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CASE SERIES

Neurofilament light chain in serum of cancer patients with acute neurological complications

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ABSTRACT

Aim: Neurofilament light chain (NfL) is a nonspecific sensitive biomarker of axonal damage.
Methods: This case series identified cancer patients with neurological complications who had serum NfL measurements and paired these results to outcomes.
Results: NfL serum levels were available in 15 patients with hematological malignancies or solid tumors. The neurological complications studied were immune effector cell–associated neurotoxicity syndrome, immune checkpoint inhibitor–related encephalopathy, anoxic brain injury, Guillain-Barre syndrome, hemophagocytic lymphohistiocytosis, transverse myelitis, paraneoplastic syndrome, central nervous system demyelinating disorder and chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids. All patients but one with serum NfL >900 pg/ml died during hospitalization.
Conclusion: Serum NfL levels consistently corresponded to death, disease severity or recovery in this series.

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cancer; central nervous system; Neurofilament light chain; neurotoxicity; peripheral nervous system

1. Introduction

Neurofilament light chain is a cytoplasmic protein that functions to maintain the axonal cytoskeleton. It is a nonspecific marker of axonal damage [1]. Longitudinal measurements of serum NfL levels have been shown to correlate with the disease course in multiple sclerosis, traumatic brain injuries, ischemic infarcts, motor neuron disease and dementia [2–5]. In oncology, the role of NfL in patients with paclitaxel induced peripheral neuropathy [6–9], metastasis in the central nervous system (CNS) [9,10] and in immune effector cell neurotoxicity syndrome (ICANS) is under investigation and has been previously described [8]. Beyond these specific conditions, the significance -if any- of NfL in cancer patients with acute, serious neurological illness from the primary tumor or as a therapy adverse effect is unknown. This study emphasizes the importance of NfL as a significant indicator of global neurological dysfunction in cancer patients and can help to prognosticate patients, predict severity of disease and or potential outcomes, prompt further work up and guide treatment.

We describe 15 cancer patients with acute and severe neurological complications who had NfL serum measurements during workup and follow-up. We paired NfL levels to their hospital outcome (death or recovery).

2. Patients & methods

This was a case series at The University of Texas-M.D. Anderson Cancer Center and included patients older than 16 years with any cancer diagnosis admitted due to an acute neurological illness and available NfL data. The study was approved by the institutional review board with waiver of patient consent. Fifteen patients met the selection criteria. We extracted the clinical, laboratory and demographic data from the electronic medical records. The serum samples were collected during hospitalization or at follow-up appointments and sent to a single outside facility for digital immunoassay of NfL levels with a Quanterix Simoa HD-X automated immunoassay analyzer (Quanterix Corp., MA, USA) using the Single-Molecule Assay (SiMoA) technique (https://www.quanterix.com/wp-content/uploads/2023/03/2023_SP-X-Brochure-download-version.pdf). Serum NfL values vary by age and to a lesser degree, gender. It has been well established that cerebrospinal fluid NfL increases by age, and only more recently have age depen-

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dent reference values been established in serum [10]. The reference values used in this study are based on the reference values per the facility where the tests were analyzed.

2.1. Statistical analysis

This report only included descriptive analysis because it does not have enough data for hypothesis testing and inference. We paired the NfL serum levels with hospital outcomes for all patients. For the five cases with serial data, we quantified the slope of increasing or decreasing values with linear regression and the R^2 value to represent proximity to a linear regression fit.

3. Results

3.1. Age & primary diagnosis

The mean age of the group was 56.5 years. The primary diagnoses were diffuse large B cell lymphoma (n = 3), myeloma (n = 2), melanoma (n = 2), metastatic renal cell carcinoma (n = 1), oropharyngeal carcinoma (n = 1), squamous cell carcinoma of the tongue and glottis (n = 1), acute myeloid leukemia (n = 1), colon cancer (n = 1), myelofibrosis (n = 1), peripheral T cell lymphoma (n = 1) and Burkitt's lymphoma (n = 1) (Table 1).

3.2. Individual case reports

3.2.1. Patient 1

A 78-year-old with diffuse large B cell lymphoma, germinal center type treated with axicabtagene ciloleucel after failure with R-CHOP. One day following administration, the patient developed grade 1 cytokine release syndrome (CRS), with improvement and discharge on day 7. The patient was readmitted on day 9 with fever and grade 2 CRS and was treated with tocilizumab and steroids. The symptoms progressed to grade 3 ICANS on days 11 to 13, with improvement after 20 mg of dexamethasone IV every 6 hours. An electroencephalogram (EEG) showed nonconvulsive status epilepticus that responded to lorazepam and levetiracetam. Clinical improvement was not seen until day 14. The repeat EEG, a brain magnetic resonance imaging scan (MRI) and cerebrospinal fluid (CSF) analysis results were normal. NfL levels on day 15 were 42.42 pg/ml (normal <37.9 pg/ml) and the patient was discharged on day 20. Repeat value on day 28 was 35.5 pg/ml (Supplementary Image S1).

3.2.2. Patient 2

A 35-year-old with diffuse large B cell lymphoma treated with axicabtagene ciloleucel. The patient developed grade 1 cytokine release syndrome (CRS) 4–6 days later and grade 3 ICANS on day 7. The patient received tocilizumab on day 5 and 6 in additional to high dose steroids for the remainder of the hospitalization. An EEG showed nonconvulsive status epilepticus which responded to lorazepam and levetiracetam, with immediate improvement in mental status and resolution of ICANS. The NfL level on day 9 was <3 pg/ml (normal <11.4 pg/ml). Repeat EEG and MRI results were normal. The patient was discharged on day 11, with continued clinical improvement (Supplementary Image S2).

3.2.3. Patient 3

A 59-year-old with relapsed/refractory multiple myeloma who received ciltacabtagene autoleucel, admitted 13 days later with fever, hyponatremia (Na^+ 129 mEq/L) and confusion. A brain MRI was consistent with posterior reversible encephalopathy syndrome (PRES). The patient was discharged on day 21 with no ICANS; NfL level following discharge was 188 pg/ml (normal <20.8 pg/ml). The patient was without significant symptoms at the 2-month clinic follow-up; however, the NfL level remained elevated was 437 pg/ml. On day 73, the patient was transferred from an outside hospital with delirium, aphasia and visual neglect despite treatment with high-dose steroids. A repeat MRI showed worse FLAIR signal in the left occipital lobe that extended anteriorly and crossed the midline at the splenium and right cerebellum. The CSF viral tests showed confirmed human polyoma virus 2. Serum NfL levels on admission were 490 pg/ml. Despite treatment with intravenous immunoglobulin and cryopreserved BK virus–specific T cells (R3), the patient worsened and NfL levels increased (952 pg/ml). The patient transitioned to hospice care and died (Supplementary Image S3).

3.2.4. Patient 4

A 62-year-old with melanoma and brain metastases treated with nivolumab and ipilimumab was admitted with confusion and neck stiffness. An EEG showed mild generalized slowing with periodic waves. The CSF showed a borderline WBC (= 7/mm^3, 98% lymphocytes) and elevated protein (81 mg/dl). Subsequently, the patient developed adrenal insufficiency. Creatine kinase was 1084 U/l (normal 38–308 U/l), aldolase 5.9 U/l (normal <7.7 U/l), total cortisol 2.83 mcg/dl (normal 4.8–19.5 mcg/dl) and ACTH <2 pg/ml (normal 7–63 pg/ml). Clinically, the patient had mild weakness and remained independent. Electromyography (EMG) showed mild generalized myopathy, with minimal irritable features. The patient was treated with high-dose steroids and plasma exchange. After two sessions of plasma exchange and 5 days of high-dose steroid treatment, the NfL level was 552 pg/ml (normal <28 pg/ml). Serum and CSF paraneoplastic antibody panels and oligoclonal bands were negative. The patient recovered fully, with normaliza-

Table 1. The table depicts the 15 patients studied.

Patient no.	Age (years)	Sex	Primary cancer	Neuro-oncological diagnosis	NfL initial value	Follow-up NfL	Reference range	Outcome	Proposed utility
1	78	Female	Diffuse large B cell lymphoma	ICANS grade 3	42.2 pg/ml,	(+2 wks) 35.5	<37.9 pg/ml	Symptoms improved	ICANS grade follow-up
2	35	Male	Diffuse large B cell lymphoma	ICANS grade 3	<3.0 pg/ml	None	<11.4 pg/ml	Symptoms improved	ICANS grade follow-up
3	59	Female	Refractory and relapsed multiple myeloma	ICANS grade 3, PML	188.0 pg/ml	(+5 wks) 437.0 (+2.5 wks) 490.0 (+2 wks) 952.0	<20.8 pg/ml	Died	ICANS grade follow-up, needing additional work-up
4	62	Male	Melanoma	ICI-induced encephalopathy and endocrine myopathy +/- mild myositis	552.0 pg/ml	None	<28.0 pg/ml	Symptoms improved	Diagnostic utility in ICI-induced encephalitis, with negative paraneoplastic Abs and follow-up
5	57	Female	Metastatic renal cell carcinoma	ICI-induced encephalopathy	>1500.0 pg/ml	None	<20.8 pg/ml	Died	Diagnostic utility in ICI-induced encephalitis, with negative paraneoplastic Abs and prognosis
6	63	Female	Malignant melanoma	ICI-induced vasculitis with multiple cranial neuropathies	124.0 pg/ml	None	<28.0 pg/ml	Symptoms resolved	Diagnostic utility in ICI-induced vasculitis and follow-up
7	80	Male	Oropharyngeal carcinoma	Cardiac arrest	124.0 pg/ml	None	<51.2 pg/ml	Mental status improved but died from acute respiratory failure	Prognosis after cardiac arrest
8	66	Male	Squamous cell carcinoma of tongue/glottis	Cardiac arrest	>1500.0 pg/ml	None	<28.0 pg/ml	Died	Prognosis after cardiac arrest
9	74	Male	Light chain myeloma	Guillain-Barre syndrome	1310.0 pg/ml	None	<37.9 pg/ml	Died	Follow-up and prognosis in Guillain-Barre syndrome
10	16	Male	Acute myeloid leukemia	Transverse myelitis	>1500.0 pg/ml	None	Not established for patients <20 years old	Died	Follow-up and prognosis in transverse myelitis
11	22	Male	Diffuse large B cell lymphoma	Hemophagocytic lymphohistiocy-tosis	327.0 pg/ml	(+5 wks) 163.0 (+4 wks) 136.0 (+3 wks) 91.5 (+7 wks) 38.9 (+5 wks) 26.1 (+8.5 wks) 22.3 (+4.5 wks) 19.2	<8.4 pg/ml	Symptoms improved	Follow-up and prognosis in hemophagocytic lymphohistiocy-tosis

It lists the patients in numerical order as in the manuscript and provides information on age, sex, primary cancer, neuro-oncological diagnosis, NfL initial values, NfL follow-up values, NfL reference ranges based on age, patient outcome and the proposed utility of NfL measurement in that subset of patients.

Follow-up: (+) indicates time since previous NfL serum test, wks (weeks).

AMAN: Acute motor axonal neuropathy; CLIPPERS: Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroid; CNS: Central nervous system; ICAN: Immune effector cell neuro-toxicity syndrome; ICI: Immune checkpoint inhibitor; PML: Progressive multifocal leukoencephalopathy; PNS: Peripheral nervous system.

Table 1. The table depicts the 15 patients studied. (cont.).

Patient no.	Age (years)	Sex	Primary cancer	Neuro-oncological diagnosis	NfL initial value	Follow-up NfL	Reference range	Outcome	Proposed utility
12	45		Colon cancer	Paraneoplastic syndrome	68.9 pg/ml	(+17 wks)15.3 (+17 wks) 11.4	<15.4 pg/ml	Symptoms stabilized	Follow-up and prognosis in paraneoplastic conditions
13	70	Female	Myelofibrosis	Demyelinating central nervous system disease not otherwise specified Toxic/Metabolic encephalopathy with status epilepticus, quadriplegia, AMAN	417.0 pg/ml	None	<28.0 pg/ml	Symptoms improved Mental status improved (tracking and nodding). Upper extremity motor strength minimal improvement	Follow-up and prognosis in demyelinating disease Follow-up and prognosis in status epilepticus and anoxic brain injury & ICU neuromyopathy/axonal GBS. Elevated titers can be from CNS + PNS
14	55	Male	Peripheral T Cell Lymphoma		>1500 pg/ml	(+3 wks) >1500	<20.8 pg/ml		
15	65	Male	Burkitt's lymphoma	Transverse myelitis CLIPPERS	239 pg/ml	(+3 wks) 123 (+12 wks) 38.1	<28.0 pg/ml	Improvement of motor strength, improved gait	Follow-up and recovery in transverse myelitis and CLIPPERS

It lists the patients in numerical order as in the manuscript and provides information on age, sex, primary cancer, neuro-oncological diagnosis, NfL initial values, NfL follow-up values, NfL reference ranges based on age, patient outcome and the proposed utility of NfL measurement in that subset of patients.
Follow-up: (+) indicates time since previous NfL serum test, wks (weeks).
AMAN: Acute motor axonal neuropathy; CLIPPERS: Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroid; CNS: Central nervous system; ICAN: Immune effector cell neuro-toxicity syndrome; ICI: Immune checkpoint inhibitor; PML: Progressive multifocal leukoencephalopathy; PNS: Peripheral nervous system.

tion of CSF pleocytosis. The patient had encephalitis and probable endocrine myopathy with mild myositis (see Supplementary Image S4).

3.2.5. Patient 5

A 57-year-old with metastatic renal cell carcinoma treated with pembrolizumab and lenvatinib was admitted for immune checkpoint inhibitor–induced encephalopathy and Guillain-Barre syndrome. The patient presented elsewhere with altered mental status, required intubation for airway protection and treatment for suspected aspiration pneumonia. A brain MRI was normal. The CSF had lymphocytic pleocytosis (WBC = 11/mm^3) and elevated protein (374 mg/dl). The CSF cytology was negative. The patient was treated with intravenous steroids and plasma exchange. On arrival at our facility, the patient was quadriplegic and encephalopathic, with serum NfL levels >1500 pg/ml (normal <20.8 pg/ml). Electromyographic studies revealed severe axonal radiculopathy. An EEG showed mild generalized slowing of 6–7 Hz, without epileptiform discharges. The patient was treated with intravenous immunoglobulin (IVIG), followed by repeat plasma exchange and rituximab. The patient worsened and died shortly after transition to comfort care (Supplementary Image S5).

3.2.6. Patient 6

A 63-year-old with melanoma treated with ipilimumab and nivolumab who presented with left-sided facial droop and ptosis. The MR brain was not different from an MR 2 months before. CSF studies showed mildly elevated WBC (= 7/mm^3) and normal protein. The CSF cytology was negative. The serum NfL level was 124 pg/ml (normal <28.0 pg/ml). A renal biopsy showed granulomatous necrotizing vasculitis consistent with polyarteritis nodosa. The patient was treated with intravenous methylprednisolone with improvement of renal and cranial nerve function (Supplementary Image S6).

3.2.7. Patient 7

An 80-year-old with oropharyngeal cancer who had pulseless electrical activity (PEA) with return of spontaneous circulation (ROSC) after 5 min of cardiopulmonary resuscitation. The management was intubation, pressor therapy and targeted temperature management. An EEG on day 1 showed a generalized theta rhythm that slowed with variability, but no clear reactivity and spontaneous

cycling. The CT of the head on day 1 after cardiac arrest was unremarkable. Neuron-specific enolase (NSE) on day 2 was normal. On day 3, the NfL level was 124 pg/ml (normal <51.2 pg/ml). Over time, the patient's mental status improved. The patient was extubated around day 7 and answered yes and no to simple questions. Unfortunately, shortly thereafter the patient developed acute respiratory failure and was transitioned to hospice and eventually died (Supplementary Image S7).

3.2.8. Patient 8

A 66-year-old treated with stereotactic radiotherapy and cisplatin for squamous cell carcinoma of the epiglottis. The patient presented with PEA, with ROSC after (min). In the immediate post-cardiac arrest period, the patient developed clinical myoclonus; the EEG showed malignant status epilepticus. On day 1, NSE was 56.0 ng/ml (normal <15.0 ng/ml) and the NfL level was >1500.0 pg/ml (normal <28.0 pg/ml). On day 2, an MRI showed restricted diffusion, with corresponding bilateral T_2 FLAIR hyperintensity in the perirolandic regions, occipital cortices, basal ganglia and thalami. Malignant status epilepticus continued, despite high-dose anesthesia and multiple seizure medications. The patient was transitioned to hospice care and died (see Supplementary Image S8).

3.2.9. Patient 9

A 74-year-old with light chain myeloma transferred for rapidly progressive ascending bilateral lower extremity weakness unresponsive to IVIG. On arrival, the patient was paraparetic and areflexic. The upper extremities were mildly weak, with bicipital areflexia. The patient also had neck flexor weakness, weak cough and autonomic instability. Sensation was intact without sensory level. An MRI of the cervical, thoracic and lumbar spine showed osteolytic lesions compatible with multiple myeloma and chronic degenerative changes of the cervical spine, with posterior disc osteophyte complexes resulting in multilevel moderate spinal canal stenosis, most prominently between C3–4 and C4–5.

CSF studies showed albumin-cytologic dissociation, with WBC = 0/mm^3 and protein = 178 mg/dl. CSF cytology was negative for malignant/plasma cells. EMG showed axonal motor sensory radiculoneuropathy. The patient was treated again with IVIG at 2.0 g/kg split over 5 days while undergoing concurrent chemotherapy without change. The respiratory status worsened, requiring intubation for airway protection. Only after the end of plasma exchange did strength in arms improve with a fluctuating course. The hemodynamic instability also continued requiring pressor support and mechanical ventilation. The NfL level after plasma exchange was 1310 pg/ml (normal <37.9 pg/ml). The patient transitioned to comfort care and died (see Supplementary Image S9).

3.2.10. Patient 10

A 16-year-old with acute myeloid leukemia with ascending bilateral leg weakness, sensory level at T6 and respiratory distress. An MRI of the brain with contrast was unremarkable. An MRI of the cervical spine showed a longitudinally extensive intramedullary cord signal abnormality at C7. An initial lumbar puncture showed neutrophilic pleocytosis with elevated protein despite being traumatic (WBC = 21/mm^3, RBC = 1600/mm^3, protein = 98 mg/dl). Serum pediatric autoimmune encephalopathy panels were negative, except for minimal elevation of GAD65 (0.27 nmol/L [normal <0.02 nmol/L]). Serum aquaporin-4 antibodies were negative. Serum NfL levels were >1500.0 pg/ml (reference range: not established for this age). An EMG/NCS revealed axonal motor greater than sensory neuropathy, in keeping with motor neuropathy (findings concerning for anterior horn cell dysfunction given paraspinal denervation). Despite a 5-day course of IVIG, the patient did not improve and died (Supplementary Image S10).

3.2.11. Patient 11

A 22-year-old with diffuse large B cell lymphoma treated with R-CHOP (cyclophosphamide, doxorubicin, prednisone, rituximab and vincristine) and axicabtagene ciloleucel after craniotomy and resection of a right frontal brain metastasis, presented with headaches, nausea, photophobia and neck pain. The patient had recently been treated for EMG-confirmed motor variant Guillain-Barre syndrome. An MRI of the brain initially showed nonspecific FLAIR hyperintensities in the periventricular white matter; MR venogram was normal. CSF analysis revealed persistent lymphocytic pleocytosis (2225/mm^3) with elevated protein (357 mg/dl) and an opening pressure of 50 cm H_2O. Despite coverage with broad-spectrum antibiotics, the patient's mental status worsened and serial EEGs confirmed nonconvulsive status epilepticus requiring multiple antiseizure medications and drug-induced burst suppression. Given the negative infectious workup, treatment with high dose steroids began. A repeat MRI revealed a newly developed right parietal lobe and leptomeningeal enhancement. Central nervous system hemophagocytic lymphohistiocytosis (HLH) was confirmed with germline VUS in the PRF1 gene, with elevated CSF interleukin-2, CSF neopterin, CXCL9 and CD10a. The patient was treated with intrathecal methotrexate, intrathecal hydrocortisone, steroids and ruxolitinib. Serum NfL levels at diagnosis of HLH were elevated to 327.0 pg/ml (normal <8.4 pg/ml). Following treatment, repeat NfL levels began to steadily decrease to 163.0

pg/ml, then 136.0 pg/ml, 91.5 pg/ml, 38.9 pg/ml, 26.1 pg/ml, 19.2 pg/ml and 22/3 pg/ml. The NfL value of 38.9 pg/ml corresponded to resolution of CSF pleocytosis to 5 cells/mm^3 and clinical improvement (Supplementary Image S11).

3.2.12. Patient 12

A 45-year-old with colon cancer and paraneoplastic syndrome with acrofacial numbness, bilateral hearing loss and dystonia of the head, left arm and left leg, with hypertonia and weakness. An MRI of the brain showed a nonspecific T2 FLAIR hyperintensity of the right temporal lobe. The infectious, inflammatory and autoimmune/paraneoplastic tests were initially negative, including right temporal lobe biopsy, which showed reactive astrogliosis and microgliosis. An initial CSF cell count showed WBC = 21/mm^3 without oligoclonal bands. IVIG, steroids and plasma exchange were unsuccessful. A biopsy following a whole-body PET scan confirmed colon cancer. Repeat CSF/serum tests for autoimmune/paraneoplastic antibodies were negative. The CSF cellularity disappeared. Given the persistence of abnormal movements, the patient was treated with two 1000-mg doses of rituximab. Serum NfL levels decreased from 68.9 pg/ml before rituximab to 15.3pg/ml and eventually 11.4 pg/ml (normal <15.4 pg/ml) simultaneously with stabilization of involuntary movements (Supplementary Image S12).

3.2.13. Patient 13

A 70-year-old with myelofibrosis with CNS demyelinating disease not otherwise specified. The symptoms were new-onset left-sided weakness, dysarthria and facial droop. An MRI of the brain showed bilateral frontoparietal T2 FLAIR hyperintensities. An extensive work-up was negative, including an autoimmune antibody panel and JC virus. The serum NfL level was 417.0 pg/ml (normal <28.0 pg/ml). The patient's symptoms improved with steroids along with MR white matter findings at 3-month follow-up (Supplementary Image S13).

3.2.14. Patient 14

A 55-year-old with peripheral T-cell lymphoma status post stem cell transplant, with septic shock and acute hypoxemic respiratory failure. The patient needed mechanical ventilation, pressure support and was complicated with an upper gastrointestinal hemorrhage followed by status epilepticus eventually controlled with levetiracetam, phenytoin and phenobarbital. With improvement, the patient opened eyes, could track and nod to verbal commands with profound quadriplegia. A limited first EMG on day 37 favored critical illness myopathy or motor neuropathy for which the patient received 5 doses of IVIG. MRI brain on day 40 showed increased T_2 FLAIR at gray-white matter differentiation suggesting anoxic injury. The CSF on day 44 was normal. A repeat EMG on day 63 was consistent with myopathy and an underlying severe axonal motor and mild sensory neuropathies, suggestive of critical illness myoneuropathy and concern for AMAN (acquired motor axonal neuropathy). The patient received another 5-day IVIG series. NfL on day 49 of hospital admission was >1500 pg/ml (normal <20.8 pg/ml). Repeat NfL level on hospital admission day 76 and 90 remained >1500 pg/ml. Patient improved cognitively (tracking and participating in speech therapy tasks utilizing trach collar and speaking valve The quadriplegia persisted with subtle improvements in upper extremities on day 90, as the patient battled posttransplant infections, GI bleeding, renal failure on renal replacement therapy and pancytopenia (Supplementary Image S14). NSE levels were 16–18 ng/ml (normal <15 ng/ml) and later normalized. NSE normalization with mental status improvement and the profound weakness suggested that the peripheral nervous system was the primary source for persistent elevated NfL (Supplementary Image S14).

3.2.15. Patient 15

A 65-year-old with remote history of Burkitt's lymphoma status post autologous stem cell transplant. The patient was admitted with dysarthria, diplopia, leg weakness and impaired gait, as well as headache, back pain and altered mental status. MRI brain showed linear and punctate enhancement in the pons. MRI spine showed an expansile intramedullary thoracic cord signal with patchy enhancement and linear enhancement in cauda equina nerve roots. Initial lumbar puncture initially showed elevated CSF WBC 35/mm^3 with lymphohistiocytic pleocytosis, protein 85 mg/dl and glucose 54 mg/dl. Cytology, flow cytometry, oligoclonal bands and meningitis panel were negative. The patient was treated for clinical/radiological diagnosis of transverse myelitis and CLIPPERS (chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids) with a 2-week course of intravenous methylprednisolone followed by a slow prednisone taper. The patient was also treated with foscarnet for CSF HHV 6 positivity, although repeat testing was negative. Repeat LP after intravenous steroid therapy showed persistent but improved lymphocytic pleocytosis and elevated protein. Lumbar puncture 33 days later showed WBC 16/mm^3, protein 52 mg/dl and glucose 73 mg/dl. Repeat imaging revealed progression of linear enhancement in the brainstem and surrounding the occipital horns of the lateral ventricles and stable thoracic lesions. The patient received an induction dose of IVIG (2 gm/kg divided over 5 days), followed by 2 doses of rituximab (total 2 grams). NfL was initially elevated at

239 pg/ml and decreased to 123 pg/ml after steroids, IVIG and rituximab. Workup at 3 months showed disappearance of brain and spine lesions and clinical improvement. Lumbar puncture revealed only WBC 6/mm^3 and normal protein. Repeat NfL 5 months later was 38.1 pg/ml (Supplementary Image S15).

3.3. Serum NfL: cross-sectional & serial levels

Five patients had serial measurements of serum NfL with steadily increasing or decreasing values (cases 1, 3, 11, 12 and 15). One patient (patient 14) had serial measurements, all of which remained above 1500 pg/ml. In four of the five patients, the levels trended down and the patients recovered. One patient (patient 3) had increasing NfL levels until death (Figure 1). In all cases, there was a linear correlation with outcome (Figure 2).

In the series, six patients had NfL levels >900 pg/ml. All but one died. The survivor had a permanent and severe neurological disability.

In Figure 2, there are two types of slopes reported: an overall slope corresponding to the linear regression fit comprising data from all visits (reported in black text) that indicates the global trend, and a slope corresponding to the change between consecutive visits (reported in blue text with blue dashed lines) that depicts more localized trends. For subject 3, there is a sharp local slope between the last and the second to last visit that indicates a negative outcome. For subjects 11, 12 and 15, there is a decreasing local slope between consecutive visits, which coincides with an improvement in conditions for these subjects. Moreover, for subjects 11 and 15 with a large negative slope, there was an improvement in symptoms, whereas for subject 12 with a small negative slope, we see a stabilization of conditions. These results imply that a large negative slope indicates a strong chance to improve whereas a large positive slope indicates a strong possibility of a negative outcome including death.

4. Discussion

Until 2023, very few studies had measured NfL in patients with acute or subacute neurological complications of cancer and its treatments. Serum NfL measured in patients with lung cancer and brain metastases were higher than controls. This rise in NfL values was on average 3 months before the diagnosis of brain metastasis and correlated with shorter survival [11]. Another study assessed the value of NfL in predicting neuroaxonal damage in patients with paclitaxel-induced polyneuropathy. This study found elevated NfL levels correlated with increased risk of polyneuropathy [6]. Other reports found that NfL levels correlated with disease severity in patients with paclitaxel-induced polyneuropathy [9].

Currently there is no literature quantifying NfL in cancer patients with other neurological complications as in this case series. We paired the available serum NfL values to cancer patients with demyelinating, inflammatory, paraneoplastic and hypoxic-ischemic etiologies resulting in widespread neuronal damage. Thus, patients 1 and 2 had grade 3 ICANS with normal or minimally elevated NfL levels. Patient 1 improved rapidly with return of NfL levels to normal after treatment of nonconvulsive status epilepticus. Patient 2 who had normal NfL values also recovered after grade 3 ICANS. Patient 3 presented with clinical deterioration and rising NfL levels after CAR-T cell therapy prompting further investigation and eventual diagnosis of progressive multifocal leukoencephalopathy. In contrast, patient 11 with HLH had decreasing NfL levels which corresponded to clinical improvement and resolution of CSF values. Similarly, patient 15 with posttransplant CLIPPERS had brainstem and spinal cord involvement with good response to immunomodulation and suppressive therapy (steroids, IVIG, Rituxan).

Patients 5 (immune checkpoint inhibitor–related encephalopathy), patient 8 (anoxic brain injury), patient 9 (severe Guillain-Barre syndrome), patient 10 (transverse myelitis) and patient 14 (toxic metabolic encephalopathy with status epilepticus and critical illness myopathy and AMAN) markedly elevated serum NfL levels >1000pg/ml. This elevation in serum NfL was associated with clinical decline and eventual death in all but patient 14. Although longitudinal tracking of NfL levels is missing in these patients, elevated serum NfL level corresponded with poor prognosis and worse outcomes (Figure 1).

In patients with demyelinating disorders, serum NfL in addition to EMG may be a useful and noninvasive biomarker for estimating disease severity, secondary axonal injury and recovery potential [7]. Patient 9 developed Guillain-Barre syndrome persisting despite intervention repeated doses of IVIG and plasma exchange. An EMG confirmed axonal motor sensory neuropathy, which portends a prolonged disease course and recovery. Serial NfL levels in these patients may allow for a more precise and timely assessment of the disease course.

NfL levels may also be used with other markers of neurologic deterioration to help improve prognostication. For example, in patient 7, NSE was normal on day 2 after cardiac arrest; however, on day 3 the NfL level was elevated (124 pg/ml [normal <51.2 pg/ml]). NSE has been used as a marker for neurologic prognostication following cardiac arrest; however, because of the lack of standardization between cutoff values and confounding factors such as targeted temperature management, the relevance of this test in question [12,13]. In such cases, NfL levels may improve accuracy in predicting neuronal injury.

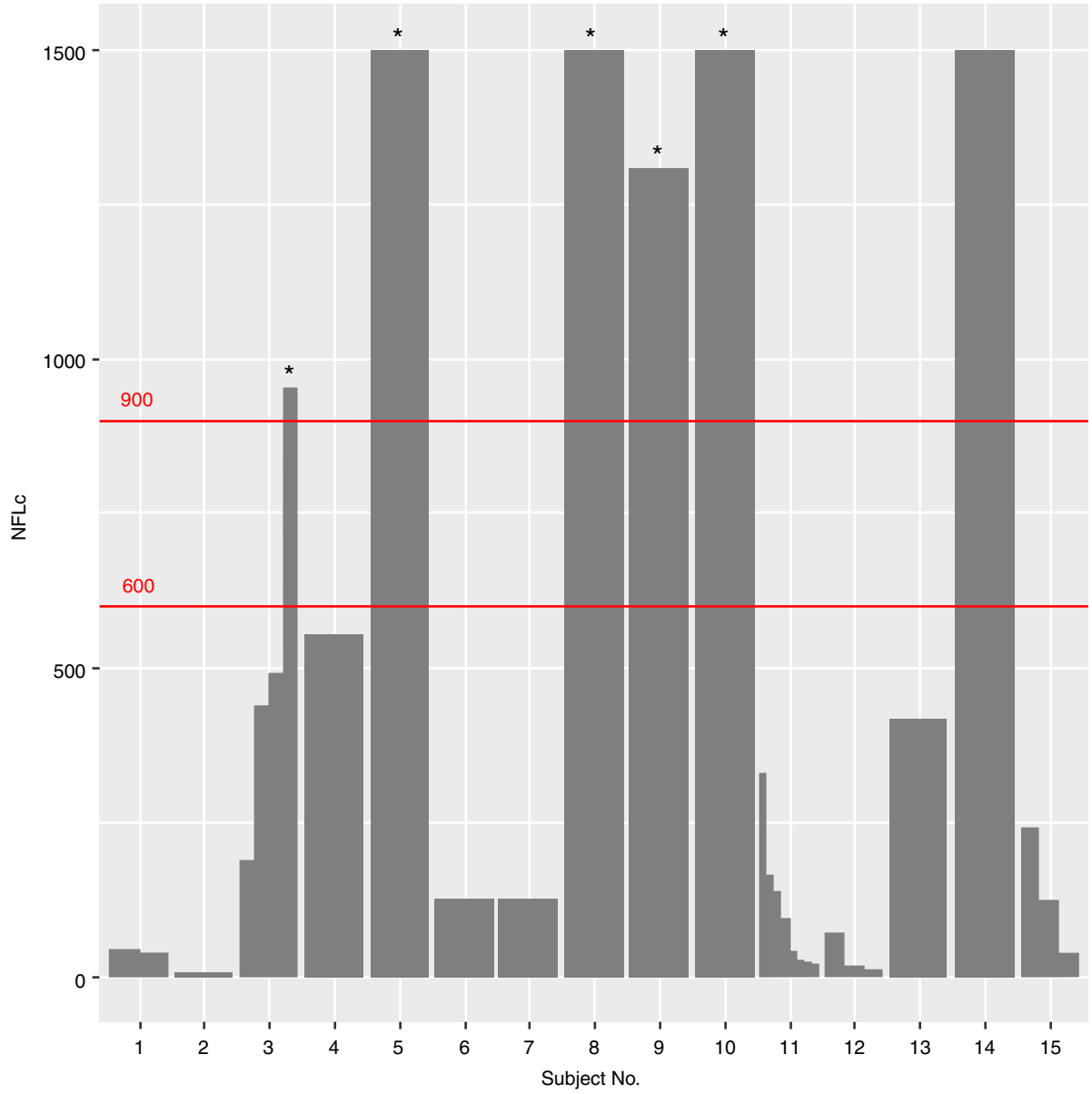


Figure 1. NfL levels for all patients across single or multiple visits. NfL levels are truncated at 1500 pg/ml. The notation * stands for the deceased subjects. It is clear that all but one subjects with NfL levels greater 600 pg/ml or more at the final visit had negative outcomes including death.

Serum NfL may be helpful in paraneoplastic disorders when serum and CSF paraneoplastic antibody testing and imaging are nondiagnostic [14,15]. Rising serum NfL with clinical deterioration can prompt further investigation and aid in prognostication of paraneoplastic syndromes. Patient 11 showcases the potential of NfL in such scenarios. The patient presented with unexplained numbness, hearing loss, weakness and abnormal involuntary movements. Serum and CSF paraneoplastic antibody panels were repeatedly done. The patient continued to deteriorate alongside rising serum NfL. Clinical progression halted after treatment with rituximab which correlated well with decreasing NfL values. In this setting, measurement of NfL could gauge response to immunosuppressive/immunomodulation therapy.

NfL levels can be above normal in central and peripheral nervous system dysfunction. Patients 9 and 14 had peripheral nervous system dysfunction in the setting of critical illness myopathy/AMSAN and GBS respectively. Although longitudinal evaluation of serum NfL was not available for patient 9, each patient had a NfL value greater than 600 pg/ml. Patient 9 died and patient 14 survived with a severe neurological disability.

Based on the linear regression models for patients with repeat measurements, the steeper the positive slope between two NfL values, the higher the likelihood of a

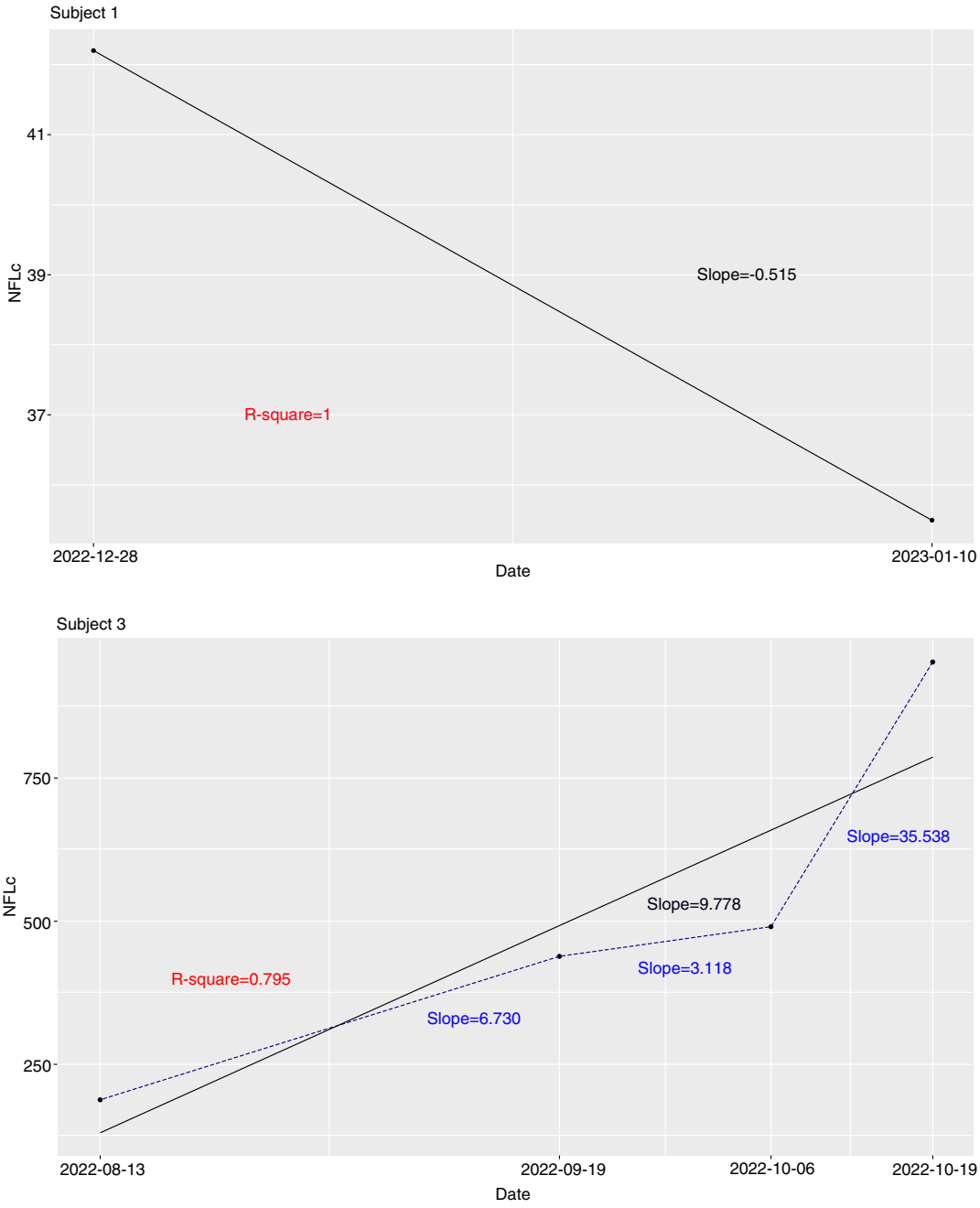
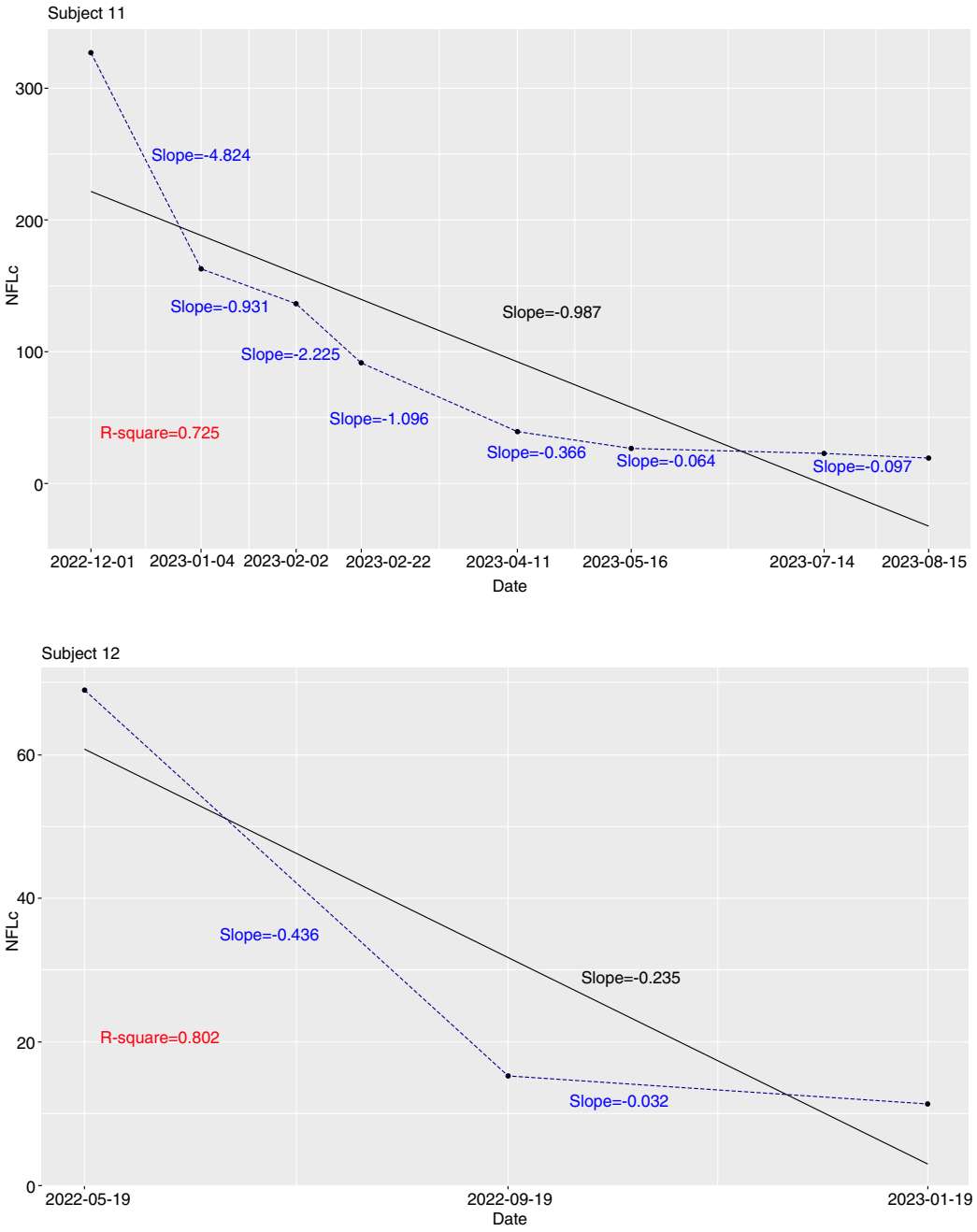


Figure 2. Analysis Methodology: In the following figures, the solid black line indicates a linear regression fit for subjects with multiple visits, for which the R-squared value and the slope values between visits are reported. The R-squared value lies between zero and one and a higher value indicates a better linear regression fit, i.e. it indicates that the longitudinal trajectory of the NfL values are indeed linear. The R-squared value will also be exactly one for individuals with only two visits, which is not very informative.
Two types of slopes are reported – an overall slope corresponding to the linear regression fit comprising data from all visits (reported in black text) that indicates the global trend, and a slope corresponding to the change between consecutive visits (reported in blue text with blue dashed lines) that depicts more localized trends. The global slope corresponding comprising all visits is obtained directly from the linear regression model. On the other hand, the local slopes between consecutive visits are calculated as the ratio of the change in the NfL value between consecutive visits and the duration between these visits. A high negative or positive value of the slope indicates a sharp decreasing or increasing trend for the NfL values, respectively.
In subject 15, there is a decreasing local slope between consecutive visits, which coincides with an improvement in conditions for these subjects. These results imply that a large negative slope indicates a strong chance to improve In summary, decreasing or stable NfL values over time that are less than the critical cut-off of 600 pg/ml can be considered to imply improving symptoms and conditions. On the other hand, increasing NfL values with large slopes between consecutive visits is a cause for concern and may potentially indicate high risk individuals with future negative outcomes. Moreover, although the NfL levels vary across the disease type, the above conclusions hold for all patients in the study.



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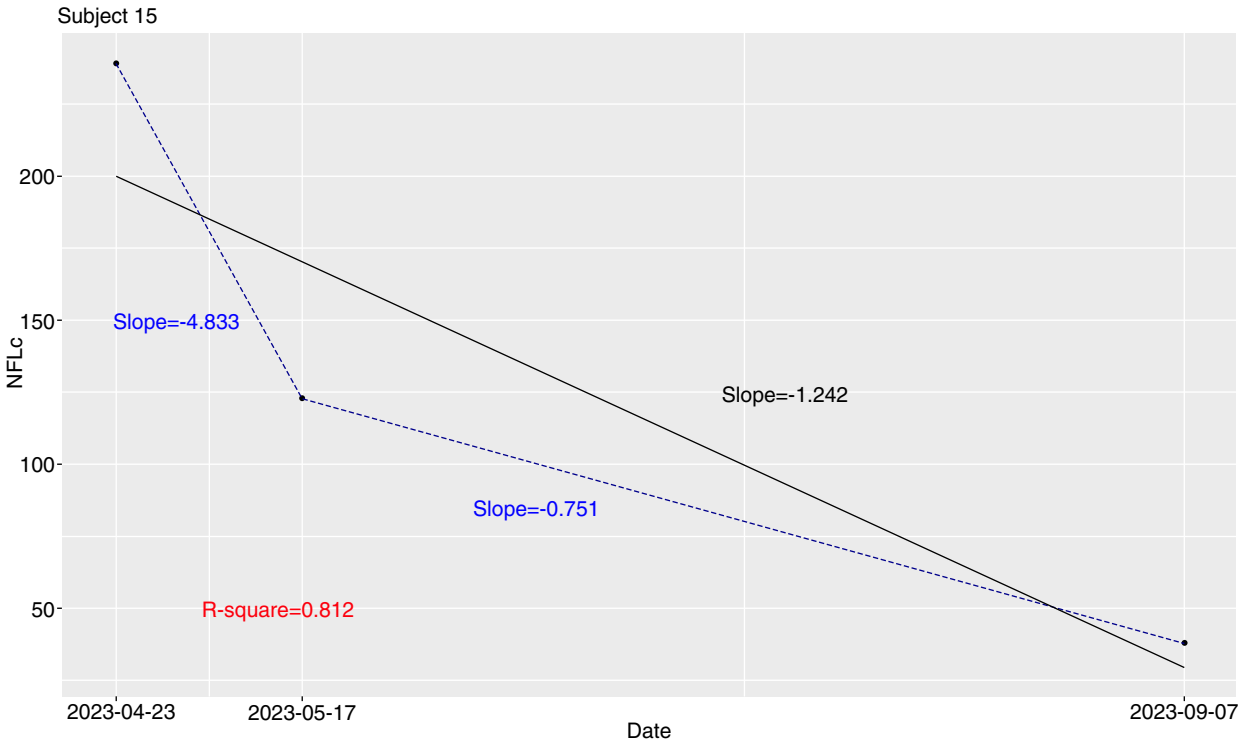

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negative outcome (patient 3). In contrast, a steeper negative slope between two consecutive NfL values correlated with symptomatic improvement (patients 11 and 15). Patient 12 had a smaller negative slope with symptom stabilization only.

The limitations of this case series are its retrospective nature, the small number of patients, the inclusion of different neurological complications and the limited availability of serial measurements. The high cost of commercial laboratory NfL measurements in routine care limited repeat testing and longitudinal tracking in several of these patients. The shipment of samples to outside laboratories and the turnaround time for results also impose limits to medical decision making in real time. We hope that the cost of testing will decrease with wider usage. We did not include CSF data because it is currently less practical especially for repeat serial measurements, and because NfL testing in CSF has not been standardized commercially.

5. Conclusion

Our results favor the use of NfL in multiple central and peripheral nervous system diagnoses in patients with cancer, proving its worthiness as a sensitive marker of neuronal stress and injury [1,3,5,7,12,14]. It may have additional value as a diagnostic biomarker in seronegative paraneoplastic neurological disorders and may guide clinical decisions if further immune modulation is necessary after CSF inflammation has normalized. Longitudinal tracking of serum NfL levels could be useful as a

noninvasive method to follow neuronal stress and help in treatment-related decisions. Elevated or increasing titers may guide prompt diagnostic work-up that could lead to alternative diagnoses and interventions. Finally, serum NfL can be a useful tool for prognostication, predicting poor or prolonged recovery in patients with persistently elevated values. We hope this case series can stimulate future studies with the appropriate design to test NfL in serum to understand its true meaning in predicting outcomes and recovery in cancer patients with acute neurological complications.

Article highlights

- Neurofilament light chain is a non-specific but sensitive marker of neuronal stress and injury with utility in various conditions affecting the central and peripheral nervous system.
- Measuring neurofilament titers can be useful in cancer patients with varied neurological diagnoses.
- Elevated neurofilament light chain levels should prompt neurological work up. Serial measurements with decreasing or increasing titers can be more useful to predict neurological recovery or worsening.
- Usefulness in chimeric antigen receptor T-cell therapy (CAR T-Cell) patients: Previous studies have shown elevated pre-treatment neurofilament light chain levels predict increased risk for developing ICANS. This case review shows utility in post CAR-T Cell infusion patients who develop ICANS, as the titer levels can help predict the severity of neuronal stress and recovery time.
- In patients with anoxic brain injury, neurofilament light chain levels are more sensitive then neuron specific enolase in prognosis.
- Measuring neurofilament light chain levels can be useful in patients with rarer neurological manifestations such as hemophagocytic lymphohistiocytosis (HLH), CLIPPERS (chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids), transverse myelitis, or progressive multifocal leukoencephalopathy (PML). Elevated baseline or rising neurofilament light chain levels correlated with clinical status and further deterioration.
- Neurofilament light chain has proven useful in patients with paraneoplastic syndromes. Titers can be more useful when paraneoplastic antibody titer and CSF evaluation are non-diagnostic to aid in immunomodulatory treatment decisions.
- Neurofilament levels can be of diagnostic and prognostic value in ICI (immune checkpoint inhibitor) encephalitis and CNS vasculitis.

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Author contributions

A Gottiparthy: gather information, wrote article.
K Lam: gather information, wrote article.
S Kundu: statistical analysis.
Z Yang: statistical analysis.
I Tremont: wrote article, review, senior author #2.
S Tummala: wrote article, review, senior author #1.

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Competing interests disclosure

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Writing disclosure

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The study was approved by the institutional review board with waiver of patient consent.

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