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Neurofilament light chain levels in neuronal surface antibody-associated autoimmune encephalitis: a systematic review and meta-analysis

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BACKGROUND: Neuronal surface antibody-associated autoimmune encephalitis (NSAE) is a group of neuro-inflammatory disorders that is mediated by autoantibodies against the cell-surface and synaptic antigens. Studies have explored the role of neurofilament light chain (NfL) in NSAE and provided inconsistent data. We performed a systematic review and meta-analysis to evaluate the NfL levels in the serum and cerebrospinal fluid (CSF) of patients with NSAE.

METHODS: The National Center for Biotechnology Information (NCBI, PubMed), Web of Knowledge, and the Cochrane Library databases were searched for studies reporting NfL levels in patients with NSAE. Random-effects meta-analysis was used to pool results across studies.

RESULTS: Thirteen studies were included in the final systematic review and meta-analysis. The serum NfL levels were significantly higher in patients with NSAE compared to unaffected controls (standardized mean difference [SMD] = 0.909, 95% confidence interval [CI]: 0.536–1.282). Similarly, the CSF NfL levels were elevated in patients with NSAE (SMD = 0.897, 95% CI: 0.508–1.286). The serum and CSF NfL levels were not significantly correlated with disease severity, prognosis, and abnormalities in magnetic resonance imaging, electroencephalography, and CSF.

CONCLUSIONS: NfL levels in the serum and CSF were higher in patients with NSAE compared to unaffected controls. However, the NfL levels were not shown to be significantly associated with clinical or paraclinical features.

INTRODUCTION

Neuronal surface antibody-associated autoimmune encephalitis (NSAE) is a group of non-infectious inflammatory disorders of the central nervous system (CNS), which is mediated by autoantibodies against cell-surface and synaptic antigens [1]. N-methyl-D-aspartate receptor (NMDAR) and leucine-rich glioma inactivated 1 (LGI1) are the most common antigens associated with NSAE [2]. The diagnosis of NSAE is based on typical clinical manifestations, abnormalities in neuroimaging, cerebrospinal fluid (CSF), and electroencephalogram, and the presence of autoantibodies [3]. Emerging evidence suggests that biomarkers contribute to our understanding and the management of neuroimmune diseases. Biomarkers are of immense value in clinical diagnosis for assessing disease severity, monitoring treatment response, and predicting disease progression and relapses [4]. A majority of biomarkers currently used in NSAE are either clinical or paraclinical; however, most molecular biomarkers are still at the early stages of development and need large-cohort studies for further validation and to attain strong conclusions [5].

Neurofilaments belong to the family of intermediate filaments and are cytoskeletal components of neurons, particularly in axons. Based on molecular weights, neurofilaments are divided into neurofilament light chain (NfL, ~68 kDa), neurofilament medium chain (~145 kDa) and neurofilament heavy chain (~200 kDa) [6]. Thereinto, NfL is the most extensively studied type. When neurons and axons of the CNS are damaged, NfL is released into the CSF and blood can be detected. NfL has been identified as a useful biomarker for disease severity and prognosis in various neuroinflammatory disorders, such as multiple sclerosis (MS) and Guillain-Barré syndrome, and neurodegenerative diseases, such as Alzheimer's disease and amyotrophic lateral sclerosis [7, 8].

Recently, several studies have also been exploring the role of NfL in NSAE [9–11]. However, the results of these studies involving different cohorts provide inconsistent data. We conducted a systematic review and meta-analysis with the aim of investigating whether NfL levels in the CSF and serum could help differentiate patients with NSAE from unaffected controls. Furthermore, we

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aimed to determine the correlations between NfL levels and clinical and paraclinical features in patients with NSAE.

METHODS
Study selection
The present systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12]. Two authors (QLL and MTC) independently searched all the relevant articles available until 30 July 2023 in the electronic databases of the National Center for Biotechnology Information (NCBI, PubMed), Web of Science, and Cochrane Library. An expanded search strategy including "neurofilament AND encephalitis" was used to find as many studies as possible. The search was limited to English-language studies of humans. Relevant article reference lists were also reviewed. Only articles with available full text were finally included in our study. Articles in languages other than English, conference abstracts, letters, comments, and reviews were excluded.

Eligibility criteria
Studies were included if they met the following inclusion criteria: (i) original data from clinical studies involving patients and unaffected controls and (ii) retrospective or prospective studies that evaluated NfL levels in patients with NSAE. The quality of the included studies was assessed using an 11-item scale proposed by the Agency for Healthcare Research and Quality (AHRQ) [13]. The scale is recommended for estimating the quality of cross-sectional/prevalence studies. The quality of studies was identified as a score of 0–3 as low quality, 4–7 as moderate quality, and 8–11 as high quality.

Data extraction
Two authors (QLL and MTC) independently evaluated and examined all the included studies. The third author (YXZ) discussed and resolved discrepancies between the first two authors. The following data were collected from each study: authors, publication year, country or region, study design, age, gender, type of autoantibodies, numbers of patients and controls, timing of sample collection, the detection method of NfL, serum or CSF NfL levels in patients with NSAE and unaffected controls, and correlations between NfL and clinical and paraclinical features.

Data analysis
If the NfL levels were presented as the initial data of each patient, they were calculated as mean with standard deviation (SD). If the NfL levels were presented as median with range or interquartile range, they were converted into mean with SD according to the method described by Wan et al. [14]. If the NfL levels were provided with mean without SD in a study, we imputed a pooled SD from all the other studies according to the method described by Furukawa et al. [15].

Standardized mean difference (SMD) with 95% confidence interval (CI) was used to measure the pooled estimates. A forest plot showing the ratios of the individual studies and the combined effect was generated to provide an overview. Heterogeneity between studies was assessed using the I^2 statistical test, with a P-value of <0.10 indicating heterogeneity. If substantial heterogeneity was detected, the analysis was performed on a random effect model using the DerSimonian and Laird method. Otherwise, the fixed effect model was used.

Sensitivity analysis was also conducted by excluding each study and recalculating the combined estimates for the remaining studies to assess the influence of an individual result on the pooled estimate. Egger's test and Begg's test were performed to evaluate publication bias; a P-value < 0.05 was considered as having significant publication bias. Data analyses were performed using the STATA software (version SE 17.0, StataCorp, College Station, TX, USA).

RESULTS
Study characteristics
Thirteen studies [9–11, 16–25] were included in the final systematic review and meta-analysis (Fig. 1). The characteristics of each study are presented in Table 1. The included studies were mainly conducted in Europe, North America, and China. One article [20] was a prospective study and 12 articles [9–11, 16–19, 21–25] were retrospective studies. Single-molecule array (SIMOA) in eight studies [9–11, 18, 19, 23–25] and enzyme-linked immunosorbent assay (ELISA) in the remaining five studies [16, 17, 20–22] was used to detect NfL in the serum and/or CSF. The AHRQ quality assessment indicated that all included studies had a high-quality score of 8–10, as indicated in Table 1.

Serum NfL levels
Serum NfL levels in patients with NSAE and unaffected controls were detected in five studies [9, 18, 23–25] involving a total of 516 participants. SIMOA was used to detect NfL in these five studies [9, 18, 23–25]. The serum NfL levels in patients with NSAE were significantly higher (SMD = 0.909, 95% CI: 0.718–1.100, P_heterogeneity = 0.009, I^2 = 70.4%) compared to controls. Given the underlying heterogeneity, we re-evaluated the SMD on the random effect model, which was changed to 0.909 (95% CI: 0.536–1.282; Fig. 2). In subgroup analysis, the heterogeneity was decreased in patients with anti-NMDAR antibodies (SMD = 0.902, 95% CI: 0.572–1.232, P_heterogeneity = 0.083, I^2 = 59.8%) [9, 23, 24], while not in patients with varied antibodies (SMD = 0.893, 95% CI: −0.506–2.292, P_heterogeneity = 0.004, I^2 = 88.2%) [18, 25], indicating that diverse antibodies might be the source of the heterogeneity.

Sensitivity analyses were performed successively by excluding each study and re-analyzing data. No study was found to significantly affect the SMD and heterogeneity. Study-specific SMD ranged from a low value of 0.790 (95% CI: 0.433–1.147), via omission of the study by Mariotto et al., [18] to a high value of 1.023 (95% CI: 0.663–1.382), via omission of the study by Kammeyer et al. [25]. No obvious publication bias was suggested based on the results of Egger's test ($P = 0.978$) and Begg's test ($P = 0.806$). The shape of the Begg's funnel plot appeared symmetrical (Supplementary Fig. 1).

CSF NfL levels
CSF NfL levels in patients with NSAE and unaffected controls were detected in six studies [16, 17, 20–22, 25] with a total of 229 participants. ELISA was used to detect NfL in five studies [16, 17, 20–22], and SIMOA was used in one study [25]. CSF NfL levels were higher in patients with NSAE compared to controls (SMD = 0.854, 95% CI: 0.573–1.135), with substantial heterogeneity (P_heterogeneity = 0.099, I^2 = 46.0%). We also re-evaluated the SMD on the random effect model, which was changed to 0.897 (95% CI: 0.508–1.286; Fig. 3).

Sensitivity analyses were also performed, and no study was found to significantly affect the result. Study-specific SMD ranged from a low value of 0.731 (95% CI: 0.410–1.052), through omission of the study by Kortvelyessy et al. [16] to a high value of 1.023 (95% CI: 0.635–1.411) through omission of the study by Li et al. [17]. Furthermore, no obvious publication bias was suggested from the results of Egger's test ($P = 0.173$) and Begg's test ($P = 0.452$). The shape of the Begg's funnel plot appeared symmetrical (Supplementary Fig. 2).

NfL levels and clinical features
The correlations between NfL levels and clinical features including 11 studies [9–11, 17–21, 23–25] are summarized in Table 2. More
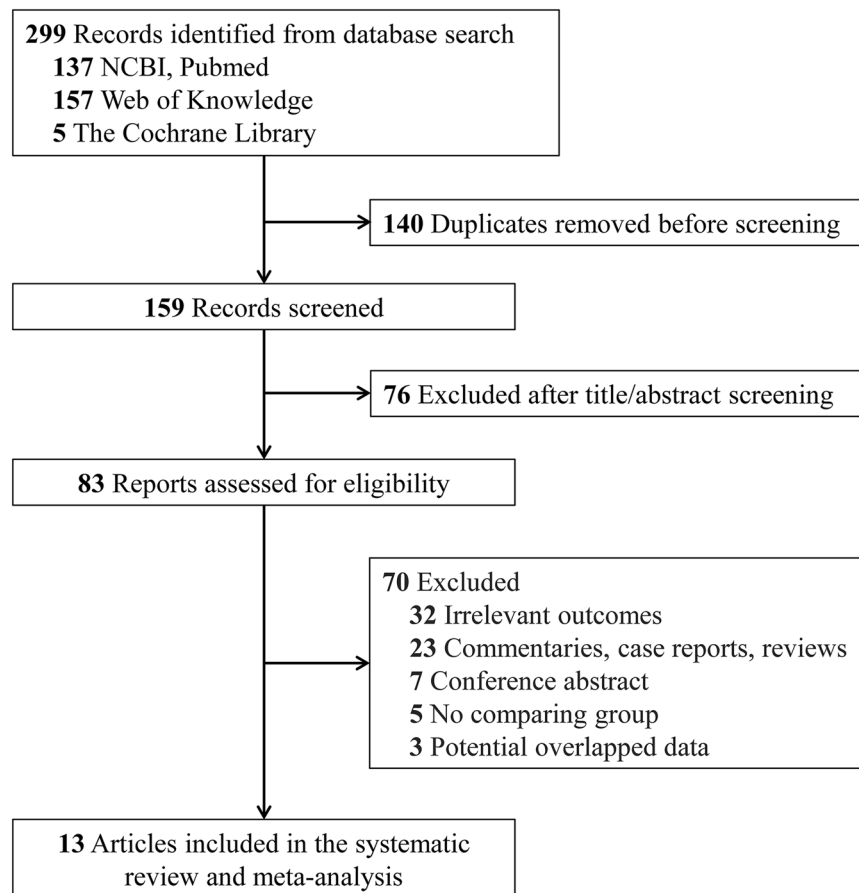
Fig. 1 Flow diagram of study selection.

number of studies suggested that NfL levels in the serum [9, 18, 25] and CSF [18, 20, 21] at disease onset or at diagnosis were not correlated to disease severity as measured by modified Rankin Scale (mRS) scores, whereas a few studies supported the correlation of disease severity and NfL levels in the serum [23] and CSF [17]. Mariotto et al. [18] concluded that serum and CSF NfL levels at disease onset were not correlated to various clinical features. High CSF NfL levels were associated with the presence of seizures in two studies [21, 24], whereas serum NfL levels were not related to seizures in another two studies [9, 23]. Serum NfL levels at diagnosis were associated with a history of herpes simplex virus-1 encephalitis in one study [9]. Serum and CSF NfL levels were not correlated with the presence of tumors in three studies [9, 23, 24]. Both serum and CSF NfL levels were associated with intensive care unit (ICU) admission and absence of immunotherapy during the first 4 weeks of the disease in one study [24], while two studies indicated that serum NfL levels were not associated with ICU admission [9, 23]. The study by Chen et al. [10] showed that the serum NfL levels at disease onset inversely correlated with the cognitive state graded by mini-mental state examination (MMSE), whereas another study by Lardeux et al. [21] indicated that CSF NfL levels were not correlated with MMSE scores at disease onset or during follow-up. Serum NfL levels were not shown to be associated with length of hospital stay in two studies [9, 23].

Two studies [19, 23] have demonstrated that serum [23] and CSF [19] NfL levels at acute stage were negatively corelated with clinical outcome assessed by mRS scores at follow-up. In a retrospective multicenter study [11] including 53 patients with anti-immunoglobulin-like cell adhesion molecule 5 (IgLON5) disease, pre-treatment serum NfL levels were positively correlated

with treatment response, mRS scores at last follow-up and death. CSF NfL levels during follow-up were positively correlated with 3-month mRS scores in a single study [17]. However, a greater number of studies revealed that serum [18, 24, 25] and CSF [18, 20, 21, 24, 25] NfL levels at acute stage were not associated with clinical outcomes measured by mRS scores at 1-year follow-up or at last follow-up. For patients with anti-NMDAR encephalitis only, no unified conclusion has been found regarding the relationship between NfL levels and clinical features.

NfL levels and paraclinical features

The correlations between NfL levels and paraclinical features analyzed from eight studies [9–11, 17–20, 24, 25] are summarized and presented in Table 3. Two studies showed that elevated serum [9] and CSF [19] NfL levels at disease onset were positively correlated with the presence of abnormalities in magnetic resonance imaging (MRI), whereas three other studies suggested that serum [18, 24] and CSF [18, 24, 25] NfL levels at disease onset were not associated with MRI abnormalities. Using resting-state functional MRI metrics, Chen et al. [10] demonstrated that the serum NfL levels at disease onset were positively correlated with intra-default mode network connectivity and limbic-sensory connectivity, and the convalescent serum NfL levels were positively correlated with thalamocortical connectivity in patients with anti-NMDAR encephalitis. Both serum and CSF NfL levels were not associated with abnormal electroencephalography in one study [24].

A study by Brenner et al. [9] demonstrated that serum NfL levels at diagnosis were not associated with antibody titers in either serum or CSF. Similarly, findings reported by Ma et al. [20] revealed that serum NfL levels were not associated with antibody titers in

Table 1. Characteristics of the studies included in the systematic review and meta-analysis.

Author, year	Country	Design	Age, mean/median	Female: male	Antibody types	NfL detection method	Timing of sample collection	Samples: case (n)/ control (n)	Quality score
Studies included in systematic review and meta-analysis									
Kortvelyessy et al., 2018 [16]	Germany	Retrospective	60	NA	Varies	ELISA	NA[a]	CSF: 12/34	9
Li et al., 2019 [17]	China	Retrospective	34	1.4:1	NMDAR	ELISA	NA[a]	CSF: 24/21	9
Mariotto et al., 2019 [18]	Italy	Retrospective	54	1.3:1	Varies	SIMOA	≤14 days	Serum: 25/25; CSF: 23/0	8
Day et al., 2021 [20]	Germany, United States, Canada	Prospective	30.5	3.1:1	Varies	ELISA	NA[a]	CSF: 21/28	10
Lardeux et al., 2022 [21]	France	Retrospective	69	1.4:1	LGI1	ELISA	NA[a]	CSF: 17/20	9
Vakrakou et al., 2022 [22]	Greece	Retrospective	51.5	1.5:1	Varies	ELISA	NA[a]	CSF: 10/10	10
Ma et al., 2022 [23]	China	Retrospective	24.5	1:1.5	NMDAR	SIMOA	NA[a]	Serum: 64/84	9
Guasp et al., 2022 [24]	Spain	Retrospective	23	4.6:1	NMDAR	SIMOA	median: 26 days	Serum: 118/36; CSF: 103/0	9
Kammeyer et al., 2022 [25]	United States	Retrospective	64	1:1	Varies	SIMOA	≤180 days	Serum: 12/20; CSF: 12/20	9
Brenner et al., 2023 [9]	Netherlands	Retrospective	32	2.9:1	NMDAR	SIMOA	NA[a]	Serum: 71/61	10
Additional studies included in systematic review only									
Nissen et al., 2021 [19]	Denmark	Retrospective	45	1.3:1	NMDAR, LGI1	SIMOA	NA[a]	CSF: 53/0	8
Gruter et al., 2023 [11]	Germany	Retrospective	63.8	1:1.5	IgLON5	SIMOA	NA[a]	Serum: 41/0	8
Chen et al., 2023 [10]	China	Retrospective	22.5	1.2:1	NMDAR	SIMOA	NA[a]	Serum: 21/24; CSF: 21/0	9

CSF cerebrospinal fluid, *ELISA* enzyme-linked immunosorbent assay, *IgLON5* immunoglobulin-like cell adhesion molecule 5, *LGI1* leucine-rich glioma-inactivated 1, *NfL* neurofilament light chain, *NMDAR* N-methyl-D-aspartate receptor, *SIMOA* single molecule array.
[a]Samples were collected by the time of diagnoses, while the exact time from disease onset was unknown.
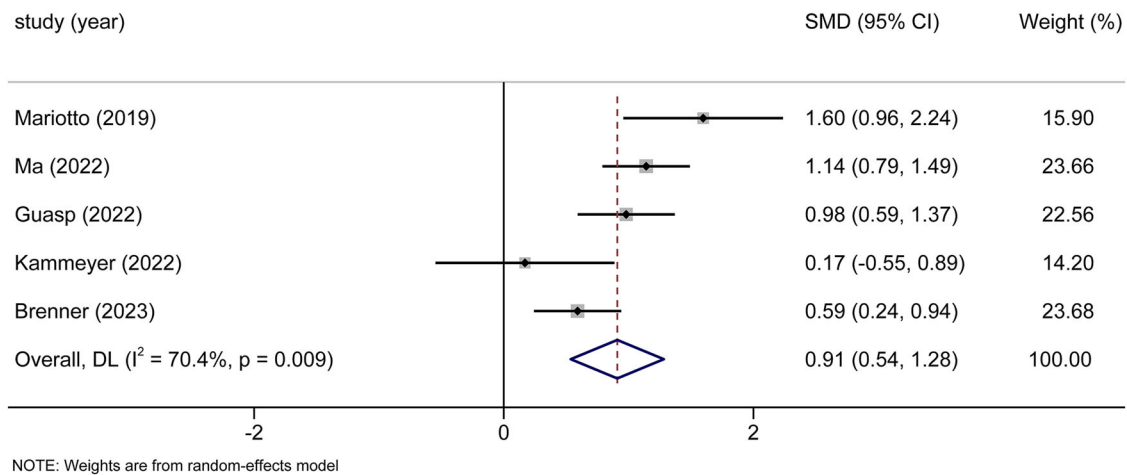
Fig. 2 Forest plot of the standardized mean difference of serum neurofilament light chain levels in patients with neuronal surface antibody-associated autoimmune encephalitis.
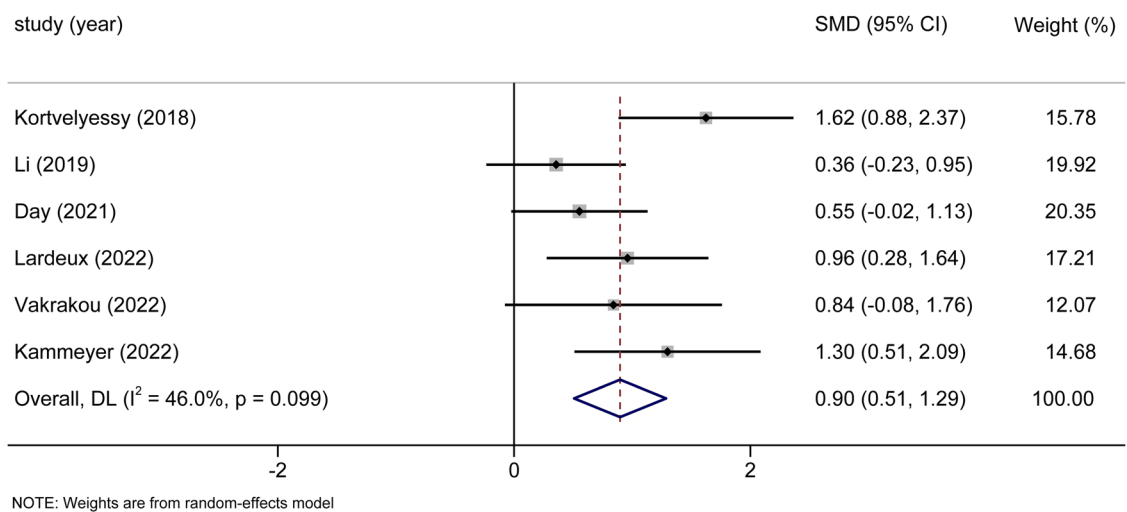

Fig. 3 Forest plot of the standardized mean difference of cerebrospinal fluid neurofilament light chain levels in patients with neuronal surface antibody-associated autoimmune encephalitis.

unspecified samples. In CSF routine analysis, Guasp and colleagues' study [24] showed that higher CSF NfL levels were positively associated with CSF pleocytosis (>20 cells/μL), whereas Gruter and colleagues' study [11] suggested that serum NfL levels were negatively correlated with the CSF cell count. However, four other studies revealed that serum [18, 20, 24] and CSF [18, 19] NfL levels at disease onset were not correlated with CSF pleocytosis. Serum and CSF NfL levels were not associated with CSF total protein in two studies [18, 20]. CSF NfL levels at diagnosis were shown to be positively correlated with CSF interleukin (IL)-1β and IL-17A in a study on anti-NMDAR encephalitis [17]. Another study demonstrated that pre-treatment serum NfL levels were positively correlated with serum glial fibrillary acidic protein in patients with anti-IgLON5 disease [11]. The associations between NfL levels and paraclinical findings were inconclusive as well for patients with anti-NMDAR encephalitis.

DISCUSSION
To the best of our knowledge, our study is the first systematic review and meta-analysis to explore the changes in NfL levels in the serum and CSF of patients with NSAE and summarize the correlations between NfL levels and clinical and paraclinical features. Our meta-analysis found that NfL levels in serum (SMD: 0.909, 95%

CI: 0.536–1.282) and CSF (SMD: 0.897, 95% CI: 0.508–1.286) were significantly higher in patients with NSAE than controls. However, our systematic review indicated that the serum and CSF NfL levels were not significantly associated with disease severity, clinical outcome, or paraclinical features in patients with NSAE.

Although inconsistent results have been reported for NfL levels in previous studies, our meta-analysis provided evidence that the NfL levels in both serum and CSF were higher in patients with NSAE compared with controls. Sensitivity analyses showing that the SMDs of serum and CSF NfL levels were not influenced by an individual study suggested that the overall results are robust and reliable. As NfL is an important part of the cytoskeletal structure of myelinated axons, elevated NfL levels in serum and CSF indicate that axonal damage occurs in the acute stage of NSAE. Our results were similar to those reported for MS and neuromyelitis optica spectrum disorder (NMOSD). Several meta-analyses have shown that serum and CSF NfL levels are higher in pediatric and adult patients with MS compared with healthy controls [26–28]. Several clinical studies have also demonstrated that serum and CSF NfL levels are significantly elevated in patients with NMOSD compared with healthy controls [29–31]. In addition to inflammatory demyelination, continuous axonal damage, indicated by increased NfL levels, also occurs in MS and NMOSD, as typical demyelinating disorders of the CNS.

Table 2. The correlations between neurofilament light chain levels and clinical features.

Author, year	Antibody types	Correlationship between NfL levels and clinical features
Li et al., 2019 [17]	NMDAR	CSF NfL levels at diagnosis were positively correlated with max mRS score. CSF NfL levels during follow-up were positively correlated with 3-month mRS score.
Mariotto et al., 2019 [18]	Varies	Serum and CSF NfL levels at disease onset were not correlated with clinical features, disease severity (mRS) or clinical outcome (mRS at last follow-up).
Nissen et al., 2021 [19]	NMDAR, LGI1	Higher pre-treatment CSF NfL levels were associated with worse long-term outcome (mRS at follow-up).
Day et al., 2021 [20]	Varies	CSF NfL levels were not associated with mRS at nadir, at discharge, or at 1-year follow-up.
Lardeux et al., 2022 [21]	LGI1	Higher CSF NfL levels were associated with presence of epileptic seizures. CSF NfL levels were not correlated with MMSE or mRS at disease onset and during follow-up.
Ma et al., 2022 [23]	NMDAR	Serum NfL levels were positively associated with the initial mRS and 1-year mRS, while not with presence of tumors, seizures, ICU admission, or length of stay.
Guasp et al., 2022 [24]	NMDAR	CSF NfL levels were associated with prodromal symptoms, seizures or status epilepticus, ICU admission, not receiving immunotherapy during the first 4 weeks of the disease, or receiving second-line immunotherapy during the subsequent disease course. Serum NfL levels were associated with ICU admission and not receiving immunotherapy during the first 4 weeks of disease. Serum and CSF NfL levels were not correlated with presence of tumors, or mRS at 1-year follow-up.
Kammeyer et al., 2022 [25]	Varies	Serum and CSF NfL levels in acute stage were not associated with mRS at 1-year follow-up.
Gruter et al., 2023 [11]	IgLON5	Lower pre-treatment serum NfL level was an independent predictor of treatment response. Pre-treatment serum NfL levels were positively correlated with mRS at last follow-up and death.
Chen et al.,2023 [10]	NMDAR	The onset serum NfL levels were inversely correlated with the cognitive state graded by MMSE.
Brenner et al., 2023 [9]	NMDAR	Serum NfL levels at diagnosis were associated with presence of preceding HSV1 encephalitis and 1-year clinical outcome (mRS score), while not with presence of tumors, seizures, movement disorders, ICU admission, disease severity (mRS score at onset), or length of stay.

CSF cerebrospinal fluid, *HSV1* herpes simplex virus 1, *ICU* intensive care unit, *IgLON5* immunoglobulin-like cell adhesion molecule 5, *LGI1* leucine-rich glioma-inactivated 1, *MMSE* mini-mental state examination, *mRS* modified Rankin Scale, *NfL* neurofilament light chain, *NMDAR* N-methyl-D-aspartate receptor.

Table 3. The correlations between neurofilament light chain levels and paraclinical features.

Author, year	Antibody types	Correlationship between NfL levels and paraclinical features
Li et al., 2019 [17]	NMDAR	CSF NfL levels at diagnosis were positively correlated with CSF IL-1β and IL-17A.
Mariotto et al., 2019 [18]	Varies	Serum and CSF NfL levels at disease onset were not correlated with MRI or CSF features.
Nissen et al., 2021 [19]	NMDAR, LGI1	Elevated pre-treatment CSF NfL levels were associated with abnormal MRI, not with CSF pleocytosis.
Ma et al., 2022 [20]	NMDAR	Serum NfL levels were not associated with antibody titers, CSF pleocytosis, or CSF total protein.
Guasp et al., 2022 [24]	NMDAR	Higher CSF NfL levels were associated with CSF pleocytosis (>20 cells/μL), while not with abnormal brain MRI or abnormal EEG. Serum NfL levels were not associated with CSF pleocytosis (>20 cells/μL), abnormal brain MRI, or abnormal EEG.
Kammeyer et al., 2022 [25]	Varies	Serum NfL levels in acute stage were not associated with presence of MRI abnormalities.
Gruter et al., 2023 [11]	IgLON5	Pre-treatment serum NfL levels were positively correlated with serum GFAP, and negatively correlated with the CSF cell count.
Chen et al., 2023 [10]	NMDAR	The onset serum NfL levels were positively correlated with intra-DMN connectivity and limbic-sensory connectivity. The convalescent serum NfL levels were positively correlated with thalamocortical connectivity.
Brenner et al., 2022 [9]	NMDAR	Serum NfL levels at diagnosis were associated with presence of MRI abnormalities, while not with serum or CSF antibody titers.

CSF cerebrospinal fluid, *DMN* default mode network, *EEG* electroencephalography, *GFAP* glial fibrillary acidic protein, *IgLON5* immunoglobulin-like cell adhesion molecule 5, *IL* interleukin, *LGI1* leucine-rich glioma-inactivated 1, *MRI* magnetic resonance imaging, *NfL* neurofilament light chain, *NMDAR* N-methyl-D-aspartate receptor.

The exact pathogenic mechanisms of NSAE remain unclear; however, two general mechanisms have been proposed [32]. First, the direct non-inflammatory mechanism is considered the main pathogenic process. The autoantibodies in the CSF combine with the target antigens, such as NMDAR and LGI1, leading to internalization and downregulation of target receptors, and directly disrupt the function of target antigens, or block protein–protein interactions. Second, the indirect inflammatory mechanism is also regarded as an important pathogenic process of NSAE, including adaptive and innate immune activation, complement deposition, and activation of microglia and macrophages, resulting in neuronal and axon injury [32]. This is a possible explanation for elevated NfL levels in serum and CSF in patients with NSAE.

Consistent conclusions are lacking in the systematic review of the correlations between NfL levels and clinical and paraclinical features. Specifically, the serum and CSF NfL levels are not significantly associated with disease severity, prognosis, or

abnormalities in MRI, electroencephalography, and CSF. Different from our results for NSAE, the NfL levels in MS were correlated with disease severity, clinical relapses, and MRI lesion burdens (including T2 lesions and enhanced T1 lesions) [33]. The variation in the results of NfL in NSAE and MS can be partially explained by the underlying pathogenic mechanisms and pathological manifestations. As mentioned before, in patients with NSAE, neuronal and axon injury may be seen but not the predominant pathological features [34]. In contrast, active lesions of MS are characterized by complete demyelination and the presence of numerous phagocytes containing myelin debris in their cytoplasm, suggesting ongoing myelin breakdown [35].

In addition to the underlying pathogenic mechanisms, other factors, including region and ethnicity, autoantibody types, sample type (serum vs CSF), detection methods, and timing of detection, may also impact our inconsistent results. For example, regarding the association between NfL levels and disease severity, the studies conducted in Europe and North America [9, 18, 20, 21, 25] were different from those in China [17, 23]. The CSF NfL levels were associated with presence of seizures in patients with anti-LGI1 encephalitis [21] and anti-NMDAR encephalitis [24], but not in patients with various autoantibodies [18]. Regarding tested samples, serum and CSF NfL levels may show different results even in the same study [24]. CSF testing is recommended more often because CSF NfL levels can accurately reflect axonal injury and be less influenced by the integrity of the blood-brain barrier and systemic comorbidities [27]. Moreover, most of the samples were obtained from the patients at the time of diagnosis or before immunotherapy. However, as patients with NSAE generally have a subacute onset, the interval between disease onset to sample collection varied from days to months, which may affect NfL levels. Additional multicenter prospective studies are needed to explore the correlations between NfL levels and clinical and paraclinical features, and the abovementioned factors should be considered.

Limitations
There are some limitations of this systematic review and meta-analysis. Firstly, our results were mostly based on retrospective studies, which may not sufficiently control all the possible confounders. Secondly, substantial heterogeneity was observed in the pooled analysis of serum and CSF NfL levels, and the number of included studies was not sufficient to conduct a subgroup analysis. Hence, a random effect model was used for the final meta-analyses, and sensitivity analyses were applied to improve the reliability of the results. Thirdly, non-normally distributed statistics (median with range or interquartile range) were converted to normally distributed statistics (mean with SD) in some studies, which may result in bias.

CONCLUSIONS
NfL levels in serum and CSF were higher among patients with NSAE compared to unaffected controls. However, serum and CSF NfL levels may be insufficient to be independent predictors of clinical or paraclinical features in NSAE. Additional multicenter prospective studies with large sample sizes and long-term follow-up are needed to explore the associations between NfL levels and clinical and paraclinical findings.

DATA AVAILABILITY
Data sharing not applicable to this article as no new datasets were generated during the current study. The data that support the findings of this study were derived from public domain resources as referenced.

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AUTHOR CONTRIBUTIONS

QLL and YXZ contributed to concept and design of the study. All authors contributed to acquisition and analysis of the data. QLL contributed to drafting the initial manuscript. JJW, QJW and YXZ contributed to revising the manuscript for intellectual content. All authors read and approved the final version before submission.

COMPETING INTERESTS

The authors declare no competing interests.

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