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RESEARCH ARTICLE

Exploring pathways leading to drug-resistant epilepsy for patients with cryptogenic new onset refractory status epilepticus

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Abstract

Objective: Cryptogenic new onset refractory status epilepticus (cNORSE) carries high risks of long-term disability and post-NORSE epilepsy, but mechanisms remain unclear. We aimed to assess the predictive value of inflammatory and brain injury biomarkers and determine whether immune disturbances persist in the chronic phase.

Methods: We enrolled 93 cNORSE patients from the Pitié-Salpêtrière Hospital and the Yale NORSE/FIRES biorepository (2013–2025). Serum and cerebrospinal fluid (CSF) samples were collected during status epilepticus (SE), with outcomes assessed 6–12 months after resolution. To investigate post-cNORSE epilepsy, we compared 39 post-cNORSE patients (25 with paired acute samples) to 40 patients with temporal lobe epilepsy due to hippocampal sclerosis (TLE-HS) and 20 with chronic immune-mediated encephalitis.

Results: During cNORSE, elevated innate cytokines (serum CXCL8, CCL2; CSF IL-6, CXCL8, CCL2, MIP-1α, G-CSF) and brain injury biomarkers (serum and

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CSF neurofilament light chain [NfL], CSF neuron-specific enolase) correlated with worse functional outcomes. Multivariate models demonstrated that adding serum NfL to cytokines improved poor outcome prediction (area under the curve = .75). In contrast, no acute biomarker predicted post-cNORSE epilepsy, which was instead associated with prolonged SE, magnetic resonance imaging abnormalities, and the need for more intensive treatment. In paired analyses, most serum cytokines normalized during the chronic phase, particularly IL-6, IL-10, and IL-1β, although new adaptive immune disturbances (IL-17A, IL-12p70, TNFα) appeared in 20% of patients. No chronic elevations of innate cytokines were observed in post-cNORSE patients. Conversely, elevated age-adjusted NfL levels were more frequent in post-cNORSE epilepsy (64%) than encephalitis (45%) and TLE-HS (20%), ($p < .001$), with elevated NfL levels correlating with poor functional outcomes ($p = .019$).

Significance: Innate immune activation is a hallmark of acute cNORSE but largely resolves in the chronic phase, arguing against persistent innate inflammation as the driver of post-cNORSE epilepsy. In contrast, persistently elevated NfL levels suggest ongoing axonal injury, potentially contributing to poor outcomes. Integrating inflammatory and neuroaxonal injury biomarkers may improve risk stratification and guide long-term management.

KEYWORDS

brain injury biomarkers, cytokines, new-onset refractory status epilepticus, NORSE outcome post, NORSE epilepsy

1 | INTRODUCTION

New onset refractory status epilepticus (NORSE) is one of the most severe forms of refractory status epilepticus.[1] Despite extensive evaluation, up to 75% of cases lack an etiology, qualifying as cryptogenic NORSE (cNORSE).[2] Patients with cNORSE often experience prolonged SE and extended intensive care unit (ICU) stays, leading to substantial long-term neurological and functional disability.[3,4] However, factors influencing long-term outcomes in cNORSE remain poorly defined, and optimal postdischarge management, particularly preventing post-cNORSE epilepsy, remains uncertain.

Cytokine analyses revealed that patients with the highest innate proinflammatory cytokine levels (e.g., IL-6, CXCL8, C-C motif chemokine ligand 2 (CCL2), macrophage inflammatory protein-1 alpha (MIP-1α)) had the worst short- and long-term outcomes.[5,6] Elevated cerebrospinal fluid (CSF) cytokine levels have also been observed in patients showing greater magnetic resonance imaging (MRI) lesion burden and worse 3-month outcomes.[7] These findings suggest that innate immune activation during status epilepticus (SE) contributes to long-term sequelae and that modulating this pathway may improve prognosis. However, early immunotherapies have not consistently improved outcomes,[8] indicating that other mechanisms might also drive poor recovery. Several brain injury biomarkers have been proposed to predict SE outcomes.[9,10] Neuron-specific enolase (NSE) is the most studied, with levels correlating with SE duration and poor prognosis.[10–12] Other markers, such as progranulin and S100-beta (S100B) protein, have been

Key points

- Acute biological biomarkers predict cNORSE long-term functional outcomes but not post-cNORSE epilepsy.
- Adding acute serum NfL to cytokines improves outcome prediction.
- Innate proinflammatory cytokines normalize in chronic post-cNORSE epilepsy.
- Twenty percent of patients (5/25) develop adaptive immune disturbances in the chronic phase.
- Elevated chronic NfL in two thirds of patients suggests sustained axonal injury in many post-cNORSE patients.

associated with mortality, functional outcomes, or MRI-defined encephalopathy.[12–14] Higher serum levels of neurofilament light chain (NfL), a marker of axonal injury, were associated with longer seizure duration and worse 30-day outcomes.[13–15]

Because brain injury can influence seizure susceptibility, biomarkers of brain injury may help identify patients at higher risk for post-cNORSE epilepsy. Additionally, neuroinflammation is increasingly recognized as a driver of epileptogenesis and ictogenesis,[16] with IL-1β promoting epileptogenesis[17] and CXCL8 or tumor necrosis factor alpha (TNFα)I enhancing neuronal excitability.[18,19] Patients with marked immune dysregulation during SE appear more likely to develop post-cNORSE epilepsy, suggesting that acute innate immune disturbances may contribute to seizure recurrence.[5] However, post-cNORSE epilepsy rates remain high despite targeted immunotherapy.[2,8] One explanation could be that immune disturbances reemerge in the chronic phase, lowering seizure threshold and supporting prolonged immunotherapy.[20,21]

Combining brain injury markers with inflammatory profiles could improve prediction of long-term outcomes and post-cNORSE epilepsy, and clarify the interplay between inflammation, neuronal damage, and epileptogenesis. Here, we aimed to (1) identify acute and chronic predictive factors for long-term outcomes and post-cNORSE epilepsy and (2) explore the underlying mechanisms of post-cNORSE epilepsy.

2 | MATERIALS AND METHODS

2.1 | Study design, settings, and participants

This study was approved by the Paris Pitié-Salpêtrière Hospital (Assistance Publique - Hôpitaux de Paris (APHP), COLETTE, and INSERM (Institut National de la santé et de la recherche médicale), TIPI) and Yale University (NORSE/FIRES biorepository, institutional review board #1511016840 and #2000031611). Informed consent was obtained from all patients or legally authorized representatives following the Declaration of Helsinki. The study followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.

For the first aim, patients with cNORSE were included if biological samples were collected during SE or within 2 days after SE resolution, with available data on functional outcome and/or seizure recurrence at 6–12 months after SE resolution. To be classified as having cNORSE, patients were required to have undergone an extensive etiological diagnostic workup, including neuroimaging and lumbar puncture. Whole genome sequencing analysis was performed in 81 (87%) patients and yielded negative findings.

For the second aim, patients with cNORSE were included if they developed post-cNORSE epilepsy and had samples collected at least 3 months after SE resolution, regardless of whether acute samples were available. Patients have been enrolled from March 2013 to February 2025. Samples collected during a recurring SE were not included. For the second aim, patients with post-cNORSE epilepsy were compared to patients with drug-resistant epilepsy, including chronic immune-mediated encephalitis (anti-GAD65 or Rasmussen encephalitis), or temporal lobe epilepsy with hippocampal sclerosis (TLE-HS).

Post-NORSE epilepsy was defined as at least one unprovoked seizure after discharge (of note, no patient had just one). Functional outcome was assessed using the Glasgow Outcome Scale Extended (GOS-E; 1 = death to 8 = upper good recovery). For patients with multiple evaluations, the best outcome score during the 6–12-month interval was retained. Poor outcome was defined as GOS-E ≤ 4.

Demographic, clinical, treatment, and MRI data during the ICU stay were extracted from a RedCap database (Yale) or medical records (Paris).

2.2 | Sample collection and processing

Red-top blood tubes were centrifuged, within 2 h, at 1500 × *g* for 10 min to obtain serum. Polypropylene tubes were used for CSF collection and centrifuged at 1500 × *g* for 10 min, and supernatants were collected. Serum and CSF samples were stored at −80°C until analysis. Only the first samples collected during SE were analyzed. CSF was collected only when clinically indicated.

2.3 | Biomarker measurements

Eleven cytokines were measured by multiplexed fluorescent bead-based immunoassay detection (BD Biosciences).[6] NSE and S100B assays were measured using immunofluorimetric assays (Kryptor, Brahms) and electrochemiluminometric sandwich immunoassays (Modular E170, Roche Diagnostics), respectively. All samples were analyzed in singlicate. Progranulin was measured using the Progranulin (human) ELISA kit (Adipogen, Coger), in duplicate, with the average value used. NfL was quantified using the automated Lumipulse G1200 system (Fujirebio) chemiluminescent immunoassay, also run in singlicate.

2.4 | Statistical analysis

Statistical analyses were conducted using RStudio (version 2023.03.1). Two-tailed $p < .05$ was considered significant.

To account for the multicenter design and long inclusion period, linear mixed-effects models were fitted for each biomarker, with year of inclusion as a fixed effect and center as a random intercept.

To evaluate whether biomarkers could predict long-term outcomes and post-cNORSE epilepsy, we performed univariable logistic regression analyses. Variables with $p < .05$ were then entered into the multivariate models. Odds ratios (ORs) and 95% confidence intervals (CIs) were derived from model coefficients. Correlations between biomarkers and GOS-E were assessed using Spearman rank or Pearson correlation. Differences between post-cNORSE epilepsy and control groups were assessed using Kruskal–Wallis with post hoc Dunn tests. CSF biomarkers were compared between post-cNORSE and autoimmune groups using the Wilcoxon rank-sum test, as CSF was unavailable for TLE-HS. Probability values were adjusted for multiple comparisons using the Benjamini–Hochberg procedure.

To determine whether combining brain injury with inflammatory biomarkers enhances predictive performance, we compared different logistic regression models. Candidate variables were first selected using least absolute shrinkage and selection operator (LASSO) logistic regression, excluding predictors with more than 20% missing data, and imputing remaining missing values by the mean. The procedure was repeated across 1000 stratified train/test resamples, and the frequency of selection identified the most consistently retained predictors. Subsequently, nested models were compared using likelihood ratio tests and receiver operating characteristic analyses with 2000 bootstrap replicates.

For patients with both acute and chronic samples, biomarker levels were compared with paired Wilcoxon signed-rank tests, with Benjamini–Hochberg correction. Cytokine concentrations were classified as normal or abnormal based on control upper limits.[6] Normalization was defined as a return from abnormal (acute) to normal (chronic) levels.

3 | RESULTS

3.1 | Prediction of long-term outcomes and post-cNORSE epilepsy

For the first aim of the study, to identify biomarkers that can predict long-term outcomes and post-cNORSE epilepsy, there were 93 patients (median age = 28 years, interquartile range [IQR] = 19–49, range = 3–87 [77% of adults], with 58% being female) with samples collected during SE (Figure 1). Patients were enrolled across more than 10 years and from 37 centers across the United States ($n = 27$), France ($n = 2$), Canada ($n = 2$), Italy ($n = 2$), Belgium ($n = 1$), Sweden ($n = 1$), the UK ($n = 1$), and Spain ($n = 1$). Linear mixed-effect models did not identify a strong center or year-of-inclusion effect on biomarker levels.

Serum samples were collected after a median of 9 days following SE onset (IQR = 5–19), and CSF samples were collected after a median of 7 days following SE onset (IQR = 3–14). Spearman correlation showed that longer delays between SE onset and sample collection were significantly associated with higher serum levels of CXCL8 (rho = .251, $p = .020$), CCL2 (rho = .270, $p = .012$), MIP-1α (rho = .227, $p = .035$), S100B (rho = .247, $p = .038$), progranulin (rho = .376, $p < .001$), and both serum and CSF NfL (serum: rho = .650, $p < .001$; CSF: rho = .321, $p = .030$). In contrast, longer delays between SE onset and CSF collection were significantly associated with lower CSF levels of IL6 (rho = −.373, $p = .0024$), CXCL8 (rho = −.477, $p < .001$), CCL2 (rho = −.382, $p = .0018$), MIP-1α (rho = −.369, $p = .0027$), IL-10 (rho = −.376, $p = .0022$), IL-1β (rho = −.354, $p = .0044$), and progranulin (rho = −.524, $p < .001$).

Patients who received a higher number of anesthetics had elevated serum levels of IL-6, CXCL8, CCL2, MIP-1α, G-CSF, IL-10, and NfL, as well as elevated CSF levels of CCL2 and NSE. Patients who received a higher number of antiseizure medications (ASMs) had elevated serum levels of MIP-1α, IL-10, NSE, progranulin, and NfL, as well as elevated CSF NSE levels. No significant correlations were observed between biomarker levels and the number of immunotherapies received. Detailed results are provided in Table S1.

Brain MRI was performed at variable time points after SE onset. The first MRI was obtained at a median of 1 day (IQR = 0–4) after SE onset, and the last MRI performed during hospitalization was at a median of 23 days (IQR = 7–42). Acute cortical hyperintensities were identified at a median of 4 days (IQR = 1–10) following SE onset, whereas cortical atrophy was detected at a median of 41 days (IQR = 24–59).

3.2 | Prediction of 12-month outcome

Among the 93 eligible patients, 49 (53%) had poor outcomes (GOS-E of ≤4), including 19 who died during their ICU stay, whereas 43 (47%) had good outcomes, and the outcome was not available for the remaining patient. Among the 19 patients who died in the ICU, death resulted

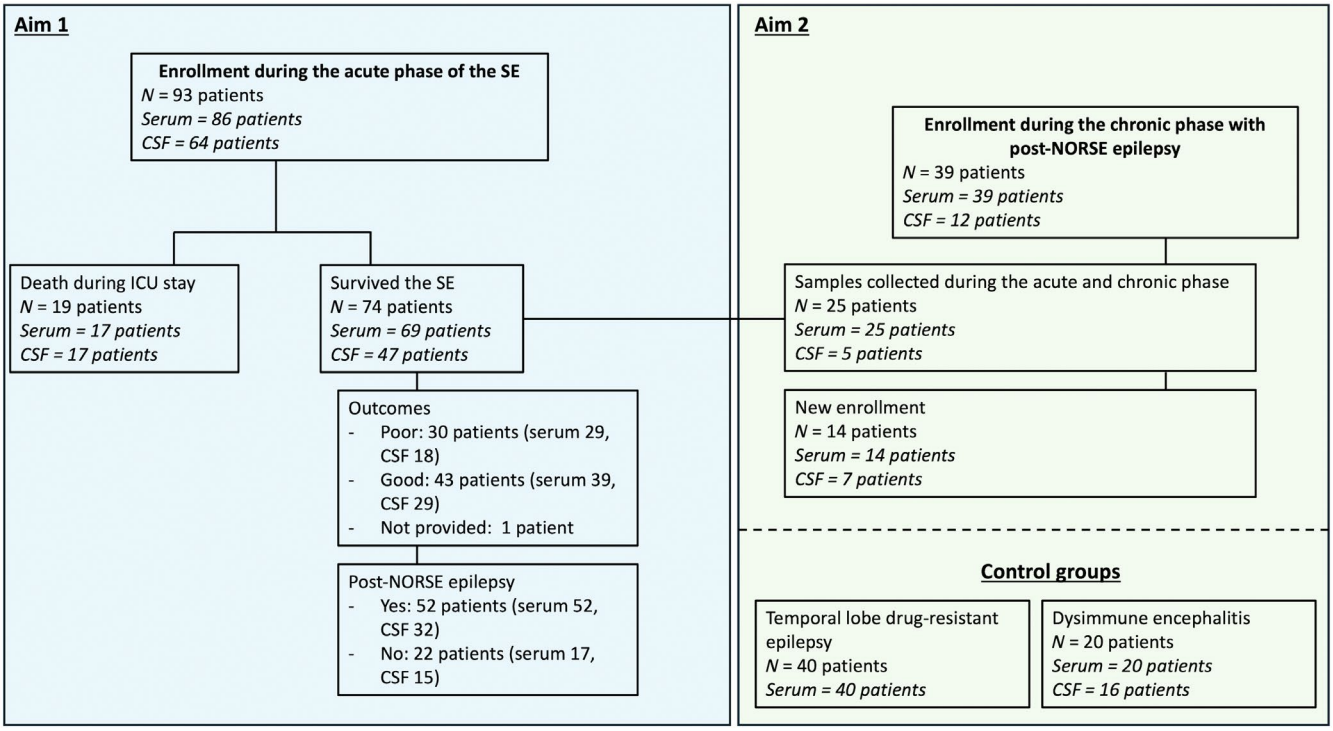

FIGURE 1 Study cohort flowchart. CSF, cerebrospinal fluid; ICU, intensive care unit; NORSE, new onset refractory SE; SE, status epilepticus.

from withdrawal of life-sustaining therapies in 12 patients, septic shock in four patients, cardiac arrest in two patients, and multiorgan failure in one patient. The outcome was assessed after a median of 361 days (IQR = 283–404) after SE resolution.

Patients with poor outcomes were more likely to develop post-cNORSE epilepsy compared to those with more favorable outcomes (87% vs. 58%, OR = 4.7, 95% CI = 1.5–18.0, $p = .013$). They required more anesthetics (3 [IQR = 3–4] vs. 2 [IQR = 2–3], $p < .001$) and ASMs (7 [IQR = 6–9] vs. 6 [IQR = 4–8], $p = .016$), although no significant differences were found in the use of immunotherapies. Additionally, they had longer SE duration (31 [IQR = 12–52] vs. 13 [IQR = 8–42] days, $p = .029$) and ICU stay (50 [IQR = 17–90] vs. 33 [IQR = 15–55] days, $p = .012$) compared to those with a good outcome. The timing of the first and last MRI examinations was comparable between patients with poor and good outcomes, and no significant differences were observed in the prevalence of acute cortical hyperintensity or brain atrophy between the two outcome groups.

Serum samples were collected from 86 patients, including 46 with poor long-term outcomes. CSF samples were obtained from 64 patients, including 35 with poor outcomes. Significant correlations were found between biological markers and long-term functional outcomes (Table 1). Patients with elevated serum levels of CXCL8 (rho = −.29, $p = .0072$), CCL2 (rho = −.36, $p < .001$), and NfL (rho = −.41, $p < .001$) had worse long-term functional outcomes, defined by lower GOS-E. Similarly, worse outcomes were associated with elevated CSF levels of IL-6 (rho = −.34, $p = .0054$), CXCL8 (rho = −.40, $p = .0012$), CCL2 (rho = −.53, $p < .001$), MIP-1α (rho = −.40, $p < .0010$), G-CSF (rho = −.40, $p = .0010$), NSE (rho = −.69, $p < .001$), progranulin (rho = −.36, $p = .014$), and NfL (rho = −.42, $p = .0035$). The multivariate logistic regression analysis revealed no association of clinical or biological variables with long-term outcomes (Table 1).

The LASSO logistic regression identified serum CXCL8 (76.5%) and serum IL-12p70 (71.3%) as the most consistently selected inflammatory predictors of long-term outcomes, and serum NfL emerged as the most relevant brain injury biomarker (43.3%). Among three logistic regression models using (A) serum CXCL8 alone, (B) its combination with serum IL-12p70, and (C) the combination of both mediators with serum NfL, the latter model showed a significantly improved predictive performance, yielding a final area under the curve of .75 (95% CI = .63–.85; $p = .001$ vs. A, $p = .023$ vs. B).

3.3 | Prediction of post-cNORSE epilepsy

Serum samples were collected during SE in 74 surviving patients, of whom 52 (70%) had post-cNORSE epilepsy. Patients received a median of 4 (IQR = 2–5) ASMs during

TABLE 1 Clinical, paraclinical, and biological findings between patients with poor ($n = 49$) and good ($n = 43$) long-term outcomes.

Characteristic	Poor outcomes, $n = 49$	Good outcomes, $n = 43$	p, univariate logistic regression	Odds ratio [95% CI]	Spearman rho	Spearman p	p, multivariate logistic regression
Epilepsy post-cNORSE	26/30 (87%)	25/43 (58%)	.013	4.7 [1.5–18.0]	NA	NA	.26
Age, years	28 [19–45]	27 [19–49]	.68	NA	−.13	.22	NA
Sex, male	20 (41%)	18 (42%)	.92	.96 [.42–2.2]	NA	NA	NA
SE type, convulsive or nonconvulsive, number of convulsive	40 (82%)	33 (77%)	.56	.74 [.27–2.1]	NA	NA	NA
FIRES	38 (78%)	34 (79%)	.86	.91 [.33–2.5]	NA	NA	NA
Number of CIVADs during ICU	3 [3–4]	2 [2–3]	<.001	NA	−.53	<.001	.12
Number of ASMs during ICU	7 [6–9]	6 [4–8]	.016	NA	−.21	.042	.71
Number of immunotherapies during ICU	3 [2–4]	3 [2–4]	.19	NA	−.19	.073	NA
Second-line immunotherapy	28 (57%)	24 (56%)	.90	1.1 [.46–2.4]	NA	NA	NA
MRI cortical hyperintensity signal	34 (69%)	29 (67%)	.84	1.1 [.45–2.7]	NA	NA	NA
Brain atrophy	16 (33%)	11 (26%)	.46	1.4 [.57–3.6]	NA	NA	NA
ICU duration, days	50 [17–90]	33 [15–55]	.012	NA	−.17	.11	>.99
SE duration, days	31 [12–52]	13 [8–42]	.029	NA	−.24	.021	.42
Serum biological markers	–	–	–	–	–	–	–
IL-6, pg/mL	38.6 [20.4–93.6]	28.9 [13.3–61.3]	.18	NA	−.19	.087	NA
CXCL8, pg/mL	62.0 [31.9–177.3]	37.3 [17.6–66.5]	.068	NA	−.29	.0072	NA
CCL2, pg/mL	71.7 [36.5–134.5]	33.5 [18.0–72.9]	.069	NA	−.36	<.001	NA
MIP-1α, pg/mL	5.4 [2.1–10.8]	4.0 [1.3–7.3]	.91	NA	−.17	.12	NA
G-CSF, pg/mL	.58 [.16–2.49]	.52 [0–1.37]	.19	NA	−.18	.097	NA
IL-10, pg/mL	2.6 [1.2–3.7]	2.0 [.47–5.6]	.20	NA	−.05	.65	NA
IL-12p70, pg/mL	.33 [0–.90]	.50 [0–2.1]	.26	NA	.13	.22	NA
IL-1β, pg/mL	0 [0–.04]	0 [0–.13]	.85	NA	.082	.46	NA
IL-4, pg/mL	0 [0–.14]	0 [0–.33]	.31	NA	.083	.45	NA
TNFα, pg/mL	.23 [0–.97]	.25 [0–1.83]	.16	NA	.098	.37	NA
IL-17A, pg/mL	0 [0–.16]	0 [0–1.04]	.77	NA	.14	.23	NA
S100B, μg/L	.07 [.04–.15]	.06 [.03–.08]	.15	NA	−.11	.38	NA
NSE, μg/L	13.8 [11.0–19.7]	13.7 [10.4–19.8]	.51	NA	−.012	.92	NA
Progranulin, ng/mL	126.8 [93.6–199.6]	134.6 [92.5–180.5]	.74	NA	.028	.81	NA
NfL, pg/mL	209.6 [77.9–477.2]	73.3 [35.5–125.0]	.055	NA	−.41	<.001	NA

(Continues)

TABLE 1 (Continued)

Characteristic	Poor outcomes, $n = 49$	Good outcomes, $n = 43$	p, univariate logistic regression	Odds ratio [95% CI]	Spearman rho	Spearman p	p, multivariate logistic regression
CSF biological markers	–	–	–	–	–	–	–
IL-6, pg/mL	38.1 [15.6–283.6]	12.7 [7.3–38.8]	.074	NA	−.34	.0054	NA
CXCL8, pg/mL	109.5 [39.1–199.0]	31.0 [13.7–84.2]	.019	NA	−.40	.0012	.92
CCL2, pg/mL	882.6 [428.1–1582.5]	269.8 [99.3–637.4]	.0092	NA	−.53	<.001	.29
MIP-1α, pg/mL	3.0 [1.7–5.0]	1.1 [.3–2.2]	.016	NA	−.40	<.001	.71
G-CSF, pg/mL	1.1 [.34–5.2]	.18 [0–.46]	.30	NA	−.40	.0010	NA
IL-10, pg/mL	.29 [0–1.8]	.58 [.12–1.2]	.13	NA	.10	.42	NA
IL-12p70, pg/mL	0 [0–.075]	0 [0–.14]	.52	NA	.081	.53	NA
IL-1β, pg/mL	0 [0–0]	0 [0–0]	.30	NA	−.18	.16	NA
IL-17A, pg/mL	0 [0–0]	0 [0–.06]	.19	NA	.11	.41	NA
S100B, μg/L	1.0 [.68–1.7]	.77 [.58–1.2]	.34	NA	−.26	.99	NA
NSE, μg/L	68.3 [41.4–102.6]	18.7 [13.7–24.7]	.0013	NA	−.69	<.001	.74
Progranulin, ng/mL	6.9 [4.0–9.2]	3.2 [2.9–3.8]	.0028	NA	−.36	.014	.25
NfL, pg/mL	6879 [2013–19 286]	3232 [615–6898]	.097	NA	−.42	.0035	NA

Note: Values are represented as median [interquartile range] or n (%).

Abbreviations: ASM, antiseizure medication; CI, confidence interval; CIVAD, continuous anesthetic; cNORSE, cryptogenic new onset refractory SE; CSF, cerebrospinal fluid; FIRES, febrile infection-related epilepsy syndrome; ICU, intensive care unit; MRI, magnetic resonance imaging; NA, not applicable; NfL, neurofilament light chain; NSE, neuron-specific enolase; S100B, protein S100-beta; SE, status epilepticus.

follow-up. Among those with post-cNORSE epilepsy, all were drug-resistant. CSF samples were obtained in 47 patients, including 32 (68%) who developed post-cNORSE epilepsy.

When tested separately, several clinical and paraclinical features assessed during the acute phase of the disease were different in patients with post-cNORSE epilepsy and those without it. Notably, patients with febrile infection-related epilepsy syndrome (FIRES; i.e., those, who had a prior febrile illness)[1] were younger and more likely to develop post-cNORSE epilepsy (79% vs. 38%, OR = 6.4, 95% CI = 2.0–22.3, $p = .0024$) compared to non-FIRES. After adjustment for age, FIRES remained independently associated with post-cNORSE epilepsy (adjusted OR = 7.5, 95% CI = 1.5–45.6, $p = .018$). Additionally, patients who developed post-cNORSE epilepsy had a significantly longer SE duration (34 [IQR = 17–55] vs. 9 [IQR = 5–17] days, $p = .0025$) and ICU stay (57 [IQR = 33–88] vs. 20 [IQR = 13–42] days, $p = .0036$) than those without epilepsy. Patients with post-NORSE epilepsy also required more continuous anesthetics (3 [IQR = 2–4] vs. 2 [IQR = 2–3], $p = .040$), ASMs (8 [IQR = 6–9] vs. 4 [IQR = 4–6], $p < .001$), and lines of immunotherapies (3 [IQR = 3–4] vs. 2 [IQR = 1–3], $p = .0047$). Moreover, they were more frequently treated with at least one targeted immunotherapy (e.g., anakinra, tocilizumab, rituximab; 67% vs. 32%, OR = 4.4, 95% CI = 1.6–13.5, $p = .0065$). The first MRI was performed at a similar time after SE onset in patients with and without post-cNORSE epilepsy; however, patients who subsequently developed post-cNORSE epilepsy had their last MRI significantly later in the disease course (35 [IQR = 22–64] vs. 8 [IQR = 2–18] days, $p < .001$). Patients with post-cNORSE epilepsy had a higher prevalence of cortical hyperintensities on brain MRI (79% vs. 45%, OR = 4.5, 95% CI = 1.6–13.5, $p = .0061$) and brain atrophy (42% vs. 14%, OR = 4.6, 95% CI = 1.4–21.5, $p = .024$) compared to those who did not develop epilepsy. The timing of detection of acute cortical hyperintensities and atrophy after SE onset was similar between the two groups. In contrast, the two groups showed no significant differences in biological parameters. All results are presented in Table 2.

In the multivariate models, only the number of ASMs (OR 1.5, 95% CI = 1.06–2.37, $p = .038$), the SE duration (OR = 1.09, 95% CI = 1.01–1.19, $p = .037$), and the functional outcome during follow-up (OR = 14.1, 95% CI = 1.8–250.9, $p = .029$) remained independently associated with the development of post-NORSE epilepsy (Table 2).

The LASSO logistic regression analysis performed on biological biomarkers revealed low selection frequencies across variables, with the highest being serum MIP-1α (15.1%), followed by CXCL8 (5.4%) and IL-17A (5.1%). All other biomarkers were retained in fewer than 5% of samples. Given these low and inconsistent selection rates, no further multivariate model analysis was pursued for this outcome.

3.4 | Analysis of pathophysiological mechanisms of post-cNORSE epilepsy

For the second aim of the study, to elucidate the mechanisms underlying post-cNORSE epilepsy, we collected serum samples from 39 patients with post-cNORSE epilepsy after a median latency of 2.03 years (IQR = .94–6.08) following SE resolution. CSF samples were available in 12 patients, collected during the chronic phase after a median delay of 2.19 years (IQR = .42–5.38). Among patients explored during the chronic phase, 25 also had samples collected during SE (serum $n = 25$, CSF $n = 5$), allowing paired comparisons. Post-cNORSE patients had a median age of 28 years (IQR = 21–36), with 46% being female. Most patients experienced at least one seizure per week (24/38, 63%). At the time of chronic sample collection, they were receiving a median of 4 ASMs (IQR = 3–5) and had a median GOS-E of 5 (IQR = 4–6).

Biomarker levels were compared to those of (1) 20 patients with chronic immune-mediated encephalitis known to be associated with T-cell disturbances (i.e., 15 Rasmussen encephalitis, including 13 with CSF, and five GAD65 encephalitis, including three with CSF; median age = 24 years, IQR = 19–39); and (2) 40 patients with drug-resistant TLE-HS for serum only (median age = 45 years, IQR = 32–53; Figure 1).

3.5 | Comparison of biological features between acute and chronic phases

Serum samples were collected from 25 patients during the acute and chronic phases. The median interval between the two time points was 389 days (IQR = 186–788).

Overall, paired analyses demonstrated significant decreases in IL-6, IL-10, IL-1β, progranulin, and NfL. The IL-6 and NfL reductions have remained significant after correction for multiple comparisons (Table 3). When analyses were restricted to patients with abnormal cytokine levels during the acute phase,[6] significant decreases were observed for IL-6, G-CSF, IL-10, IL-1β, and IL-17A in the chronic phase (Table 3). Among these patients, normalization was observed frequently, occurring in 92% of cases for IL-10, 83% for IL-17A, and 81% for IL-6. The normalization occurred in all patients with initially abnormal levels of CCL2 and MIP-1α.

Despite the predominant trend toward normalization, five of 25 (20%) patients developed new abnormalities in the chronic phase, particularly for IL-17A ($n = 4$), IL-6,

TABLE 2 Clinical, paraclinical, and biological findings between patients with ($n = 52$) and without ($n = 22$) post-cNORSE epilepsy.

Characteristic	Post-cNORSE epilepsy, $n = 52$	Without post-cNORSE epilepsy, $n = 22$	p, univariate logistic regression	Odds ratio [95% CI]	p, multivariate logistic regression
Poor long-term outcomes	26/51 (51%)	4/22 (18%)	.013	4.7 [1.5–18.0]	.029
Age, years	26 [19–35]	42 [8–57]	.060	NA	NA
Sex, male (%)	25 (48%)	7 (32%)	.2	2.0 [.7–5.9]	NA
SE type, convulsive or nonconvulsive	41 (79%)	16 (73%)	.57	.72 [.23–2.37]	NA
FIRES	46 (88%)	12 (55%)	.0024	6.4 [2.0–22.3]	.077
Number of CIVADs during ICU	3 [2–4]	2 [2–3]	.040	NA	.10
Number of ASMs during ICU	8 [6–9]	4 [4–6]	<.001	NA	.038
Number of immunotherapies during ICU	3 [3–4]	2 [1–3]	.0047	NA	.96
Second-line immunotherapy	35 (67%)	7 (32%)	.0065	4.4 [1.6–13.5]	.49
MRI cortical hyperintensity signal	41 (79%)	10 (45%)	.0061	4.5 [1.6–13.5]	.45
Brain atrophy	22 (42%)	3 (14%)	.024	4.6 [1.4–21.5]	.90
ICU duration, days	57 [33–88]	20 [13–42]	.0036	NA	.11
SE duration, days	34 [17–55]	9 [5–17]	.0025	NA	.037
Serum biological markers	–	–	–	–	
IL-6, pg/mL	29.2 [17.7–70.8]	30.2 [18.7–52.1]	.69	NA	NA
CXCL8, pg/mL	42.0 [20.3–82.5]	37.5 [26.8–68.3]	.33	NA	NA
CCL2, pg/mL	42.1 [16.9–96.2]	43.8 [31.3–102.0]	.49	NA	NA
MIP-1α, pg/mL	4.7 [1.6–7.7]	5.0 [3.6–7.5]	.31	NA	NA
G-CSF, pg/mL	.43 [0–1.69]	.63 [.079–1.5]	.56	NA	NA
IL-10, pg/mL	2.5 [1.2–5.4]	.95 [.64–3.3]	>.99	NA	NA
IL-12p70, pg/mL	.34 [0–2.0]	.50 [.01–2.0]	.67	NA	NA
IL-1β, pg/mL	0 [0–.22]	0 [0–.10]	.34	NA	NA
IL-4, pg/mL	0 [0–.54]	0 [0–.24]	.80	NA	NA
TNFα, pg/mL	.17 [0–1.7]	.73 [0–1.8]	.67	NA	NA
IL-17A, pg/mL	.03 [0–.91]	0 [0–1.2]	.46	NA	NA
S100B, μg/L	.064 [.036–.13]	.054 [.045–.070]	.21	NA	NA
NSE, μg/L	14.5 [10.7–19.7]	13.9 [10.5–25.2]	.56	NA	NA
Progranulin, ng/mL	128.1 [91.0–201.0]	143.4 [102.2–178.1]	.39	NA	NA
NfL, pg/mL	91.0 [44.5–262.5]	88.5 [34.6–144.2]	.52	NA	NA

TABLE 2 (Continued)

Characteristic	Post-cNORSE epilepsy, $n=52$	Without post-cNORSE epilepsy, $n=22$	p, univariate logistic regression	Odds ratio [95% CI]	p, multivariate logistic regression
CSF biological markers	–	–	–	–	
IL-6, pg/mL	18.0 [7.1–45.5]	15.6 [7.4–56.6]	.58	NA	NA
CXCL8, pg/mL	41.0 [21.3–77.5]	84.2 [12.8–182.7]	.40	NA	NA
CCL2, pg/mL	436.1 [177.9–804.7]	269.8 [165.9–814.4]	.37	NA	NA
MIP-1α, pg/mL	1.9 [.67–4.1]	1.1 [.0094–2.2]	.15	NA	NA
G-CSF, pg/mL	.44 [0–1.6]	.39 [.11–.60]	.53	NA	NA
IL-10, pg/mL	.42 [.071–1.3]	.29 [.069–.71]	.34	NA	NA
IL-12p70, pg/mL	0 [0–.081]	0 [0–.11]	.77	NA	NA
IL-1β, pg/mL	0 [0–0]	0 [0–0]	.74	NA	NA
IL-17A, pg/mL	0 [0–0]	0 [0–0]	.41	NA	NA
S100B, μg/L	.63 [.55–.94]	1.0 [.72–1.3]	.86	NA	NA
NSE, μg/L	23.7 [16.4–47.5]	18.7 [9.6–27.5]	.24	NA	NA
Progranulin, ng/mL	3.4 [3.0–5.1]	3.7 [2.6–7.6]	.98	NA	NA
NfL, pg/mL	2599 [1836–5388]	5796 [603–7389]	.91	NA	NA

Note: Values are represented as median [interquartile range] or *n* (%).

Abbreviations: ASM, antiseizure medication; CI, confidence interval; CIVAD, continuous anesthetic; cNORSE, cryptogenic new onset refractory SE; CSF, cerebrospinal fluid; FIRES, febrile infection-related epilepsy syndrome; ICU, intensive care unit; MRI, magnetic resonance imaging; NA, not applicable; NfL, neurofilament light chain; NSE, neuron-specific enolase; S100B, protein S100-beta; SE, status epilepticus.

TABLE 3 Comparison of serum biological markers between the acute and chronic phases.

Marker	Acute phase	Chronic phase	*p*, paired Wilcoxon	*p*, paired Wilcoxon corrected	Median differences	Proportion of normalization, %	*p*, paired Wilcoxon, for abnormal values only	Median differences for abnormal values only
IL-6, pg/mL	36.1 [13.7–70.5]	3.2 [2.7–10.9]	<.001	<.001	−26.9	81.0% (17/21)	<.001	−37.6
CXCL8, pg/mL	31.3 [17.6–57.7]	14.8 [7.5–30.3]	.067	.17	−10.8	50.0% (3/6)	.094	−111.1
CCL2, pg/mL	40.1 [11.8–67.9]	63.0 [28.1–89.2]	.33	.44	16.3	100% (2/2)	Not applicable	−321.4
MIP-1α, pg/mL	2.5 [1.2–7.0]	3.4 [2.5–6.3]	.64	.69	0	100% (1/1)	Not applicable	−56.0
G-CSF, pg/mL	.45 [0–1.4]	.21 [0–.76]	.26	.38	−.0051	53.8% (7/13)	.027	−.69
IL-10, pg/mL	2.0 [.94–5.1]	.99 [.53–1.6]	.030	.097	−.85	91.7% (11/12)	.034	−3.90
IL-12p70, pg/mL	.31 [0–2.0]	0 [0–.45]	.19	.32	−.24	66.7% (6/9)	.13	−1.97
IL-1β, pg/mL	0 [0–.22]	0 [0–0]	.032	.097	0	80.0% (8/10)	.027	−.27
IL-4, pg/mL	0 [0–.11]	0 [0–0]	.18	.32	0	60.0% (3/5)	.63	−1.49
TNFα, pg/mL	.046 [0–1.8]	0 [0–.56]	.51	.64	0	55.6% (5/9)	.13	−1.84
IL-17A, pg/mL	.017 [0–.82]	0 [0–.24]	.090	.19	0	83.3% (5/6)	.031	−1.20
S100B, μg/L	.062 [.035–.093]	.053 [.03–.091]	>.99	>.99	0	–	–	–
NSE, μg/L	13.5 [10.4–17.4]	12.6 [10.2–15.0]	.65	.69	1.11	–	–	–
Progranulin, ng/mL	132.1 [106.9–183.4]	101.9 [90.4–116.4]	.028	.097	−41.3	–	–	–
NfL, pg/mL	84.5 [45.3–150.6]	14.4 [8.6–23.3]	.0013	.0095	−54.7	–	–	–

Note: Values are represented as median [interquartile range]. *p*-Values were obtained using paired Wilcoxon tests, with and without correction for multiple comparisons (Benjamini–Hochberg method). "Median differences" indicate the median change (chronic – acute) for all patients. "Proportion of normalization" corresponds to the percentage and number of patients whose abnormal values in the acute phase returned to the normal range during the chronic phase. For cytokines with at least five patients above the normal threshold in the acute phase, paired Wilcoxon tests and median differences were additionally calculated in this subgroup ("abnormal values only").

Abbreviations: NfL, neurofilament light chain; NSE, neuron-specific enolase; S100B, protein S100-beta.

IL-12p70, or TNFα ($n = 3$ each). Interestingly, these new disturbances predominantly involved markers of the adaptive immune system, except for IL-6, which is a mediator of innate immunity. The abnormalities were largely present in the same patients, with three or more cytokines elevated in three patients, and two cytokines elevated in two additional patients.

CSF samples were obtained from five patients during the acute and chronic phases, with a median interval of 161 days (IQR = 155–175) between collections. Innate-related cytokines normalized in most patients. However, after correction for multiple comparisons, no significant differences were observed in biomarker levels between the two phases. Only a trend toward decreased IL-6 levels was noted before correction ($p = .063$).

3.6 | Impact of collection delay and seizure frequency on biomarker levels

Spearman correlation analyses showed that longer delays between SE resolution and sample collection were significantly associated with lower levels of serum IL-10 (rho = −.478, $p = .0021$) and CSF IL-10 (rho = −.616, $p = .033$), IL-12p70 (rho = −.734, $p = .0065$), and NfL (rho = −.636, $p = .040$). In contrast, no significant associations were observed between serum or CSF biomarker levels and seizure frequency in post-cNORSE.

3.7 | Comparison of patients with post-cNORSE to chronic immune-mediated encephalitis and TLE-HS

Intergroup serum analyses revealed significant differences among the three patient groups for CCL2 ($p = .0053$), TNFα ($p = .046$), IL-17A ($p = .0027$), and NfL ($p = .0026$; Table 4). Notably, patients with post-cNORSE epilepsy had significantly lower levels of TNFα and IL-17A compared with patients with TLE-HS (TNFα: median = .020 [IQR = 0–1.04] vs. .44 [IQR = .13–1.11] pg/mL, $p = .020$; IL-17A: median = .0042 [IQR = 0–.24] vs. .31 [IQR = .15–.72] pg/mL, $p = .0012$). In contrast, they exhibited higher serum levels of CCL2 than TLE-HS patients (median = 53.5 [IQR = 27.9–77.5] vs. 22.5 [IQR = 7.8–42.0] pg/mL, $p = .0016$), although all these values remained within the normal range. No significant differences were observed for most cytokines involved in innate immunity (e.g., IL-6, CXCL8, G-CSF, IL-1β) among the three groups, and no patient exhibited elevated levels of all innate immunity markers during the chronic phase. Moreover, there were no significant differences in the proportions of patients with abnormal cytokine levels among the three tested groups.

In contrast, serum NfL levels were significantly higher in post-cNORSE patients compared with TLE-HS (median = 12.9 [IQR = 8.6–19.9] vs. 9.0 [IQR = 7.0–10.8] pg/mL, $p < .001$), despite the post-cNORSE group being significantly younger ($p < .001$). When age-adjusted normal values were considered, the proportion of elevated NfL levels differed significantly across groups (post-cNORSE: 64%, encephalitis: 45%, and TLE-HS: 20%; $p < .001$). No significant differences were observed in the duration of SE or ICU stay, nor in the number of continuous anesthetics or ASMs used for SE management, between patients with elevated NfL levels during the chronic phase and those without such elevations. Higher NfL levels correlated with worse chronic functional outcome (Pearson rho = −.375, $p = .019$).

No significant differences were observed between post-cNORSE and encephalitis patients for any serum or CSF biomarkers, either in absolute values or in the proportion of abnormal cytokine levels (Table 4). Unsupervised hierarchical clustering did not reveal distinct patient subclusters that separated the post-cNORSE, TLE-HS, and encephalitis groups (Figure 2). Instead, a heterogeneous and intermingled pattern was observed, suggesting substantial intragroup biological variability. Several factors may contribute to this intragroup heterogeneity, including the frequency of seizures, timing of biomarker sampling relative to the last seizure or initial injury, and prior or ongoing treatments. This underscores the potential relevance of further cluster-based analyses (Figure 2).

4 | DISCUSSION

Mechanisms underlying long-term disability and post-cNORSE epilepsy are unclear. In this study, we highlighted that several innate cytokines and brain injury biomarkers measured during SE were associated with long-term poor functional outcomes, whereas only clinical and MRI features were independently associated with the development of post-cNORSE epilepsy. Paired analyses between acute and chronic phases showed that innate cytokine levels largely normalized during chronic phase. However, new disturbances in adaptive immune-related cytokines were found in a few recovering patients.

Disturbances in innate immunity during cNORSE are well established. Previous studies have shown that elevated serum and CSF levels of innate cytokines are associated with worse short- and long-term functional outcomes,[5,6] whereas others have linked CSF cytokine elevations to a greater burden of MRI abnormalities and subsequent disabilities.[7] These findings correlate with

TABLE 4 Comparisons of serum and CSF levels among the three patient subgroups.

Marker	Post-cNORSE	Encephalitis	TLE-HS	*p*, Kruskal–Wallis test	*p*, Dunn test (serum) or Wilcoxon test (CSF, encephalitis vs. post-cNORSE)[a]	*p* by χ^2 or Fisher test for the proportion of abnormal values[a]
Serum biological markers	–	–	–	–	–	–
IL-6, pg/mL	3.1 [1.8–8.6]	3.1 [1.4–4.4]	2.6 [1.5–5.2]	.63	–	.68
CXCL8, pg/mL	14.1 [7.3–27.2]	11.5 [7.6–17.9]	15.2 [7.8–20.8]	.81	–	.38
CCL2, pg/mL	53.5 [27.9–77.5]	45.0 [10.4–96.1]	22.5 [7.8–42.0]	.0053	Encephalitis vs. post-NORSE: .52 Encephalitis vs. TLE-HS: .052 Post-NORSE vs. TLE-HS: .0016	.27
MIP-1α, pg/mL	3.3 [2.3–6.4]	3.1 [2.3–5.0]	3.9 [1.5–7.5]	.66	–	.38
G-CSF, pg/mL	.19 [0–.61]	.37 [.19–.67]	.51 [.14–.99]	.15	–	.26
IL-10, pg/mL	.70 [.29–1.3]	.60 [.28–.74]	.57 [.28–.79]	.30	–	.26
IL-12p70, pg/mL	.087 [0–.62]	.45 [.10–1.2]	.40 [.042–.73]	.069	–	.098
IL-1β, pg/mL	0 [0–0]	0 [0–0]	0 [0–.0055]	.27	–	.22
IL-4, pg/mL	0 [0–0]	0 [0–0]	0 [0–0]	.32	–	.68
TNFα, pg/mL	.02 [0–1.04]	.69 [.0057–1.6]	.44 [.13–1.11]	.046	Encephalitis vs. post-NORSE: .082 Encephalitis vs. TLE-HS: .87 Post-NORSE vs. TLE-HS: .020	.86
IL-17A, pg/mL	.0042 [0–.24]	.042 [0–.42]	.31 [.15–.72]	.0027	Encephalitis vs. post-NORSE: .76 Encephalitis vs. TLE-HS: .017 Post-NORSE vs. TLE-HS: .0012	.43
S100B, μg/L	.053 [.03–.093]	.06 [.04–.10]	.042 [0–.08]	.12	–	–
NSE, μg/L	13.7 [11.0–19.0]	14.0 [12.7–19.9]	13.9 [11.3–15.9]	.54	–	–
Progranulin, ng/mL	104.6 [90.9–119.1]	97.9 [90.2–119.6]	100.5 [83.0–129.5]	.90	–	–
NfL, pg/mL	12.9 [8.6–19.9]	10.7 [7.5–19.0]	9.0 [7.0–10.8]	.0026	Encephalitis vs. post-NORSE: .16 Encephalitis vs. TLE-HS: .16 Post-NORSE vs. TLE-HS: <.001	<.001 (age-corrected)
CSF biological markers	–	–	–	–	–	–
IL-6, pg/mL	4.6 [2.8–5.6]	6.3 [5.0–9.2]	–	–	.25	>.99
CXCL8, pg/mL	6.3 [3.3–9.6]	11.8 [7.6–16.8]	–	–	.27	>.99
CCL2, pg/mL	238.6 [206.9–313.9]	226.2 [175.9–285.9]	–	–	.60	>.99
MIP-1α, pg/mL	.064 [0–.39]	.46 [.20–.77]	–	–	.25	.96
G-CSF, pg/mL	0 [0–0]	0 [0–.0053]	–	–	.65	.96
IL-10, pg/mL	.0037 [0–.17]	.086 [0–.15]	–	–	.82	>.99

TABLE 4 (Continued)

Marker	Post-cNORSE	Encephalitis	TLE-HS	*p*, Kruskal–Wallis test	*p*, Dunn test (serum) or Wilcoxon test (CSF, encephalitis vs. post-cNORSE)[a]	*p* by χ^2 or Fisher test for the proportion of abnormal values[a]
IL-12p70, pg/mL	0 [0–.0042]	0 [0–0]	–	–	.70	.96
IL-1β, pg/mL	0 [0–0]	0 [0–0]	–	–	>.99	.96
IL-17A, pg/mL	0 [0–0]	0 [0–0]	–	–	.38	>.99
S100B, μg/L	.63 [.53–.73]	.70 [.54–.95]	–	–	.70	–
NSE, μg/L	10.5 [9.0–12.7]	15.1 [11.7–19.7]	–	–	.27	–
Progranulin, ng/mL	2.4 [2.2–2.6]	2.2 [2.1–2.8]	–	–	.70	–
NfL, pg/mL	194 [128.5–705]	154.5 [117.5–301.2]	–	–	.70	–

Note: Values are represented as median [interquartile range].

Abbreviations: cNORSE, cryptogenic new onset refractory status epilepticus; CSF, cerebrospinal fluid; NfL, neurofilament light chain; NSE, neuron-specific enolase; S100B, protein S100-beta; TLE-HS, temporal lobe epilepsy with hippocampal sclerosis.

[a]The *p*-values have been adjusted for multiple comparisons with the Benjamini–Hochberg procedure.

findings from animal models of SE, showing increased neuronal damage in the setting of monocyte infiltration.[22] However, variations in cytokine profiles have been observed in cNORSE, and even patients with no specific sign of inflammation can have poor long-term outcomes.[5] In this study, we confirmed that elevated serum CXCL8 and CCL2, as well as CSF IL-6, CXCL8, CCL2, MIP-1α, and G-CSF, were associated with poor long-term outcomes. Elevated levels of innate immune proinflammatory cytokines likely reflect dysregulation of innate immune pathways and may contribute to sustained excitability and long-term consequences.[23] Such immune signatures were previously suspected to underlie the disease mechanism in a subset of patients with cNORSE, particularly those classified within cluster B, and may support the use of anakinra or tocilizumab.[5] We further demonstrated the prognostic value of NfL. Specifically, we show that adding NfL to cytokine profiles improved the predictive performance of the model for cNORSE long-term prognosis. The prognostic role of serum NfL in SE has been previously described, with higher levels associated with worse 30-day outcomes.[13,14] More recently, elevated NfL levels in NORSE have also been shown to correlate with MRI abnormalities and functional outcomes.[24] Consistent with prior studies, we found that patients with higher CSF NSE and progranulin levels had worse long-term outcomes,[12] supporting the notion that the extent of acute brain injury critically shapes recovery potential, as has also been observed with NSE following cardiac arrest or head injury.[25,26] Several factors may influence biomarker levels, including disease duration or treatments received. In this cohort, longer SE duration before sample collection was associated with higher serum levels of most biomarkers, whereas lower levels of several CSF proinflammatory cytokines were observed. These divergent patterns between serum and CSF may reflect compartment-specific inflammatory dynamics or different responses to immunotherapies. Second-line immunotherapies have been reported to exert differential effects on peripheral versus central inflammatory markers.[27,28] Controlled experimental models are needed to further distinguish the treatment effect from disease-related inflammatory responses. To our knowledge, no prior study has investigated the prognostic relevance of combining immune and injury biomarkers in cNORSE, despite growing interest in multimodal biomarker approaches in critical care patients.[12,29] In this context, longitudinal biomarker profiling may ultimately enable a more personalized therapeutic approach, in which immune signatures guide immunotherapies, and the combination of inflammatory biomarkers with injury markers informs prognosis. In contrast to prior studies reporting

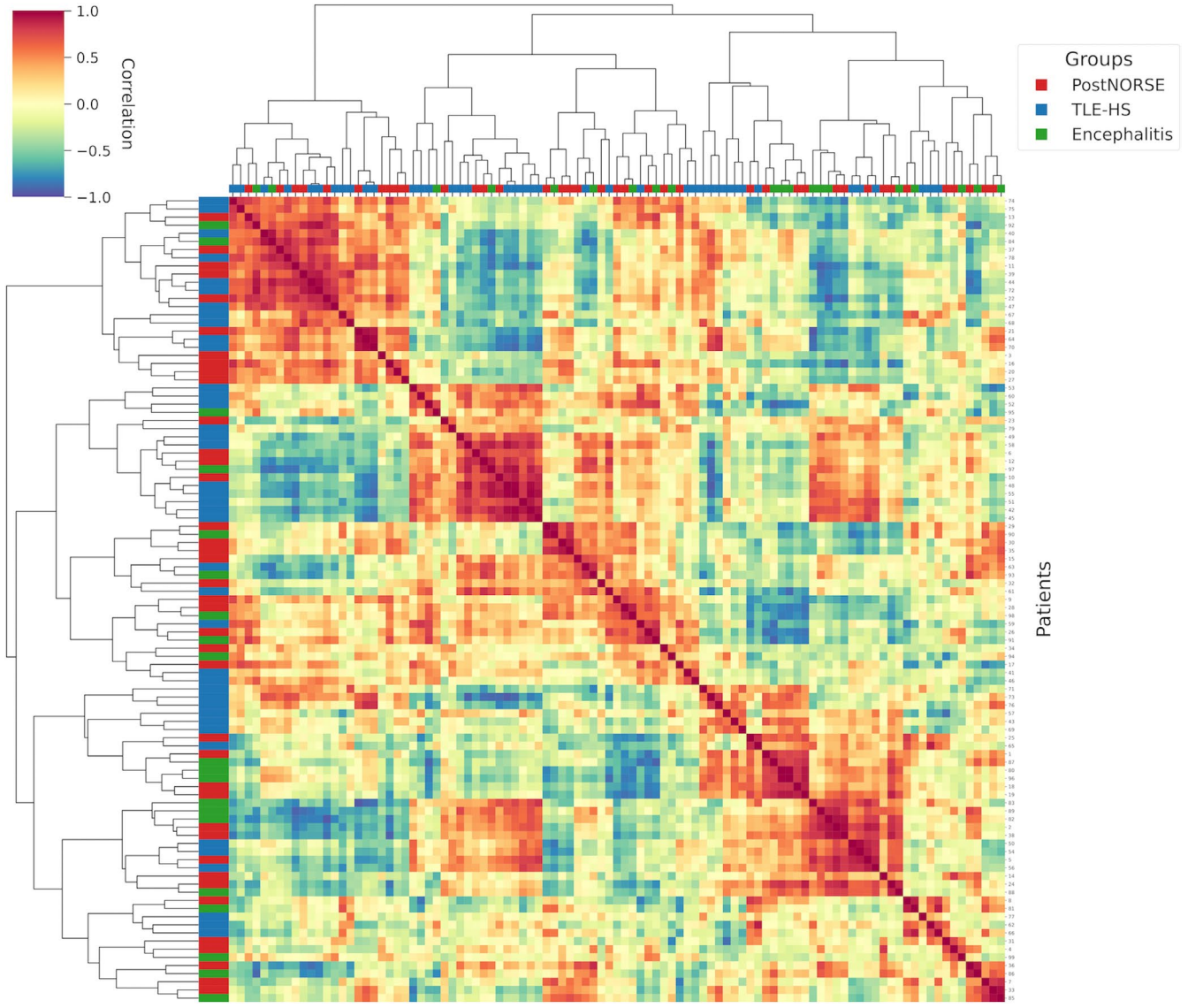

FIGURE 2 Heatmap from serum biological biomarkers in patients with chronic post-new onset refractory status epilepticus (NORSE) epilepsy, encephalitis, and temporal lobe epilepsy with hippocampal sclerosis (TLE-HS). Data were first standardized for each variable (z-scored) before computing the Pearson correlation between patients (see heatmap matrix). Hierarchical clustering of patients (shown on the left and top of the matrix) was performed using the complete-linkage method.

associations between biological biomarkers, MRI abnormalities, and clinical outcomes,[7,24] MRI findings in this study were not associated with long-term outcomes. One possible explanation is that MRIs are sometimes performed before biospecimen collection, which may have precluded the detection of the downstream impact of neuronal injury captured by biological biomarkers on neuroimaging. In this context, biomarkers may reflect acute inflammatory and neuronal injury processes whose structural consequences are not yet visible on early MRIs. Further analyses using MRIs obtained after hospital discharge are warranted to allow a more delayed assessment of structural brain changes and their relationship with long-term outcomes. Another possible explanation is that we are assessing long-term functional outcomes that do not merely reflect brain injury and can be negatively impacted by post-ICU neuropathy.

Inflammation has been described as a key mechanism of epileptogenesis, with several proinflammatory cytokines known to increase neuronal excitability.[16] This raises the question of whether immune disturbances during cNORSE could exert a proepileptogenic effect, thereby contributing to post-cNORSE epilepsy. Although we have previously reported a higher prevalence of post-cNORSE epilepsy in patients with marked innate immune disturbances during the acute phase of NORSE,[5] acute cytokine levels were not significantly associated with the development of post-cNORSE epilepsy

in this study. Similarly, acute-phase brain injury biomarkers were not predictive of post-cNORSE epilepsy, although serum NSE has been suggested as a potential biomarker to assess the risk of seizure recurrence.[30] These findings suggest that circulating biomarkers may primarily reflect disease severity and functional outcome rather than mechanisms directly involved in epileptogenesis. However, the prevalence of post-cNORSE epilepsy in our cohort might have differed if we had performed subgroup analysis based on biomarker levels, given the well-recognized biological heterogeneity among these patients. In contrast, we found that patients with cortical hyperintensities or brain atrophy on MRI were more likely to develop post-cNORSE epilepsy, highlighting the relevance of longitudinal imaging in this condition, where reversible imaging findings were previously described.[31,32] These findings suggest that chronic epilepsy in cNORSE may arise less from acute inflammatory events than from the sequelae of brain injury. In this framework, inflammation may act as a permissive factor, whereas structural injury represents the final common pathway leading to epilepsy. This is consistent with the temporal dynamics of cNORSE, with the MRIs frequently unremarkable early in the course, but evolving toward structural changes over days to weeks, reflecting cumulative tissue damage.[24,33–36] Capturing this temporal dynamic with biological markers is challenging and would require repeated, longitudinal measurements, with integration of cumulative exposure rather than reliance on a single early measurement. Unfortunately, our retrospective, multicenter design did not allow for such analyses, highlighting an important limitation of current biomarker studies. Taken together, these findings suggest that the biological determinants of long-term functional outcomes and post-cNORSE epilepsy only partially overlap. Although inflammatory and brain injury biomarkers appear to capture the severity of acute insult and its systemic consequences, which are not necessarily reflected on MRI, the development of post-cNORSE epilepsy may depend more specifically on the presence and extent of structural brain injury.

Patients with poor long-term outcomes were more likely to develop post-cNORSE epilepsy (OR = 4.7), and the presence of poor long-term outcomes was an independent factor associated with the development of post-cNORSE epilepsy in our multivariate model. The association between post-cNORSE epilepsy and poor long-term functional outcomes emphasizes the urgent need to better manage chronic epilepsy. Improving seizure control may represent a key lever to reduce disability, limit psychosocial burden, and improve quality of life for patients and their families.[3,37] One of the most frequent questions arising for the management of post-cNORSE epilepsy is the relevance of continuing immunotherapies, due to possible reemergence of immune disorders in the case of chronic post-cNORSE epilepsy. Here, we observed a normalization of the levels of most proinflammatory innate cytokines during the chronic phase when compared to the acute phase. Similarly, patients with post-cNORSE epilepsy did not present with higher innate immunity cytokines compared to controls. Although innate central nervous system (CNS) cells, including astrocytes and microglia, are thought to contribute to hyperexcitability, the absence of a specific inflammatory signature in chronic cNORSE argues against prolonged treatment with immunotherapies targeting the innate immunity, such as anakinra or tocilizumab.[38,39] In the literature, only a few patients were treated with these treatments for chronic post-cNORSE epilepsies.[20,21] The authors reported a beneficial effect for four of the six cases, with 20%–50% reduction in seizure frequency. However, similar reductions were reported in drug-resistant epilepsy patients with newer ASMs, or non-pharmacological therapies.[40–42]

Interestingly, some patients developed adaptive immune signatures, with elevated serum levels of IL-12p70, IL-17A, and TNFα. This raises the question of the conversion between innate and adaptive immune disturbances.[43] However, levels of adaptive immune cytokines were lower than those of patients with TLE-HS. No significant elevation was observed in patients with chronic immune-related conditions, despite the known role of T-cells in both Rasmussen and GAD65 encephalitis; however, most of these patients received targeted immunotherapies.[44,45] Infiltration of lymphocytes in the CNS has been reported in multiple epileptic disorders, including autoimmune encephalitis, focal cortical dysplasia, and cortical tubers.[46] In TLE-HS, T-cell infiltration was found to correlate with neuronal loss and seizure frequency.[47,48] A T-cell cluster was observed using single-nuclei RNA sequencing in some patients with cNORSE.[49] Although this mechanism seems to concern only a few patients, it offers new therapeutic options, because reducing T-cell infiltration in other conditions was found to reverse cognitive deficits.[50] In NORSE, T-cell therapies have been rarely used, although limited reports suggest that they may be effective in shortening SE duration and reducing the risk of subsequent post-NORSE epilepsy.[51–54] To date, only one case report has described the use of cyclophosphamide in a patient with post-NORSE epilepsy due to vasculitis, with a dramatic response[55]; however, there are no data available on cryptogenic NORSE cases. Nonetheless, these agents are used in the management of chronic dysimmune encephalitis associated with drug-resistant epilepsy and could therefore be considered in selected NORSE cases.[56–59] In addition, JAK–STAT inhibitors warrant discussion as

potential therapeutic options in chronic post-cNORSE epilepsy, given their ability to suppress Th1- and Th17-mediated immune responses.[60,61]

Patients with post-cNORSE epilepsy had higher levels of NfL compared to controls, with elevated levels correlating with poor outcomes. Given that chronic samples were collected at a median of 2.03 years after SE resolution, these persistent elevations cannot be solely attributed to acute increases. Additionally, there were no significant differences in the duration of SE or ICU stay, or in the number of treatments used for SE management between patients with chronic abnormal NfL levels and those without elevation, arguing against a difference in the SE severity. Similarly, levels did not correlate with chronic seizure frequency, arguing against seizure-induced elevations. These findings suggest that patients with chronic post-cNORSE epilepsy may have sustained neuroaxonal injury. Additional factors, such as psychiatric comorbidities or neurocognitive symptoms, may also contribute to elevated NfL levels in some patients.[62,63] Depression is frequently reported among NORSE survivors, even more than 2 years after SE resolution.[37] Elevated NfL levels have also been described in patients with ICU-acquired weakness[64]; however, systematic data on peripheral neuropathy were not available for all patients at the time of sample collection and therefore could not be analyzed. No significant differences were observed for other brain injury biomarkers, reinforcing the previously reported superiority of NfL as a predictor of long-term functional outcomes.[65]

This is the first study to investigate the added value of combining inflammatory and brain injury biomarkers for predicting cNORSE outcomes. However, biomarkers were measured at a single time point, which prevented us from assessing their longitudinal dynamics. Patients were enrolled across 37 centers over more than 10 years. During this period, treatment practices evolved toward a more frequent use of second-line immunotherapies,[8] some of which are likely to influence inflammatory biomarker levels.[66,67] It remains challenging to determine whether elevated biomarker levels reflect delayed or insufficient treatment, the effects of second-line immunotherapies, greater disease severity, or underlying pathophysiological mechanisms. In addition, the high number of centers limited our ability to assess center-specific effects, and residual center- or time-related variability cannot be excluded. Daily ictal burden was not available for all patients, which precluded us from investigating the impact of daily seizures on biomarker levels. In addition, samples were not collected at the same time point for all patients, with most being obtained after 24 h and the administration of a first-line immunotherapy, which may have introduced bias related to delayed sampling on biomarker levels and precluded us from conducting subgroup analysis on early collected samples. Moreover, CSF samples were not available for all patients, limiting our ability to include CSF biomarkers in multivariate models. Despite the relatively large cohort size for such a rare condition, patients showed heterogeneity in seizure type and frequency, as well as in the interval between sample collection and the last seizure. Additionally, the enrolled patients likely represent among the most severe cNORSE cases, as centers typically contact biorepositories when seeking guidance for managing superrefractory or prolonged superrefractory cases. Because of the retrospective and multicenter design of the study, MRI methodology was not standardized across patients, and detailed acquisition parameters were not always reported. Nevertheless, most MRIs included T2-weighted and fluid-attenuated inversion recovery sequences, which are the most relevant for detecting SE-related signal abnormalities. No pre-SE imaging was available, precluding definitive exclusion of preexisting abnormalities; however, imaging did not reveal structural lesions or alternative etiologies that could explain SE onset, and observed abnormalities were considered consistent with seizure-related changes. In addition, MRI timing varies across patients, and follow-up imaging was not systematically performed, raising the possibility that abnormalities may have been missed in some cases. These limitations should be considered when interpreting the prognostic value of MRI findings. The post-cNORSE group may also represent the most severe cases, as patients with milder forms or without post-cNORSE epilepsy were less likely to be followed long-term at our reference centers. We cannot rule out that some patients had some type of infection or postinfectious exacerbation when samples were collected. Additionally, heterogeneity was also observed within the control groups, highlighting the need for further cluster-based analyses incorporating a broader panel of biomarkers. In this study, we aimed to investigate the outcomes at 6–12 months, and post-cNORSE samples were collected after a median of 2 years; this represents an important step in predicting outcomes. However, families sometimes report that patients, especially children, initially improved but then regressed over the years, with progressive atrophy.[36] Additional studies should follow patients for years to assess long-term outcome evolution. Moreover, additional studies should investigate the mechanisms underlying sustained neuroaxonal injury in these patients and how to prevent it.

5 | CONCLUSIONS

Taken together, these findings suggest that combining cytokines with NfL may support risk stratification and trial design for long-term outcomes. Moreover, post-NORSE

epilepsy may be less the consequence of persistent inflammatory activation and more a downstream effect of sustained neuronal injury. This interpretation does not exclude a role for inflammation in post-cNORSE epilepsy but rather points to its indirect contribution to ictogenesis. Future studies should aim to disentangle these pathways by combining high-frequency biomarker monitoring, advanced neuroimaging, and longitudinal clinical follow-up.

AUTHOR CONTRIBUTIONS

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interests. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

Anonymized data will be made available upon request from any qualified investigator.

ETHICS STATEMENT

We identified eligible patients for inclusion from the following sources: (1) NORSE multicenter study and NORSE/FIRES biorepository at Yale (IRB #1511016840 and #2000031611); and (2) Pitié-Salpêtière Hospital in Paris, France (Assistance Publique Hôpitaux de Paris (AP-HP), COLETTE, and Institut National de la Santé et de la Recherche Médicale (INSERM), TIPI). The local governing committee for human subject research for each participating center approved the study.

CONSENT TO PARTICIPATE

Patients or relatives were informed and gave their consent.

CODE AVAILABILITY

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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