kit (Quanterix)	11.7 (IQR: 8.2–16.3)
	Ozanimod 0.92 mg daily	82	Simoa® NF-light™ Kit (Quanterix)	11 (IQR: 7.7–15)
Kuhle 2022 [75]	Alemtuzumab	354	Simoa assay (Quanterix)	31.7 (IQR: 17.1–60.4)
	SC IFNβ−1a	159	Simoa assay (Quanterix)	31.4 (IQR: 17.5–61.1)

Table 2 (continued)

Author year	Intervention	*N*	Assay	Mean (SD)/median (range) in pg/mL
Kuhle 2022 [76]	Ponesimod	248	Simoa® NF-light™ Advantage Kit (Quanterix)	14.9 (15.66)
	Teriflunomide	268	Simoa® NF-light™ Advantage Kit (Quanterix)	15.8 (21.17)
Masanneck 2022 [63]	DMTs	46	Simoa® NF-light™ Advantage Kit (Quanterix) using HD-1 analyzer	14.5 (17.5)
Paolicelli 2022 [38]	Cladribine	18	Simoa® NF-light™ Advantage Kit (Quanterix) using SR-X analyzer	21.78 (14.75)
Pauwels 2022 [67]	DMTs	87	Simoa® NF-light™ Advantage Kit (Quanterix) using HD-1 analyzer	10.66 ± IQR: 6.93
Sotirchos 2022 [17]	NR	316	Simoa assay (Quanterix) using HD-1 analyzer	7.7 (IQR: 5.8–11)
Stenberg 2022 [77]	NR	44	Simoa assay	12.1 (IQR: 8.4–23.5)
Tiu 2022 [62]	DMTs	50	Simoa assay	20.5 (3.2–208.0)[d]
Zhou 2022 [47]	Teriflunomide	NR	Simoa® NF-light™ Advantage Kit (Quanterix) using HD-1 analyzer	35.82 (IQR: 47.5)
Akgün 2021 [78]	Fingolimod	131	Simoa assay	9.8 (95% CI 7.7–12.5)
Bridel 2021 [79]	Natalizumab	89	Simoa® NF-light™ Advantage Kit (Quanterix)	14.8 (IQR: 10–27.1)
Calabresi 2021 [80]	Pooled (natalizumab/placebo)	792	Simoa® NF-light™ Advantage Kit (Quanterix)	16.7 (21.1)
Dal-Bianco 2021 [46]	DMTs	29	Simoa® NF-light™ Kit (Quanterix) using SR-X analyzer	5.7 (3.2–23.7)
Harris 2021 [55] (SUNBEAM)	IFNβ−1a	448	Simoa® NF-light™ Advantage Kit (Quanterix) using HD-1 analyzer	14.8 (IQR: 9.8–24.4)
	Ozanimod 0.46 mg	451	Simoa® NF-light™ Advantage Kit (Quanterix) using HD-1 analyzer	14.1 (IQR: 9.7–22.4)
	Ozanimod 0.92 mg	447	Simoa® NF-light™ Advantage Kit (Quanterix) using HD-1 analyzer	15.1 (IQR: 10.9–22.8)
Harris 2021 [55] (RADIANCE)	Ozanimod 0.46 or 0.92 mg/IFNβ−1a (pooled)	1109	Simoa® NF-light™ Advantage Kit (Quanterix) using HD-1 analyzer	13.35 (IQR: 9.42–20.41)
Uher 2021 [81], Uher 2021 [82]	IFNβ−1a	142	Simoa assay	21.7 (IQR: 13.5–43)
Vollmer 2021 [83]	Ocrelizumab	582	NR	14.5[e]
Walo-Delgado 2021 [84]	Dimethyl fumarate	80	Simoa assay (Quanterix) using SR-X analyzer	10.1 (6.3–15.6)
Anderson 2020 [53]	DMTs	164	Simoa® NF-light™ Advantage Kit (Quanterix) using HD-1 analyzer	13.7 (2.7–159.3)
Bsteh 2020 [85]	DMTs	80	Simoa® NF-light™ Advantage Kit (Quanterix) using SR-X analyzer	6.7 (IQR: 4.5–10.1)

Table 2 (continued)

Author year	Intervention	*N*	Assay	Mean (SD)/median (range) in pg/mL
Delcoigne 2020 [86]	Alemtuzumab	89	Simoa® NF-light™ Advantage Kit (Quanterix)	10.5 (IQR: 6.3–24.8)[f]
	Dimethyl fumarate	339	Simoa® NF-light™ Advantage Kit (Quanterix)	11.1 (IQR: 8.2–15.6)[f]
	Fingolimod	275	Simoa® NF-light™ Advantage Kit (Quanterix)	12.3 (IQR: 8.7–16.9)[f]
	Natalizumab	284	Simoa® NF-light™ Advantage Kit (Quanterix)	15.5 (IQR: 9.9–26.9)[f]
	Rituximab	122	Simoa® NF-light™ Advantage Kit (Quanterix)	12.3 (IQR: 9.7–18.2)[f]
	Teriflunomide	152	Simoa® NF-light™ Advantage Kit (Quanterix)	9.0 (IQR: 7.0–12.2)[f]
Ferraro 2020 [87]	NR	21	Simoa assay (Quanterix) using HD-1 analyzer	9.7 (IQR: 8.3–11.2)
Häring 2020 [42]	Fingolimod	301	Simoa assay (Quanterix)	29.7 (NR)[e]
Hauser 2020 [88] (ASCLEPIOS I)	Ofatumumab	465	Simoa® NF-light™ Kit (Quanterix)	13.3 (13.2)
	Teriflunomide	462	Simoa® NF-light™ Kit (Quanterix)	11.7 (9.3)
Hauser 2020 [88] (ASCLEPIOS II)	Ofatumumab	481	Simoa® NF-light™ Kit (Quanterix)	14.7 (18.2)
	Teriflunomide	474	Simoa® NF-light™ Kit (Quanterix)	13.4 (14)
Jakimovski 2020 [49]	DMTs	85	Simoa assay	18 (IQR: 12.6–26.6)
Manouchehrinia 2020 [89] (EIMS cohort)	DMTs	3092	Simoa® NF-light™ Advantage Kit (Quanterix)	11.19 (IQR: 7.81–17.43)
Manouchehrinia 2020 [89] (IMSE cohort)	DMTs	1293	Simoa® NF-light™ Advantage Kit (Quanterix)	12.46 (IQR: 8.69–18.66)
Mattioli 2020 [90]	IFNβ−1a	18	Simoa assay (Quanterix) using SR-X analyzer	7.22 (4.23–11.7)
de Flon 2019 [91]	Rituximab	75	Simoa assay (Quanterix)	9.73 (7.04)
Gafson 2019 [92]	Dimethyl fumarate	27	Simoa assay (Quanterix)	13.2 (18.56)
Kuhle 2019 [41] (FREEDOMS)	Pooled (fingolimod/placebo)	269	Assay using the capture mAB 47:3 and the biotinylated detector mAB 2:1 from Uman-Diagnostics and transferred onto the Simoa HD-1 instrument (Quanterix)	27.1 (8.4–589.5)
Kuhle 2019 [41] (TRANSFORMS)	Pooled (fingolimod/placebo)	320	Assay using the capture mAB 47:3 and the biotinylated detector mAB 2:1 from Uman-Diagnostics and transferred onto the Simoa HD-1 instrument (Quanterix)	24.1 (2.2–372.7)
Sejbaek 2019 [93]	Dimethyl fumarate	52	Simoa assay (Quanterix)	16.4 (14.4)
Chitnis 2018 [94], Galetta 2021 [95]	DMTs	304	Simoa assay (Quanterix)	7.885 (1.23–78.3)
Novakova 2017 [22]	DMTs	204	Simoa® NF-light™ Kit (Quanterix)	16.9 (1.6–1480)

Table 2 (continued)

Author year	Intervention	*N*	Assay	Mean (SD)/median (range) in pg/mL
Progressive multiple sclerosis (SPMS, PPMS)				
Bar-Or 2023 [44] (ORATORIO)	Ocrelizumab	391	Simoa® NF-light™ Kit (Quanterix) using HD-X analyzer	10.3 (2.7–198.9)
	Placebo	205	Simoa® NF-light™ Kit (Quanterix) using HD-X analyzer	10.3 (3.3–102)
Chow 2023[35]	Dimethyl fumarate	20	Simoa assay (Quanterix)	12.8 (IQR: 8.5–16.6)
	Placebo	22	Simoa assay (Quanterix)	13.4 (IQR: 11–16.2)
Brune 2022 [45]	DMTs	52	Simoa assay (Quanterix)	10.7 (IQR: 4.2–28.4)
Comabella 2022 [37]	IFNβ−1b	51	Simoa assay (Quanterix) using HD-1 analyzer	9.1 (IQR: 7.5–13.7)
Leppert 2022 [96] (EXPAND)	Siponimod/ placebo	1452	Simoa assay	32.1 (1.3–538.2)[e]
Leppert 2022 [96] (INFORMS)	Fingolimod/ placebo	378	Simoa assay	22.0 (1.8–208.4)[e]
Pauwels 2022 [67]	DMTs	28	Simoa® NF-light™ Advantage Kit (Quanterix) using HD-1 analyzer	15.76 ± IQR: 8.88
Sotirchos 2022 [17]	NR	87	Simoa assay (Quanterix) using HD-1 analyzer	10.8 (IQR: 8.3–15.4)
Giarraputo 2021[48]	DMTs	25	Simoa Neurology 4-Plex B assay (NF-light) (Quanterix) using SR-X analyzer	2.42 (IQR: 2.19–2.67)[g]
Ferraro 2020 [87]	NR	70	Simoa assay (Quanterix) using HD-1 analyzer	12.8 (IQR: 10–16)
Jakimovski 2020 [49]	DMTs	42	Simoa assay	26.9 (IQR: 19.9–39.3)
Chitnis 2018 [94], Barro 2023 [97]	DMTs	257	Simoa assay (Quanterix)	11.8 (IQR: 8.5–16.5)
Novakova 2017 [22]	DMTs	82	Simoa® NF-light™ Kit (Quanterix)	23 (5.6–310)

pg/mL and ng/L were considered equivalent units as 1 pg/mL = 1 ng/L. Some studies reported use of log normal sNfL levels for analysis; however, no information was reported for other studies

CI, confidence interval; *CIS*, clinically isolated syndrome; *DMT*, disease-modifying therapy; *IFNβ*, interferon beta; *IM*, intramuscular; *IQR*, interquartile range; *mAB*, monoclonal antibody; *NF*, neurofilament; *NR*, not reported; *PPMS*, primary progressive multiple sclerosis; *RRMS*, relapsing–remitting multiple sclerosis; *SC*, subcutaneous; *SD*, standard deviation; *sNfL*, serum neurofilament light chain; *SPMS*, secondary progressive multiple sclerosis

[a]Median ± IQR

[b]Unit reported as pg/L in the article

[c]Ofatumumab/ofatumumab: patients receiving continuous ofatumumab; teriflunomide/ofatumumab: patients who switched from teriflunomide to ofatumumab

[d]Unit not reported

[e]Geometric mean

[f]sNfL normalized to age 40 years

[g]Log-transformed data

MRI outcomes (relapse, MRI lesions)

RMS (studies with ≥ 80% relapsing–remitting MS [RRMS])

A positive correlation between sNfL levels and relapse activity was observed in ≥ 85% of studies investigating this outcome, and higher sNfL levels were associated with higher risk of relapses within the following 2 years (Table 3). A study by Kuhle et al. revealed that patients with high blood NfL concentrations (> 60 pg/mL) at baseline had 2.5 times more relapses compared with those with low baseline NfL concentrations (< 30 pg/mL) (difference 153%) [41]. Patients with a baseline sNfL level ≥ 16 pg/mL were reported to have a shorter mean time to the first relapse (by 100.5 days) compared with those with a baseline sNfL level < 16 pg/mL (384.3 vs. 484.8 days, $p = 0.0404$) [50]. As

Table 3 List of studies reporting association of sNfL and relapse/MRI outcomes

Author year	Key outcomes relevant to the current SLR
Relapsing multiple sclerosis (studies with ≥ 80% RRMS)	
Bar-Or 2023 [44] (OPERA 1 & II)	Relapse
	Higher baseline NfL levels were independently associated (multiple linear regression model) with shorter duration since the last relapse (effect on $\log_{10}$sNfL = − 0.03, 95% CI − 0.05 to − 0.02, $p < 0.0001$)
	Lesions
	Higher baseline NfL levels were independently associated (multiple linear regression model) with greater Gd + lesion count (effect on $\log_{10}$ sNfL = 0.11, 95% CI 0.09–0.12, $p < 0.0001$) and higher T2LV (effect on $\log_{10}$ sNfL = 0.10, 95% CI 0.08–0.11, $p < 0.0001$)
Bar-Or 2023 [21] (APLIOS)	Relapse or lesions
	Compared with low baseline sNfL levels, high baseline sNfL levels were associated with an increased risk of subsequent on-study confirmed clinical relapses or Gd + T1 lesions (HR = 2.81, 95% CI 1.78–4.42, $p < 0.0001$) in the overall population
	Among patients who were free of Gd + T1 lesions at baseline, high baseline sNfL levels also predicted an increased risk of on-study confirmed clinical relapses or Gd + T1 lesions compared with low baseline sNfL levels (HR = 2.48, 95% CI 1.15–5.39, $p = 0.0213$)
	Relapse
	The proportion of patients with confirmed clinical relapses was higher among patients with sNfL levels constantly above the baseline median (15%) vs. patients with sNfL levels that crossed the baseline median (2.7%) or were constantly below the baseline median (2.6%)
	Lesions
	The proportion of patients with Gd + T1 lesions was higher among patients with sNfL levels above the baseline median vs. those with sNfL levels that crossed the baseline median or were below the baseline median, respectively
	Week 4: 64.7% vs. 31.1% and 16.2%
	Week 8: 25.9% vs. 10.8% and 9.0%
	Week 12: 11.9% vs. 4.4% and 3.9%
Bose 2023 [59], Galetta 2021 [95], Chitnis 2018 [94]	Relapse
	There was a limited correlation with ARR during the 2 years following baseline assessment ($r_s = 0.010$, $p = 0.870$)
	Lesions and brain volume
	Higher 10-year T2LV was associated with higher baseline sNfL (univariate analysis; $\beta = 0.37$, 95% CI 0.25–0.50, $p < 0.001$)
	When sNfL and sGFAP were included together, only baseline sNfL remained associated with worse T2LV ($\beta = 0.34$, 95% CI 0.21–0.48, $p < 0.001$)
	Without consideration of clinical measures, a lower BPF was significantly associated with higher sNfL levels at baseline ($\beta = -1.22\%$, 95% CI − 2.17 to − 0.27, $p = 0.012$)
	Higher follow-up sNfL levels remained significantly associated with lower BPF ($\beta = -2.53\%$, 95% CI − 4.18 to − 0.89, $p = 0.003$) following the incorporation of both baseline and 1-year follow-up levels in the same model
Cutter 2023 [50]	Relapse
	Baseline sNfL ≥ 16 pg/mL significantly predicted relapse within 90 days (HR = 2.01, $p = 0.0149$) and 6 months (HR = 1.51, $p = 0.0449$) but not at 12 months from baseline (HR = 1.33, $p = 0.0877$) nor over the entire 3-year study duration (HR = 1.06, $p = 0.6468$)
	The mean time to the first relapse was 100.5 days shorter in patients with baseline sNfL ≥ 16 pg/mL compared with those with baseline sNfL < 16 pg/mL (384.3 vs. 484.8 days, $p = 0.0404$)
	Baseline Gd + lesions and sNfL ≥ 16 pg/mL were synergistic predictors of relapse as the combination of these two factors was a stronger predictor of relapse within 90 days than either factor alone
Fedičová 2023 [58]	Relapse
	Among patients with an annual sNfL increase of > 10%, a significantly higher proportion had experienced a relapse in the past year compared with patients who had either any annual decrease or an annual increase of up to 10% in sNfL levels (40% vs. 8.3%, $p < 0.001$)
	Lesions and brain volume

Table 3 (continued)

Author year	Key outcomes relevant to the current SLR
	Patients with an annual sNfL increase of > 10% experienced greater T1LV compared with patients who had either any annual decrease or an annual increase of up to 10% in sNfL levels (median [IQR] = 7.04 [3.9–14.3] vs. 5.1 [1.8–12.2])
	Patients with an annual sNfL increase of > 10% experienced greater annual brain volume reduction compared with patients who had either any annual decrease or an annual increase of up to 10% in sNfL levels (% median [IQR] volume change = − 0.29 [− 0.57 to − 0.02] vs. − 0.12 [− 0.29–0.1], $p < 0.001$)
Fernandez 2023 [98]	Relapse
	Baseline sNfL correlated with relapses in the previous 2 years (rho = 0.268, $p < 0.001$)
	sNfL at the 1-year follow-up correlated with relapses (rho = 0.222, $p < 0.001$)
Benkert 2022 [51], Abdelhak 2023 [15]	Relapse
	SMSC cohort
	Higher sNfL Z-scores were associated with a greater probability of relapse (OR 1.41, 95% CI 1.30–1.54, $p < 0.0001$)
	Validation cohort (EIMS, IMSE, COMBAT-MS)
	Higher sNfL Z-scores were associated with a higher probability of relapses in the following year (OR 1.24, $p < 0.05$)
Brune 2022 [45]	Relapse
	High baseline sNfL levels (≥ 8 pg/mL) were associated with an increased risk of experiencing a new clinical relapse (OR 3.3, 95% CI 1.38–7.8, $p = 0.007$) in the follow-up period
	High baseline sNfL levels (≥ 75th age-corrected percentile) were not associated with an increased risk of experiencing a new clinical relapse (OR 1.978, 95% CI 0.914–4.281, $p = 0.083$)
	However, sNfL levels ≥ 80th and 85th age-corrected percentiles were associated with an increased risk of experiencing a new clinical relapse in the follow-up period
	Lesions
	Higher baseline sNfL levels were significantly associated with higher T2 lesion count at baseline ($r_p = 0.15$, $p = 0.02$)
	High baseline sNfL levels (≥ 8 pg/mL) were associated with an increased risk of developing new T2 lesions (OR 3.97, 95% CI 1.7–9.3, $p = 0.002$) in the follow-up period
	High baseline sNfL levels (≥ 75th age-corrected percentile) were associated with an increased risk of developing new T2 lesions (OR 2.3, 95% CI 1.1–4.9, $p = 0.034$)
	High baseline sNfL levels were significantly associated with the presence of new lesions ($r_p = 0.28$, $p < 0.001$) as well as increase in lesion volumes ($r_p = 0.21$, $p = 0.01$) in the follow-up period
Kuhle 2022 [52], Kuhle 2023 [36]	Relapse
	Compared with low baseline sNfL (< 11.36 pg/mL), high baseline sNfL levels (≥ 11.36 pg/mL) were associated with significantly higher odds of qualified relapse (OR 6.07, $p = 0.0038$)
	A higher proportion of patients with an NfL Z-score ≥ 1 experienced relapses vs. those with an NfL Z-score < 1 stratified at Week 48
	Weeks 48–96 (NfL Z-score < 1 vs. ≥ 1):
	No relapse: 90.5% vs. 82.5%
	1 relapse: 7.1% vs. 12.5%
	≥ 2 relapses: 2.4% vs. 5%
	A similar, albeit less pronounced, trend was observed in the relapse activity between Week 96 and Week 144 (stratified at Week 96)
	Weeks 96–144 (NfL Z-score < 1 vs. ≥ 1):
	No relapse: 95.4% vs. 94.1%
	1 relapse: 4.6% vs. 2.9%
	≥ 2 relapses: 0% vs. 2.9%
	Lesions
	Patients with high baseline sNfL levels had higher Gd + T1 and T2 activity
	The proportions of patients with no T1 Gd + lesions and no new/enlarging T2 lesions (both at Week 96 and Week 144) were higher among patients with an NfL Z-score < 1 vs. those with an NfL Z-score ≥ 1
	Week 96 (NfL Z-score < 1 vs. ≥ 1):

Table 3 (continued)

Author year	Key outcomes relevant to the current SLR
	No T1 Gd + lesion: 89.4% vs. 50%
	1 T1 Gd + lesion: 6.1% vs. 12.5%
	2 T1 Gd + lesions: 4.5% vs. 6.3%
	3 T1 Gd + lesions: 0% vs. 9.4%
	≥ 4 T1 Gd + lesions: 0% vs. 21.9%
	Week 144 (NfL Z-score < 1 vs. ≥ 1):
	No T1 Gd + lesion: 84.5% vs. 57.1%
	1 T1 Gd + lesion: 12.1% vs. 25%
	2 T1 Gd + lesions: 3.4% vs. 7.1%
	3 T1 Gd + lesions: 0% vs. 3.6%
	≥ 4 T1 Gd + lesions: 0% vs. 7.1%
	Week 96 (NfL Z-score < 1 vs. ≥ 1):
	No T2 Gd + lesion: 53% vs. 25%
	1–2 T2 Gd + lesions: 25.8% vs. 12.5%
	3–5 T2 Gd + lesions: 15.2% vs. 6.3%
	6–10 T2 Gd + lesions: 6.1% vs. 21.9%
	> 10 T2 Gd + lesions: 0% vs. 34.4%
	Week 144 (NfL Z-score < 1 vs. ≥ 1):
	No T2 Gd + lesion: 65.5% vs. 28.6%
	1–2 T2 Gd + lesions: 13.8% vs. 14.3%
	3–5 T2 Gd + lesions: 12.1% vs. 10.7%
	6–10 T2 Gd + lesions: 6.9% vs. 28.6%
	> 10 T2 Gd + lesions: 1.7% vs. 17.9%
Masanneck 2022 [63]	Relapse
	sNfL levels were associated with the occurrence of relapses (coefficient = 0.03, 95% CI 0.01–0.06, p = 0.02)
van Lierop 2022 [99], Bridel 2021 [79]	Lesions and brain volume
	High sNfL levels at Year 1 predicted worse PBVC (std. $\beta = -0.257$, $p = 0.016$), worse thalamus volume change (std. $\beta = -0.259$, $p = 0.016$), and worse ventricle volume change (std. $\beta = 0.338$, $p = 0.001$)
	Lesion volume did not show any longitudinal associations with sNfL
Ziemssen 2022 [54]	Relapse
	sNfL at baseline was not prognostic for on-study ARR, and relapse rates were not statistically different between high and low sNfL groups (relative rate reduction: ofatumumab, 27.0%, $p = 0.075$; teriflunomide, 6.6%, $p = 0.614$). Results were similar in the subgroup of recently diagnosed, treatment-naive patients
	Lesions and brain volume
	High versus low sNfL at baseline was prognostic of increase in new or enlarging T2 lesions
	Relative increase (vs. baseline) at Year 1: ofatumumab, 157.5% and teriflunomide, 68.6%, $p < 0.001$ for both
	Relative increase (vs. baseline) at Year 2: ofatumumab, 64.5%, $p = 0.124$ and teriflunomide, 45.6%, p = 0.003
	Baseline sNfL had a significant correlation with the percentage change in whole brain volume from baseline to 12 months
	Ofatumumab: $R = -0.200$, $p < 0.0001$
	Teriflunomide: $R = -0.203$, $p < 0.0001$
Akgün 2021 [78]	Relapse
	Change from baseline in sNfL levels was significantly correlated with relapse activity in the first 12 months (r = − 0.226)

Table 3 (continued)

Author year	Key outcomes relevant to the current SLR
Calabresi 2021 [100]	Lesions and brain volume
	Reduction in sNfL to < 16 pg/mL at 12 months was associated with 3-fold decrease in the number of new T2 lesions compared with patients with no reduction in sNfL levels ($p < 0.01$)
	Reduction in sNfL to < 16 pg/mL at 6 months was associated with a decrease in 4-year PBVC (0.89%, $p = 0.05$)
Fox 2021 [101], Fox 2022 [102]	Lesions
	Patients in the high quartile of baseline sNfL levels had high incidence of combined unique active lesions at 24 weeks (mean [SD] lesions = 1.1 [2.3] vs. 1.2 [2.4] vs. 7.4 [22.2] vs. 9.0 [16.9] for 1st, 2nd, 3rd, and 4th quartiles respectively)
Harris 2021 [55]	Relapse
	Baseline sNfL was higher in those with vs. without on-treatment relapse
	sNfL reduction was associated with lower ARR
	The probability of having ≥ 1 relapse in the next 12 months (SUNBEAM) or 24 months (RADIANCE) increased with increasing baseline sNfL
	SUNBEAM
	Based on model estimates, a 25% and 13% reduction in sNfL (similar to that observed with ozanimod 0.92 mg and IFNβ−1a in SUNBEAM) predicted an ARR (SE) of 0.22 (0.04) and 0.36 (0.04), respectively
	At 12 months, the model-predicted ARR was 0.5111 + 0.0116 × ΔNfL
	RADIANCE
	Based on model estimates, a 25% and 13% reduction in sNfL (similar to that observed with ozanimod 0.92 mg and IFNβ−1a in SUNBEAM) predicted an ARR (SE) of 0.19 (0.04) and 0.29 (0.04), respectively
	At 24 months, the model-predicted ARR was 0.4079 + 0.0088 × ΔNfL
	Lesions and brain volume
	Baseline Gd + and T2 lesion counts increased and brain volume decreased with increasing baseline sNfL
Srpova 2021 [57], Uher 2020 [103], Uher 2021 [81]	Relapse
	sNfL change showed a weak association with cumulative number of relapses (regression coefficient = 0.058, $p = 0.036$)
	High sNfL levels were associated with higher odds of experiencing a relapse in the following year (41.3% vs. 26.2%; β_{OR} 2.10, 95% CI 1.07–4.12, $p = 0.031$)
	Lesions and brain volume
	Higher sNfL levels were associated with higher odds of whole brain volume loss during the following year ($\beta = -0.36\%$, 95% CI −0.60 to −0.13, $p = 0.002$); Early increase in sNfL levels were associated with delayed brain volume loss after 48 months ($p < 0.001$)
	For every 10% increase in the sNfL level, whole brain volume loss in the following year increased by 0.015% ($\beta_{add} = -0.15$, 95% CI −0.028 to −0.001, $p = 0.033$)
	sNfL levels showed a strong association with T1LV (rho = 0.36, $p < 0.001$) and T2LV (rho = 0.46, $p < 0.001$)
	Percentage changes in sNfL levels over time (change between Months 1 and 12, Months 1 and 24, and Months 1 and 36) were most closely associated with the following:
	T2LV absolute change (regression coefficient = 0.104, $p < 0.001$)
	T1LV absolute change (regression coefficient = 0.256, $p < 0.001$)
	Increase in T2 lesion number (regression coefficient = 0.062, $p < 0.001$) (change between Months 0 and 12, Months 0 and 24, and Months 0 and 36)
	In the multivariate model, T1LV absolute change and T2 lesion number change were the best independent correlates of sNfL percentage change over follow-up
	In multivariable-adjusted analysis, sNfL > 90th percentile was linked to a higher likelihood of having ≥ 3 active lesions compared with those in the 31st–90th percentile (OR 7.8, 95% CI 4.1–14.8, $p < 0.0001$)
Uphaus 2021 [104], Steffen 2023 [105]	Lesions
	sNfL levels at study entry correlated with signs of inflammatory activity at baseline such as the following:
	Number of Gd + lesions (r = 0.391, $p < 0.001$)

Table 3 (continued)

Author year	Key outcomes relevant to the current SLR
	T2 hyperintense lesion number (r = 0.185, $p = 0.022$)
	T2 hyperintense lesion number at Year 6 (r = 0.232, $p = 0.004$)
	Moreover, development of new T2 hyperintense lesions after 6 years correlated with Year 0 sNfL values (r = 0.280, $p < 0.001$)
	However, a correlation was found between Year 0 sNfL and development of new T1 hypointense lesions (r = 0.336, $p < 0.001$), suggesting that although initially high Year 0 sNfL values reflect current inflammatory activity, they also have a predictive value for the future development of new T1 hypointense and T2 hyperintense lesions
Anderson 2020 [53]	Relapse
	No significant association was noted between baseline sNfL levels and odds of relapse at 12 months when adjusted for age and DMT use (log-transformed sNfL OR 1.15, 95% CI 0.86–1.53, $p = 0.351$; sNfL </> 13.7 pg/mL OR 1.93, 95% CI 0.95–3.92, $p = 0.071$) or the hazard of relapse over 5 years of follow-up
Delcoigne 2020 [86], Piehl 2018 [23]	Relapse
	Baseline sNfL showed a tendency for association with the number of relapses (0 or 1 vs. 2 or 3) before treatment start (univariate analysis: $\beta = 0.101$, SE = 0.060, $p = 0.097$), and the association remained significant using multivariate analysis as well ($\beta = 0.144$, SE = 0.069, $p = 0.04$)
	Change in sNfL levels from baseline to 12 months was highly associated with the number of relapses in the year before the start of fingolimod (univariate analysis: $\beta = 11.90$, SE = 4.02, $p = 0.0035$; multivariate analysis: $\beta = 7.43$, SE = 3.08, $p = 0.017$)
Kuhle 2020 [39]	Brain volume
	sNfLlevels at Year 3 were associated with BPF change at the 8-year follow-up (r = − 0.36, $p < 0.05$)
Häring 2020 [42]	Brain volume
	High baseline sNfL (≥ 30 pg/mL) compared with low baseline sNfL (< 30 pg/mL) levels was prognostic of a higher brain volume loss over 120 months (least squares mean difference = − 1.12%, 95% CI − 2.07 to − 0.17)
	Similar trends (though not always significant) were observed following stratification based on the geometric mean of sNfL measured over either 12 or 24 months
Manouchehrinia 2020 [89]	Relapse
	ARR in the years before sampling was significantly higher in patients with sNfL levels above vs. below the respective calculated percentiles of the controls
	Mean (SD) ARR:
	≥ 80th vs. < 80th percentile: 0.43 (0.62) vs. 0.30 (0.46)
	≥ 95th vs. < 95th percentile: 0.49 (0.67) vs. 0.31 (0.48)
	≥ 99th vs. < 99th percentile: 0.52 (0.73) vs. 0.34 (0.51)
Kuhle 2019, [41], Sormani 2019 [106]	Relapse
	FREEDOMS
	sNfL at 6 months significantly correlated with number of relapses (r = 0.25, $p < 0.001$)
	High (> 60 pg/mL) baseline sNfL levels were associated with 2.5 times more MS relapses compared with low baseline sNfL levels (< 30 pg/mL) (difference = 153%; rate ratio = 2.53, 95% CI 1.67–3.83, $p < 0.0001$)
	Lesions and brain volume
	FREEDOMS
	sNfL at 6 months significantly correlated with active lesions (r = 0.46, $p < 0.001$) and brain volume loss (r = − 0.41, $p < 0.001$) at Month 24
	Post-treatment effect on 24-month relapse and brain volume loss based on 6-month NfL was 25% (95% CI 8% to 60%) and 60% (95% CI 32% to 132%), respectively
	sNfL concentrations were strongly associated with high baseline T2LV (geometric mean ratio = 1.027, 95% CI 1.016–1.039, $p < 0.0001$) and presence of Gd + T1 lesions (geometric mean ratio = 1.642, 95% CI 1.398–1.930, $p < 0.0001$)
	Compared with low baseline sNfL levels (< 30 pg/mL), high baseline sNfL levels (> 60 pg/mL) were associated with 2.6 times more number of new or enlarging T2 lesions (difference = 164%; mean ratio = 2.64, 95% CI 1.51–4.60, $p = 0.0006$) and 2.9 times more brain volume loss (difference = 195%; mean difference = − 0.78%, 95% CI − 1.02 to − 0.54, $p < 0.0001$)
	TRANSFORMS

Table 3 (continued)

Author year	Key outcomes relevant to the current SLR
	sNfL concentrations were strongly associated with high baseline T2LV (geometric mean ratio = 1.039, 95% CI 1.025–1.054, $p < 0.0001$) and presence of Gd + T1 lesions (geometric mean ratio = 1.480, 95% CI 1.251–1.752, $p < 0.0001$)
All multiple sclerosis subtypes (RRMS, SPMS, PPMS, CIS)	
Schaefer 2023 [107]	Lesions
	In an analysis adjusted for age, DMT, EDSS, and disease course, a point change in sNfL levels was associated with an increased odds of contrast enhancement (OR 1.045, 95% CI 1.001–1.090, $p = 0.043$)
	NfL *Z*-scores were more predictive of contrast enhancement compared with sNfL levels (OR 1.521, 95% CI 1.061–2.181, $p = 0.023$)
Sotirchos 2023 [40]	Lesions
	Elevated sNfL was associated with lower BPF and higher T2LV compared with normal sNfL (adjusted differences in Z-scores—BPF = − 0.20, 95% CI − 0.28 to − 0.12; T2LV = 0.42, 95% CI 0.33–0.51, $p <$ 0.001 for both)
	17.2% of patients with elevated sNfL vs. 6.4% of patients with normal sNfL had ≥ 1 Gd + lesion (adjusted OR 3.68, 95% CI 1.97–6.79, $p < 0.001$)
	Over 2 years of follow-up, patients with elevated sNfL exhibited 63% faster whole brain atrophy compared with those with normal sNfL (annualized percent change in BPF = − 0.26%/year vs. − 0.16%/year; adjusted difference = − 0.10%/year; 95% CI − 0.14% to − 0.06%, $p < 0.001$)
	26.3% of patients with elevated sNfL vs. 10.9% of patients with normal sNfL had ≥ 1 new T2 lesion (adjusted OR 2.66, 95% CI 1.86–3.77, $p < 0.001$)
	Over 2 years of follow-up, 20.5% of patients with elevated sNfL vs. 12.1% of patients with normal sNfL had ≥ 1 new T2 lesion (adjusted OR 1.94, 95% CI 1.42–2.62, $p < 0.001$)
Disanto 2017 [14], Meier 2023 [61], Abdelhak 2023 [15]	Relapse
	The probability of having experienced a relapse within 60 days before sampling was increased for sNfL levels above vs. below the 80th, 90th, 95th, 97.5th, and 99th percentiles
	Patients with sNfL levels > 97.5th percentile had ~ 4.0-fold odds of having experienced a relapse in the previous 60 days (OR 3.89, 95% CI 2.30–6.58, $p < 0.001$)
	The incidence of relapses 1 and 2 years before sampling was ~ 1.5 − 2.0 times higher for sNfL levels > 97.5th percentile (IRR = 2.08, 95% CI 1.64–2.63, $p < 0.001$ and IRR = 1.39, 95% CI 1.18–1.64, $p <$ 0.001, respectively)
	The incidence of relapses was ~ 2.0 times higher both 1 and 2 years after sampling for sNfL levels > 97.5th percentile (IRR = 1.94, 95% CI 1.21–3.10, $p = 0.006$ and IRR = 1.96, 95% CI 1.22–3.15, $p = 0.005$, respectively)
	Lesions and brain volume
	Patients with either brain or spinal (43.4 pg/mL, IQR: 25.2–65.3) or both brain and spinal Gd + lesions (62.5 pg/mL, IQR: 42.7–71.4) had higher sNfL levels than those without lesions (29.6 pg/mL, IQR = 20.9–41.8; $\beta = 1.461$, $p = 0.005$ and $\beta = 1.902$, $p = 0.002$, respectively)
	Doubling of baseline sNfL levels was associated with an additional loss of white matter volume (− 0.26%, 95% CI − 0.38% to − 0.15%, $p < 0.001$) but not gray matter volume (− 0.01%, 95% CI − 0.11–0.09, $p =$ 0.78)
Lin 2021 [56]	Relapse
	Abnormal sNfL[a] alone was not associated with risk of a new relapse (HR = 2.21, 95% CI 0.97–5.03, $p =$ 0.058); risk was numerically higher in patients with high sNfL levels
	However, compared with abnormal sNfL alone, Cox regression analysis showed a higher risk associated with
	Abnormal sNfL + thin GCIPL (HR = 5.38, 95% CI 1.61–17.98, $p = 0.006$)
	Abnormal sNfL + thin pRNFL (HR = 4.77, 95% CI 1.39–16.38, $p = 0.013$)
	Abnormal sNfL + thick INL (HR = 3.26, 95% CI 1.09–9.76, $p = 0.034$)
	Lesions
	Abnormal baseline sNfL alone was associated with a higher risk of developing a new brain lesion (HR = 2.47, 95% CI 1.30–4.69, $p = 0.006$)
	Compared with abnormal sNfL alone, abnormal sNfL + thin GCIPL was associated with an even higher risk of developing a new brain lesion (HR = 3.19, 95% CI 1.51–6.76, $p = 0.002$)

Table 3 (continued)

Author year	Key outcomes relevant to the current SLR
Uher 2020 [103], Barro 2018 [16]	Relapse
	Univariate analyses showed a significant positive association of sNfL with presence of relapse within 120 days before sampling ($\beta_{mult} = 1.118$, 95% CI 1.034–1.208, $p = 0.005$)
	Multivariate analysis confirmed the association of higher sNfL levels with a recent relapse ($\beta_{mult} = 1.144$, 95% CI 1.054–1.241, $p = 0.001$), whereas higher values of progressive vs. relapsing MS were no longer statistically significant
	Lesions
	In multivariate analysis, contrast-enhancing and new/enlarging T2 lesions were independently associated with increased sNfL (17.8% increase per lesion; $\beta_{mult} = 1.178$, 95% CI 1.078–1.287, $p < 0.001$ and 4.9% increase per lesion; $\beta_{mult} = 1.049$, 95% CI 1.031–1.067, $p < 0.001$), respectively)
	The higher the sNfL percentile level, the more pronounced was future brain and cervical spinal volume loss
	sNfL above the 97.5th percentile was associated with an additional average loss in brain volume of 1.5% ($p < 0.001$) and spinal cord volume of 2.5% over 5 years ($p = 0.009$)
	A 10 pg/mL increase in sNfL was associated with an average additional reduction in brain volume of 0.17% after 2 years (univariable $\beta_{add} = 0.171\%$, 95% CI 0.226% to 0.116%, $p < 0.001$, $n = 197$ observations). An estimated additional 0.35% reduction was observed in brain volume over 5 years per 10 pg/mL increase in sNfL levels at baseline
	Confirming the 2-year results, baseline sNfL was a highly significant predictor of percentage brain volume change over 5 years of follow-up (multivariate $\beta_{add} = 0.287\%$, 95% CI 0.432% to 0.142%, $p < 0.001$, $n = 132$)
	In multivariable-adjusted analysis, sNfL > 90th percentile was linked to a higher likelihood of having ≥ 3 active lesions compared with those in the 31st–90th percentile (OR 5.8, 95% CI 3.2–10.6, $p < 0.05$)
Canto 2019 [60], Abdelhak 2023 [15]	Relapse
	Baseline sNfL levels were significantly associated with presence of relapse in the 90 days before sampling ($\beta = 1.478$, 95% CI 1.279–1.707, $p < 0.001$)
	Compared with lower sNfL levels, higher sNfL levels were associated with a greater risk of having experienced a relapse in the 60 and 360 days before sampling; however, extreme sNfL levels were not associated with future relapses
	At the last visit available for each participant, sNfL levels did not show an association with presence of relapse in the 90 days before sampling ($\beta = 1.031$, 95% CI 0.817–1.300, $p = 0.80$)
	Lesions and brain volume
	sNfL levels over time were associated with T2LV ($\beta = 3.361$, 95% CI 2.300–4.420, $p = 5.8 \times 10^{-10}$)
	sNfL levels over time were associated with brain fraction ($\beta = 2.0 \times 10^{-4}$, 95% CI 4×10^{-6} to 0.000396, $p = 0.02$)
Jakimovski 2019 [108], Jakimovski 2020 [49]	Lesions and brain volume
	sNfL levels at baseline were associated with baseline volumes of T1-, T2-, and gadolinium-enhancing lesions (q = 0.002, q = 0.001, and q < 0.001, respectively); however, correlation was not observed with the longitudinal changes in lesion volumes
	sNfL at baseline was correlated with a longitudinal decline in the whole brain volume ($\beta = -0.356$, q = 0.002)
Chitnis 2018 [94]	Lesions and brain volume
	sNfL levels at Year 5 had a negative correlation with BPF at Year 10 ($r_s = -0.22$, $p = 0.0479$)
	In univariate analysis, a 10 pg/mL increase in the average yearly NfL levels (from Years 1–5) was associated to an average decrease of 0.849% in BPF. Average reduction in BPF was 0.920% when adjusted for sex, baseline age, and disease duration in the multivariate analysis
	Higher sNfL levels were associated with an increased T2 brain lesion load (Year 1 $r_s = 0.39$, $p < 0.01$, Year 2 $r_s = 0.38$, $p < 0.01$, Year 3 $r_s = 0.24$, $p = 0.04$, Year 4 $r_s = 0.32$, $p < 0.01$)
Progressive multiple sclerosis (SPMS, PPMS)	
Bar-Or 2023 [44] (ORATORIO)	Lesions
	Higher baseline NfL levels were independently associated (multiple linear regression model) with greater Gd + lesion count (effect on $\log_{10}$ sNfL = 0.06, 95% CI 0.05–0.08, $p < 0.0001$) and higher T2LV (0.04, 95% CI 0.03–0.06, $p < 0.0001$)

Table 3 (continued)

Author year	Key outcomes relevant to the current SLR
Brune 2022 [45]	Lesions
	Higher sNfL concentrations at baseline were significantly associated with higher T2 lesion count (r_p = 0.41, p = 0.004) and increased T2LV (r_p = 0.39, p = 0.01) at baseline
	Furthermore, higher sNfL concentrations at follow-up were significantly associated with higher T2 lesion count (r_p = 0.36, p = 0.04)
Comabella 2022 [37]	Lesions and brain volume
	Baseline sNfL levels were associated with T2LV (β = 1.01, 95% CI 1.00–1.01, p = 0.004), T1LV (β = 1.02, 95% CI 1.00–1.03, p = 0.005) but remained at trend level for BPF (β = 0.97, 95% CI 0.95–1.001, p = 0.05)
	sNfL levels at baseline showed a significant correlation with changes in lesion volume
	T1LV after the first year: β = −9.69, 95% CI −18.66 to −0.73, p = 0.03
	T1LV after the second year: β = −10.52, 95% CI −21.64–0.59, p = 0.06
	T2LV after the second year: β = −10.38, 95% CI −21.24–0.49, p = 0.06
Leppert 2022 [96]	EXPAND cohort
	Relapse
	High baseline sNfL levels were strongly and independently associated with relapses in the previous 2 years (geometric mean ratio = 1.075, 95% CI 1.016–1.137, p = 0.0116)
	Lesions and brain volume
	High baseline sNfL levels were strongly and independently associated with high baseline T2LV (geometric mean ratio = 1.007, 95% CI 1.005–1.009, p < 0.0001) and presence of Gd + T1 lesions (1.441, 1.347–1.541, p < 0.0001)
	High vs. low sNfL baseline levels were associated with higher rates of brain volume loss at Months 12 and 24
	INFORMS cohort
	High baseline sNfL levels were strongly and independently associated with high baseline T2LV (geometric mean ratio = 1.014, 95% CI 1.008–1.020, p < 0.0001) and presence of Gd + T1 lesions (1.571, 1.306–1.890, p < 0.0001)
	High vs. low sNfL baseline levels were associated with higher rates of brain volume loss at Months 12 and 24
Barro 2018 [16]	Lesions
	Patients with vs. without contrast-enhancing lesions had higher sNfL levels (median [IQR] = 51.4 [40.9–60.2 vs. 40.8 [30.6–52.5] pg/mL), but this did not reach statistical significance (β_{mult} = 1.121, 95% CI 0.933–1.346, p = 0.223; after age correction: β_{mult} = 1.123, 95% CI 0.932–1.352, p = 0.222)
Chitnis 2018 [94], Barro 2023 [97]	Relapse
	sNfL was associated with relapse within the previous 90 days (adjusted β = 1.69, 95% CI 1.32–2.17, p < 0.001)
	Lesions
	sNfL was associated with Gd + lesions within the previous 30 days (adjusted β = 1.46, 95% CI 1.08–1.96, p = 0.014)

sNfL levels reported in pg/mL; pg/mL and ng/L were considered equivalent units as 1 pg/mL = 1 ng/L. Some studies reported use of log normal sNfL levels for analysis; however, no information was reported for other studies

ARR, annualized relapse rate; *BPF*, brain parenchymal fraction; *CI*, confidence interval; *CIS*, clinically isolated syndrome; *DMT*, disease-modifying therapy; *EDSS*, Expanded Disability Status Scale; *GCIPL*, ganglion cell and inner plexiform layer; *Gd+*, gadolinium-enhancing; *HR*, hazard ratio; *IFN*, interferon; INL, inner nuclear layer; *IQR*, interquartile range; *IRR*, incidence rate ratio; *MRI*, magnetic resonance imaging; *MS*, multiple sclerosis; *NfL*, neurofilament light chain; *OR*, odds ratio; *PBVC*, percentage brain volume change; *PPMS*, primary progressive multiple sclerosis; *pRNFL*, peripapillary retinal nerve fiber layer; r_p, partial correlation; *RRMS*, relapsing–remitting multiple sclerosis; *SD*, standard deviation; *SE*, standard error; *sGFAP*, serum glial fibrillary acidic protein; *SLR*, systematic literature review; *sNfL*, serum neurofilament light chain; *SPMS*, secondary progressive multiple sclerosis; *T1LV*, T1 lesion volume; *T2LV*, T2 lesion volume

[a]In this study, abnormal sNfL was defined as sNfL levels > 80th percentile of age-corrected reference values

reported by Brune et al., patients with high sNfL (≥ 8 pg/mL) at baseline had an increased risk of experiencing a new clinical relapse (odds ratio [OR] = 3.3, 95% confidence interval [CI] 1.38–7.8, p = 0.007) in the follow-up period. However, the association between sNfL and the occurrence of new clinical relapse was observed only among patients having sNfL ≥ 80th age-corrected percentiles [45]. Notably, the association between recent relapse (within the past

4 months before sampling) and sNfL *Z*-scores was stronger compared with that with absolute sNfL concentrations. Individuals with higher sNfL *Z*-scores had a higher probability of relapses in the 1-year follow-up period (OR 1.41, 95% CI 1.30–1.54, $p < 0.0001$), as indicated by a model with Z-score as a continuous predictor [51].

Evidence from a subset of studies ($n = 2$) suggested that the association of sNfL with relapse activity weakens after 24 months. A study by Cutter et al. reported that a baseline sNfL level of ≥ 16 pg/mL was associated with a relapse occurrence within 90 days and 6 months. However, this association was not observed at 12 months or throughout the entire 3-year study duration [50]. Another study revealed that a higher proportion of patients with an NfL *Z*-score ≥ 1 experienced relapses compared with those with an NfL *Z*-score < 1 between Week 48 and Week 96 (stratified at Week 48), but the association with relapse activity was less pronounced between Week 96 and Week 144 (stratified at Week 96) [36, 52]. Only a couple of studies suggested no significant association between high sNfL levels and the risk of new relapse [53, 54]. The study by Ziemssen et al. reported that sNfL at baseline was not prognostic for on-study annualized relapse rate (ARR) and relapse rates were not statistically different between high and low sNfL groups. This may be explained by the low ARR observed in both treatment groups, pooled across two trials (ofatumumab = 0.11 and teriflunomide = 0.24) [54]. Notably, a study by Cutter et al. demonstrated that the combination of baseline Gd + lesions and sNfL ≥ 16 pg/mL had a synergistic predictive value for relapse within 90 days compared with either factor alone [50].

A predictive modeling study conducted based on data from the SUNBEAM and RADIANCE studies suggested a linear relationship between the median percentage change in baseline sNfL and the ARR [55]. Specifically, a 25% reduction in sNfL among patients receiving ozanimod 0.92 mg in SUNBEAM predicted an ARR of 0.22 (standard error [SE] = 0.04), while a 13% reduction in sNfL with interferon beta-1a predicted an ARR of 0.36 (SE = 0.04). A similar relationship was observed in the RADIANCE study, where patients receiving ozanimod demonstrated 25% reduction in sNfL and had an ARR of 0.19 (SE = 0.04) compared with a 13% sNfL level reduction and an ARR of 0.29 (SE = 0.04) among patients receiving teriflunomide [55]. A study by Ziemssen et al. reported that ofatumumab resulted in a significantly lower ARR compared with teriflunomide, with relative reductions of 60% and 48% in the high and low sNfL groups, respectively [54]. Furthermore, Kuhle et al. reported that there was no significant treatment-by-NfL category interaction, suggesting consistent treatment effects of fingolimod across all NfL categories and demonstrating the prognostic value of sNfL in both placebo- and fingolimod-treated patients [41].

Higher baseline sNfL levels were associated with a higher risk of developing MRI lesions (Table 3). Multiple linear regression modeling demonstrated that higher baseline NfL levels were independently associated with greater Gd + lesion count (effect on $\log_{10}$ sNfL = 0.11, 95% CI 0.09–0.12, $p < 0.0001$), higher T2 lesion volume (effect on $\log_{10}$ sNfL = 0.10, 95% CI 0.08–0.11, $p < 0.0001$) [44]. Another study provided evidence of early associations between sNfL levels and Gd + T1 lesions. At Week 4, the patients with sNfL levels above the baseline median demonstrated a higher proportion of Gd + T1 lesions compared with those with sNfL levels that either crossed the baseline median or fell below it (64.7% vs. 31.1% and 16.2%). This trend persisted at Week 8 (25.9% vs. 10.8% and 9.0%) and Week 12 (11.9% vs. 4.4% and 3.9%), indicating a consistent relationship between sNfL levels and the presence of Gd + T1 lesion [21]. The study by Brune et al. reported that patients with high sNfL levels at baseline had a significantly increased risk of developing new T2 lesions during the follow-up period (OR 3.97, 95% CI 1.7–9.3, $p = 0.002$) [45]. The study by Kuhle et al. demonstrated a significant correlation between patients having baseline sNfL levels ≥ 60 pg/mL compared with those < 30 pg/mL and a significant increase in the number of new or enlarging T2 lesions. Specifically, patients with higher NfL levels experienced a 2.6-fold rise in the occurrence of these lesions (difference = 164%; ratio of mean = 2.64 [1.51–4.60], $p = 0.0006$). Furthermore, elevated baseline NfL levels were associated with a 2.9 times higher rate of brain volume loss (difference = 195%; difference in means = − 0.78% [− 1.02 to − 0.54], $p < 0.0001$) [41]. The results were corroborated in another study wherein the proportion of patients with no T1 Gd + lesions and no new/enlarging T2 lesions (both at Week 96 and Week 144) were higher among patients with NfL Z-score < 1 vs. those with an NfL Z-score ≥ 1 [36, 52]. These results underscore the considerable impact of elevated NfL levels on both the occurrence of new or enlarging T2 lesions and the extent of brain volume loss (Table 3).

All MS subtypes (RRMS, secondary PMS [SPMS], primary PMS [PPMS], and clinically isolated syndrome [CIS])

Among studies included in the SLR ($n = 75$), the association between sNfL levels and relapse activity appeared comparable across patients with different types of MS, mirroring the patterns observed in those with RMS. The elevated sNfL levels were indicative of a higher likelihood of experiencing relapses and MRI lesions (Table 3). A study by Lin et al. reported a numerically higher risk of new relapse among patients with high sNfL levels (hazard ratio [HR] = 2.21, 95% CI 0.97–5.03, $p = 0.058$); however, the risk of relapse was significantly higher in patients with abnormal sNfL levels combined with thin GCIPL (HR = 5.38, 95%

CI 1.61–17.98, $p = 0.006$), thin pRNFL (HR = 4.77, 95% CI 1.39–16.38, $p = 0.013$), or thick inner nuclear layer (INL; HR = 3.26, 95% CI 1.09 to 9.76, $p = 0.034$) [56]. A study by Disanto et al. reported that patients exhibiting sNfL levels > 97.5th percentile had a twofold increase in the rate of relapses at both 1 and 2 years after sampling (incident rate ratio [IRR] = 1.94, 95% CI 1.21 to 3.10, $p = 0.006$ and IRR = 1.96, 95% CI 1.22–3.15, $p = 0.005$) [14]. The multivariate analysis conducted as a part of the Barro et al. study confirmed the association of higher sNfL levels and presence of relapse within 120 days before sampling ($\beta_{mult} = 1.144$, 95% CI 1.054–1.241, $p = 0.001$) [16]. It was also observed that increase in sNfL levels were associated with higher contrast-enhancing, new/enlarging T2 lesions and reduction in brain volume (Table 3). Furthermore, compared with patients with abnormal sNfL levels, those with both abnormal sNfL levels and thin GCIPL had an even higher risk for new brain lesions (HR = 3.19, 95% CI 1.51–6.76, $p = 0.002$) [56].

PMS (SPMS and PPMS)

Only a few studies ($n = 6$) that included SPMS and PPMS reported an association between sNfL levels and MRI lesions/relapse activities; however, the results were in line with those reported for patients with RMS. Higher sNfL levels were associated with higher number of prior relapses and MRI lesions (Table 3). Higher sNfL levels at follow-up were significantly associated with greater Gd + lesion count (effect on $\log_{10}$ sNfL = 0.06, 95% CI 0.05–0.08, $p < 0.0001$) [44], higher T2 lesion volume (effect on $\log_{10}$ sNfL = 0.04, 95% CI 0.03–0.06, $p < 0.0001$) [44], and higher T2 lesion count ($r_p = 0.36$, $p = 0.04$) [45].

Disease worsening (EDSS worsening, disability, and cognition)

RMS (studies with ≥ 80% RRMS)

Most studies (~ 75%) investigating the association between sNfL levels and disease worsening consistently demonstrated a strong link between sNfL and disease worsening/progression (Table S4; Online Resource). Patients with higher sNfL *Z*-scores were found to have a greater likelihood of experiencing EDSS worsening (OR 1.11, 95% CI 1.03–1.21, $p = 0.0093$) and evidence of disease activity-3 (EDA-3; OR 1.43, 95% CI 1.31–1.57, $p < 0.0001$). Moreover, patients with higher sNfL *Z*-scores also displayed a higher probability of experiencing EDA-3 in the following year (OR 1.33, $p < 0.001$). The risk of EDA-3 increased incrementally with higher sNfL Z-score cutoffs, with a maximum 2.1-fold risk observed in patients with sNfL above the 97.7th percentile (*Z*-score > 2.0) compared with those below it. Among patients with NEDA-3 status, those with sNfL levels above the 93.3rd percentile (*Z*-score > 1.50) had a 2.64-fold (95% CI 1.30–5.37, $p = 0.0074$) higher risk of experiencing EDA-3 in the following year [51]. A study by Bar-Or et al. reported that the proportion of patients achieving NEDA-3 status was higher in those with sNfL levels below the baseline median (65.4%) compared with those with levels above (21.7%) or crossing the baseline median (50.0%) [21]. These findings are supported by the study by Srpova et al., which showed that patients who lost NEDA-3 status within 36 months had higher sNfL levels over follow-up among patients with active MS. High sNfL levels were associated with higher odds of having EDSS worsening at 12 months (8.0% vs. 2.8%; β_{OR} 3.70, 95% CI 1.09–12.60, $p = 0.036$); however, the association between sNfL levels and EDSS worsening weakened over a period of 3 years (rho = 0.21, $p = 0.01$) [57]. It was also observed that patients who experienced an annual sNfL increase of > 10% had a significantly higher number of patients with EDSS worsening compared to those who either experienced any annual decrease or an annual increase of up to 10% in sNfL levels (42.2% vs. 6.3%, $p < 0.001$) [58].

In contrast to the aforementioned evidence, a study by Anderson et al. found only a modest association between log-transformed baseline sNfL levels and baseline EDSS scores ($\beta = 0.272$, 95% CI 0.051–0.494, $p = 0.016$). Furthermore, the study found no significant association between baseline sNfL levels and changes in EDSS scores over a 5-year period ($\beta = -0.180$, 95% CI −0.436–0.076, $p = 0.167$) [53]. Similarly, another study by Bose et al. reported no significant association between sNfL levels, both at baseline or during the follow-up, and 10-year EDSS progression [59] (Table S4; Online Resource).

All MS types (RRMS, SPMS, PPMS, and CIS) and PMS (SPMS and PPMS)

In accordance with the reported association between sNfL levels and disease progression in patients with RMS, most studies conducted across all MS types and PMS further supported these findings (Table S4; Online Resource). Baseline sNfL levels were found to have significant associations with EDSS scores ($\beta = 1.080$, 95% CI 1.047–1.114, $p < 0.001$), indicating that with each EDSS increment, sNfL levels rose by 8.0%. Furthermore, a significant interaction was observed between EDSS worsening and changes in sNfL levels over time, with progressors exhibiting a steeper trajectory of sNfL levels ($\beta = 1.015$, 95% CI 1.007–1.023, $p < 0.001$). This result remained significant even after accounting for age, sex, and disease duration [60]. According to the Jakimovski et al., initial sNfL levels were found to be predictive of 5-year EDSS scores ($r = 0.25$, $q = 0.012$), and in a cross-sectional analysis using follow-up data, sNfL levels were strongly associated with the EDSS score ($r = 0.356$, $q =$

0.002) [49]. The findings from the included studies reported that patients with elevated sNfL levels (*Z*-score > 1.3) had a twofold increased risk of future CDW (HR = 2.26, 95% CI 1.24–4.14, $p = 0.008$) [61]. The results also align with those observed in patients with PMS, further supporting the association between sNfL levels and disease progression (Table S4; Online Resource).

Cognition and data gaps

A total of 13 studies found a correlation between sNfL levels and cognitive impairment, as assessed by Symbol Digit Modalities Test (SDMT) performance, Paced Auditory Serial Addition Test (PASAT), California Verbal Learning Test-II (CVLT-II), or Montreal Cognitive Assessment (MoCA) scores. The available evidence predominantly focused on the RMS population, with limited studies reporting the association of sNfL with cognition in patients with PMS ($r_p = -0.32$, $p = 0.03$) [45]. Based on the findings from the included studies, it was evident that higher sNfL levels were linked to reduced cognitive function, particularly reflected by lower performance on the SDMT score (Table S4; Online Resource). Additionally, there was a negative correlation observed between sNfL levels and follow-up MoCA scores (baseline: $R = -0.33$, $p = 0.019$; 3 months: $R = -0.32$, $p = 0.021$; 6 months: $R = -0.42$, $p > 0.001$) [62]. Furthermore, a study by Häring et al. demonstrated that sNfL levels measured in patients with RMS over a 12- or 24-month timeframe were indicative of a 20% decline in PASAT scores (12 months HR = 2.59, 95% CI 1.04–6.47, $p = 0.0410$; 24 months HR = 3.03, 95% CI 0.72–12.69, $p = 0.1300$) [42].

Only a few of studies included in the SLR reported on the association between sNfL and progression associated with relapse activity (PARA), PIRA, and RAW (Table S4; Online Resource). Among them, the only study that examined the link between sNfL levels and RAW revealed a weak but statistically significant association with the occurrence of RAW (coefficient = 0.03, 95% CI 0.01–0.05, $p = 0.01$), indicating the predictive value of sNfL levels in the occurrence of RAW [63]. In addition, the available evidence was limited in showing that baseline sNfL levels could serve as a predictor for PARA (HR = 2.3, 95% CI 1.1–5.1, $p = 0.037$) [64]. There was insufficient evidence to establish a clear association between sNfL and PIRA. However, a study by Meier et al. reported that baseline sNfL levels showed potential prognostic value for future PIRA (HR = 1.77, 95% CI 1.11–2.83, $p = 0.02$). Nevertheless, these results did not reach statistical significance after adjusting for factors such as age, sex, body mass index, and disease duration [61]. Taking into consideration the available evidence, there is a clear need to understand the impact of sNfL levels on both PARA and PIRA in future studies. This is especially important given recent findings that indicate a substantial occurrence of PIRA in a noteworthy percentage of patients with CIS/early MS [65].

Discussion

This is the first SLR to extensively investigate the role of sNfL as a prognostic and monitoring biomarker, as well as its association with disease progression and treatment response. Among the studies included in the SLR, the Simoa immunoassay was the most-used method for measuring sNfL levels. The use of varying cutoff values to define abnormal or elevated sNfL levels across the included studies led to significant heterogeneity in reporting the relationship between higher sNfL levels and clinical outcomes. This variation reflects the complexity and diversity of the patient populations, including differences in prior therapies, age, disease duration, and gender. These factors emphasizes the importance of defining standardized cutoff values for sNfL to ensure its effective and reliable use in routine clinical care. The present review emphasized the elevated levels of sNfL in patients with MS compared with healthy controls, highlighting its reliability as a biomarker for MS. Notably, sNfL levels were generally higher in patients with PMS as opposed to those with RMS. Furthermore, this review demonstrated a correlation between increased sNfL levels and advanced age, as well as a higher frequency of relapses in the previous 12 months or a higher baseline EDSS score among patients.

The included studies in the SLR consistently demonstrated an association between higher sNfL levels and an increased risk of future relapses and disease progression. The higher levels of sNfL were also linked to a higher likelihood of experiencing GD + T1 and T2 lesions, as well as worsening EDSS scores. Additionally, there was a notable correlation between lower sNfL levels and a higher likelihood of achieving NEDA-3, while higher sNfL levels were associated with an elevated risk of experiencing EDA-3, 3-month confirmed disability progression (CDP), and 6-month CDP. Patients who displayed disease progression generally exhibited higher sNfL levels compared with nonprogressors. Some studies highlighted the persistence of the association between sNfL and relapse activity for up to 2 years of follow-up, although the strength of this association tended to diminish thereafter. Further, combining sNfL levels with other markers like thin GCIPL, thin pRNFL, and thick INL demonstrated greater sensitivity in disease management compared with sNfL levels alone. In addition to sNfL levels, the NfL Z-score has also emerged as a sensitive prognostic marker for predicting future relapses, MRI disease activity, and disease progression. Thus, future research should focus on exploring the potential use of sNfL Z-score

or a combination of sNfL with other biomarkers as promising tools in the management of MS.

Multiple clinical trials have consistently demonstrated the clinical benefits of DMTs in patients with MS [44, 54, 66]. The studies included in the current SLR reported that treatment with DMTs resulted in a reduction in sNfL levels. In clinical setting, monoclonal antibodies such as alemtuzumab, natalizumab, ofatumumab, and ocrelizumab have demonstrated higher efficacy compared with oral therapies (such as dimethyl fumarate, fingolimod, siponimod, and teriflunomide) and platform therapies (such as interferons and glatiramer acetate). These differences in efficacy were mirrored by the effects on sNfL levels, where monoclonal antibodies led to a more pronounced reduction in sNfL levels compared with oral and platform therapies. These findings highlight the potential role of sNfL as a valuable marker for evaluating the treatment response to DMTs in MS. Further research is needed to explore the utility of sNfL as a biomarker for monitoring treatment effectiveness in MS.

The results of this SLR should be interpreted with caution, considering that it is based on secondary research. As with any SLR, the findings of this study were derived from a diverse set of primary studies that encompassed various study designs (including clinical and real-world studies) and study populations with variations in age, disease severity, and treatment settings. However, it is important to note that the included studies generally demonstrated a low risk of bias when assessed using the RoB 2.0 and Downs and Black checklist tools. This suggests that the overall quality of the included studies was acceptable, enhancing the reliability of the findings.

Consistent with the recent study by van Lierop et al. [20], this SLR highlighted the robust and significant association between sNfL levels and the progression of disease in patients with MS. Importantly, measuring sNfL is a simple, reliable, and cost-effective approach compared with measuring cNfL and traditional imaging tools such as MRI. With its ease of use, sNfL measurement can effectively contribute to routine clinical practice by facilitating the monitoring of MS disease progression and assessing treatment response. These findings underscore the potential value of sNfL as a valuable tool for clinical decision-making in the management of MS. Further research and implementation studies are recommended to establish the integration of sNfL measurement into standard clinical practice.

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Data Availability No original data were generated for this review. Data utilized from studies included in this review are presented in the manuscript/supplementary files.

Declarations

Conflicts of interest Mark S. Freedman, in the previous 2 years, received research or educational grants from Sanofi-Genzyme Canada; received honoraria or consultation fees from Alexion/AstraZeneca, Biogen Idec, EMD Inc./EMD Serono/Merck Serono, Find Therapeutics, Hoffman La-Roche, Horizon Therapeutics/Amgen, Novartis, Sandoz, Sanofi-Genzyme, Sentrex, and Teva Canada Innovation; was a member of a company advisory board, board of directors, or other similar groups for Alexion/AstraZeneca, Actelion/Janssen (J&J), Atara Biotherapeutics, Bayer Healthcare, Celestra Health, EMD Inc./Merck Serono, Find Therapeutics, Hoffman La-Roche, Neurogenesis, Novartis, Sanofi-Genzyme, and Sentrex, Setpoint Medical; and participated in a speaker's bureau sponsored by Hoffman La-Roche, Novartis, and EMD Inc. Ahmed Abdelhak received research funding from the German Multiple Sclerosis Society, the Department of Defense, and the UCSF Weill Institute for Neurosciences. He received speaker fees from Roche and consultation fee from Octave Bio. Jason Freeman is an employee of Novartis Pharmaceuticals, USA. Sharmilee Gnanapavan had received consultation fees and grant support from Novartis, Sanofi-Genzyme, Merck and Roche, UK MS Society, NMSS, NIHR, and NHS Digital. Friedemann Paul has no conflict of interest. Sheshank Madiraju, Salman Hussain, and Mohit K. Bhutani are employees of Novartis Healthcare Private Limited, India.

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