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CSF Neurofilament Light Chain Concentrations Predict Outcome in Bacterial Meningitis

Nora Chekrouni, MD, Thijs M. van Soest, MD, Matthijs C. Brouwer, MD, PhD, Eline A.J. Willemse, MSc, Charlotte E. Teunissen, PhD, and Diederik van de Beek, MD, PhD

Correspondence
Dr. van de Beek
d.vandebeek@amsterdamumc.nl

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Abstract

Background and Objectives

Neurofilament light chain (NfL) is a biomarker for neuroaxonal damage and has been found to be elevated proportionally to the degree of neuronal damage in neurologic diseases. The objective of this study was to determine the prognostic accuracy of NfL concentrations on unfavorable outcome in adults with community-acquired bacterial meningitis.

Methods

We measured NfL concentration CSF samples from a prospective cohort study of adults with community-acquired bacterial meningitis in The Netherlands and determined associations between NfL CSF concentrations, clinical characteristics, and outcome in multivariate analyses. We identified independent predictors of an unfavorable outcome (Glasgow Outcome Scale scores 1–4) by logistic regression.

Results

CSF NfL concentrations were evaluated in 429 episodes of 425 patients with community-acquired bacterial meningitis. The median age of 429 episodes was 62 years (interquartile range, 50–69 years). Of note, 290 of 422 (68%) episodes presented with an altered mental status (Glasgow Coma Scale score < 14). Most common causative pathogens were *Streptococcus pneumoniae* (73%), *Neisseria meningitidis* (7%), and *Listeria monocytogenes* (5%). The overall case fatality rate was 62 of 429 (15%), and unfavorable outcome occurred in 57 (37%) of 429 episodes. In multivariate analysis, predictors of unfavorable outcome were older age (OR 1.03, 95% CI 1.01–1.05), cranial nerve palsy (OR 4, 95% CI 1.6–10.3), high serum C-reactive protein concentration (OR 1.3, 95% CI 1.01–1.05), and high CSF NfL concentration (OR 1.5, 95% CI 1.07–2.00). CSF NfL concentrations were higher in patients presenting with focal cerebral deficits (717 pg/mL [416–1,401] vs 412 pg/mL [278–731]; $p < 0.001$). The area under the curve (AUC) for predicting unfavorable outcome in bacterial meningitis of CSF NfL concentration was 0.69 (95% CI, 0.64–0.74).

Discussion

CSF NfL concentration is independently associated with unfavorable outcome in adults with community-acquired bacterial meningitis, suggesting that CSF NfL concentration may be a useful biomarker for prognostic assessment in bacterial meningitis.

Classification of Evidence

Can the level of NfL in CSF (the index test) predict unfavorable outcome in patients with bacterial meningitis, in a cohort of bacterial meningitis patients with a favorable and unfavorable outcome? This study provides Class II evidence that NfL level in CSF is a moderate predictor, with the AUC for predicting unfavorable outcome in bacterial meningitis being 0.69 (95% CI, 0.64–0.74).

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From the Department of Neurology (N.C., T.M.S., M.C.B., D.B.), University of Amsterdam, Amsterdam Neuroscience, Amsterdam UMC, Meibergdreef; and Department of Clinical Chemistry (E.A.J.W., C.E.T.), Vrije Universiteit Amsterdam, Amsterdam Neuroscience, Neurochemistry Laboratory, Amsterdam UMC, De Boelelaan 1117, Amsterdam, The Netherlands.

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Glossary

ALS = amyotrophic lateral sclerosis; **AUC** = area under the curve; **FTD** = frontotemporal dementia; **GCS** = Glasgow Coma Scale; **GOS** = Glasgow Outcome Scale; **IQR** = interquartile range; **MS** = multiple sclerosis; **NfL** = neurofilament light chain.

Bacterial meningitis is a life-threatening disease associated with high mortality and morbidity and is predominantly caused by *Streptococcus pneumoniae*.[1-3] About half of survivors of pneumococcal meningitis have neurologic sequelae, including hearing loss, focal cerebral deficits, and cognitive impairment.[4-7] Unfavorable outcome after meningitis is mainly caused by an excessive inflammation reaction of the host's immune system in reaction to the bacterial infection, leading to injury to the CNS.[8,9] Brain autopsy of pneumococcal meningitis cases has shown that vascular damage is key in the process of cortical necrosis and brain damage.[10] The use of an objective and dynamic fluid biomarker for neuronal damage might provide clinicians with an additional tool for prognostic assessment.

Neurofilaments are cylindrical proteins that are exclusively located in the neuronal cytoplasm and form an integral component of the axonal cytoskeleton.[11] Neurofilaments consist of 3 subunits: neurofilament light chain (NfL), heavy chain, and medium chain. As NfL is the backbone of neurofilaments, it can be robustly measured in body fluids. Although low concentrations of NfL are continuously being released in an age-dependent manner from axons, a wide variety of CNS diseases that cause axonal damage result in elevated NfL concentrations proportionally to the degree of axonal damage.[12] This includes multiple sclerosis (MS), frontotemporal dementia (FTD), and amyotrophic lateral sclerosis (ALS), in which NfL has been suggested to be valuable not only in diagnosis (ALS) but also as a serum marker of disease progression (FTD and ALS) and treatment response (MS).[11-14] Few studies have described neurofilaments in CNS infections,[15,16] with a study in children with bacterial meningitis showing that peak concentrations of neurofilament heavy chain in CSF were higher in patients with neurologic sequelae than in those without.[17] In an experimental pneumococcal rat model, CSF NfL concentrations were increased after injection with experimental *S. pneumoniae* compared with mock-infected rats.[18]

Our objective was to determine the prognostic accuracy of NfL in bacterial meningitis in adults. We hypothesized that NfL in CSF might be increased in patients with bacterial meningitis and that the quantification of neuronal damage could allow for prognostic assessment. In this prospective nationwide cohort study, we evaluated the prognostic value of concentrations of NfL in CSF in adults with community-acquired bacterial meningitis.

Methods

Patients

The MeninGene study is an ongoing nationwide cohort study in The Netherlands that started in 2006 to identify host and pathogen factors influencing the risk and outcome of bacterial meningitis.[2,19,20] Detailed methods of the cohort have been described previously.[2] In summary, patients aged 16 years or older with community-acquired bacterial meningitis were prospectively included following a report from the Netherlands Reference Laboratory for Bacterial Meningitis. This laboratory receives bacterial strains from over 85% of all patients with bacterial meningitis in the Netherlands and notifies the investigators with the name of the treating physicians, who are then contacted to include the patient in the study. Written informed consent was obtained from participating patients or their legal representatives.

Inclusion and Exclusion Criteria

Patients were included in the MeninGene study if they had a positive CSF culture or if the CSF showed at least 1 individual finding predictive of bacterial meningitis according to the Spanos criteria (glucose <1.9 mmol/L, CSF serum glucose ratio <0.23, protein concentration >2.20 g/L, white cell count >2,000 cells/mm^3, or CSF neutrophil count >1,180 cells/mm^3)[21] in combination with a positive CSF PCR, CSF antigen, or blood culture. Patients who developed meningitis while in hospital or within 1 week after discharge, following head trauma or neurosurgery in the previous month, or with a neurosurgical device in situ were excluded.[22]

Neurofilament Light Chain (NfL) Measurement in CSF

CSF from the diagnostic lumbar puncture (at presentation or on admission) was collected in a central biobank in Amsterdam UMC and was available for ±60% of included episodes. After withdrawal, the samples were centrifuged, frozen, and stored in 96-well plates at −80°C until further analysis. For the current measurements, 6 CSF plates were randomly selected. NfL in CSF (5 μL) was measured using the Simoa NF-light Advantage Kit (ref. 103186) on an HD-X instrument (Quanterix, Billerica, MA) at the Neurochemistry Laboratory at Amsterdam UMC, location VUmc, according to the manufacturer's instructions.

Quality of the assay is monitored using 3 serum pools from patients, having different NfL levels spanning the measurement range. The interassay coefficient of variability over 146 runs was 7.7%. The intra-assay variation of the assays has been extensively tested, being consistently <3%.

Clinical Data Collection and Definitions

Data on patients' baseline characteristics, symptoms on admission, clinical course, treatment, and (neurologic) outcome were prospectively collected with a secured online case record form. Immunocompromised state was defined as having active cancer, a splenectomy, diabetes mellitus, HIV, alcoholism, or the use of immunosuppressive drugs. At discharge, neurologic

Table 1 Baseline and Clinical Characteristics of the Neurofilament Light Chain (NfL) Cohort (Total, N = 429)

Characteristic	Data	Characteristic	Data
Age, y[a]	62 (50–69)	Blood and CSF culture	
Female sex	210/429 (49%)	Positive blood culture	288/376 (77%)
Symptoms <24 h	196/403 (49%)	Positive CSF culture	400/429 (93%)
Recurrent meningitis	28/428 (7%)	Causative pathogen	
Previously diagnosed infection	192/422 (46%)	*S. pneumoniae*	314/429 (73%)
Otitis or sinusitis	163/405 (40%)	*N. meningitidis*	32/429 (7%)
Pneumonia	27/406 (7%)	*L. monocytogenes*	21/429 (5%)
Endocarditis	6/399 (2%)	Other	62/429 (14%)
Immunocompromised state	111/427 (26%)	Indices of CSF inflammation	
Cancer	59/427 (14%)	Opening pressure (cm water)[j]	36 (23–43)
Diabetes	43/421 (10%)	Protein (g/L)[k]	4 (2.2–6.3)
Alcoholism	21/424 (5%)	CSF/serum glucose ratio[l]	0.07 (0.01–0.26)
Immunosuppressive treatment	41/421 (10%)	White cell count per mm3[m]	2,233 (577–5,697)
Splenectomy	12/426 (3%)	<100/mm^3	50/412 (12%)
Other predisposing factors		100–999/mm^3	90/412 (22%)
CSF leak	15/418 (4%)	>999/mm^3	272/412 (66%)
Remote head trauma	14/402 (4%)	Radiologic examination	
Clinical signs and symptoms		Abnormal brain CT or MRI	166/374 (44%)
Median temperature[b]	38.8 (37.9–39.7)	Adjunctive dexamethasone therapy	364/414 (88%)
Classic triad	152/399 (38%)	Clinical course	
Fever (>38°C)	291/366 (80%)	Cardiorespiratory failure	108/406 (27%)
Headache	296/362 (82%)	Seizures	63/403 (16%)
Neck stiffness	283/392 (72%)	Pneumonia	54/400 (14%)
Nausea	200/329 (61%)	Cerebrovascular accident	51/395 (13%)
Glasgow Coma Scale score[c]	11 (9–14)	Glasgow Outcome Score	
Altered mental status (GCS score <14)	290/422 (68%)	1 (death)	62/429 (15%)
Coma (GCS score ≤8)	75/422 (18%)	2 (vegetative state)	2/429 (1%)
Aphasia, monoparesis, or hemiparesis	76/348 (22%)	3 (severe disability)	21/429 (5%)
Seizures	33/402 (8%)	4 (moderate disability)	72/429 (17%)
Babinski reflex	55/357 (15%)	5 (mild or no disability)	272/429 (63%)
Cranial nerve palsies	27/365 (7%)	Neurologic sequelae at discharge	
Heart rate (beats/min)[d]	99 (84–114)	Hearing impairment	101/343 (29%)
Systolic blood pressure (mm Hg)[e]	145 (128–163)	Cognitive impairment	65/284 (23%)
Diastolic blood pressure (mm Hg)[f]	80 (70–90)	Cranial nerve palsy	43/287 (15%)
Blood chemical tests		Focal cerebral deficits	38/269 (14%)

Continued

Table 1 Baseline and Clinical Characteristics of the Neurofilament Light Chain (NfL) Cohort (Total, N = 429) *(continued)*

Characteristic	Data	Characteristic	Data
C-reactive protein (mg/L)[g]	167 (76–288)	Mono- or hemiparesis	26/284 (9%)
Thrombocyte count (per μL)[h]	195 (153–251)	Aphasia	15/289 (5%)
Leukocyte count (per μL)[i]	16 (13–22)	Days to discharge[n]	12 (11–14)

Abbreviations: ICU = intensive care unit; LP = lumbar puncture.
Data are median (IQR) or n/N (%).
[a] Age known in all episodes.
[b] Temperature known for 395 episodes.
[c] Glasgow Coma Scale score known for 422 episodes.
[d] Heart rate is known for 395 episodes.
[e] Systolic blood pressure known for 395 episodes.
[f] Diastolic blood pressure known for 395 episodes.
[g] C-reactive protein known for 415 episodes.
[h] Thrombocyte count known for 401 episodes.
[i] Leukocyte count know for 421 episodes.
[j] Opening pressure known for 118 episodes.
[k] Protein known for 406 episodes.
[l] CSF/serum glucose ratio known for 379 episodes.
[m] White cell count in CSF known for 412 episodes.
[n] Days to discharge known for 354 episodes.

examination was assessed using the Glasgow Outcome Scale (GOS) score, ranging from a score of 1 = death to a score of 5 = mild or no disability (able to return to work or school). An unfavorable outcome was defined as a GOS score of 1–4, and a favorable outcome was defined as a score of 5.

Statistical Analysis

Categorical variables are expressed as counts and proportions, and continuous variables are expressed as median with interquartile range (IQR). CSF NfL concentrations between groups were compared using the Mann-Whitney *U* test or the Kruskal-Wallis test. Logistic regression was used to analyze the association between CSF NfL level with unfavorable outcome, providing ORs and 95% CIs. We chose possible confounding variables for NfL and predictors of an unfavorable outcome on the basis of previous research[2] and pathophysiologic interest. Linearity of the association between continuous predictors and outcome was assessed with the Hosmer-Lemeshow goodness of fit test and by visual inspection. If there was no linear relationship, the continuous predictor was either transformed or categorized for further analysis. We estimated both univariable and multivariable ORs corrected for all other variables in the model. We used multiple imputation for missing data in the multivariable analysis and used all predictors together to impute missing values. For the multivariable model, missing values in the selected prognostic factors (median 4.9% per prognostic factor [IQR 3.9–6.6]) were imputed, subsequently combining the coefficients of each data set (N = 5) according to Rubin rule.[23] All tests were 2 tailed, and a p value <0.05 was considered significant. Statistical analysis was conducted using IBM SPSS Statistics data Editor (v.26).

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by the Medical Ethical Review Committee of the Amsterdam UMC (number METC 2013_043). Written informed consent was obtained from all participants or their representatives.

Data Availability

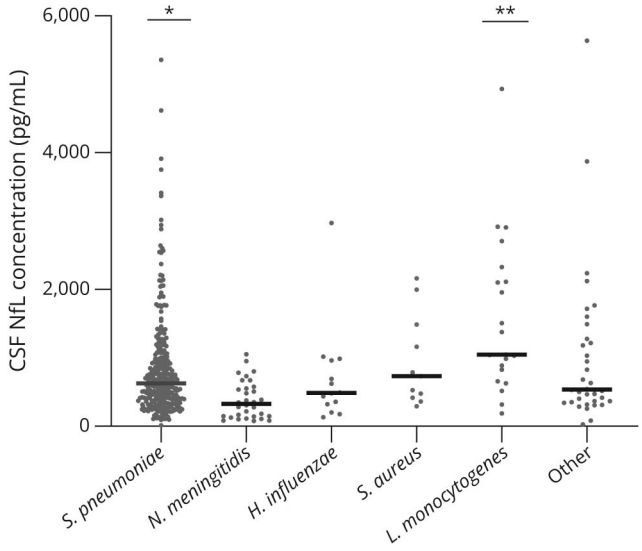
Anonymized data not published within the article will be shared on the request from any qualified investigator.

Results

Between 2006 and July 2018, a total of 2,116 episodes of bacterial meningitis were included in our cohort study. For the current analyses, we used 429 episodes with an available CSF sample from the diagnostic lumbar puncture (eFigure 1, links.lww.com/NXI/A673). Characteristics between selected and nonselected patients for this analysis were similar (eTable 1, links.lww.com/NXI/A673). The 429 episodes occurred in 425 patients; 4 patients had recurrent meningitis within the cohort study period.

The median patient age in the 429 episodes was 62 years (IQR 50–69 years), and 210 of 429 episodes occurred in females (49%; Table 1). Immunocompromising conditions were present in 111 of 427 (26%) of episodes, predisposing infection foci in 192 of 422 (46%) episodes, and 15 of 418 (4%) of episodes had a CSF leak. An altered mental status (defined as Glasgow Coma Scale [GCS] score <14) was present on admission in 290 of 422 (68%) episodes, of whom 75 episodes presented with coma (GCS score <8). The classical triad consisting of fever, altered mental status, and neck stiffness was present in 152 of 399 episodes (38%). *Streptococcus pneumoniae* and *Neisseria meningitidis* were the most common causative pathogens causing 314 of 429 (73%) and 32 of 429 (7%) of the cases. An unfavorable outcome occurred in 157 of 429 (37%) of episodes, and 62 of 429 (15%) patients died. Most common neurologic sequelae at discharge were hearing impairment (101 of 343 episodes, 29%), cognitive impairment (65 of 284 episodes, 23%), cranial nerve palsies (43 of 287 episodes, 15%), and focal cerebral deficits (38 of 269 episodes, 14%).

Figure 1 Comparison of NfL Level (Median) in CSF Between Different Causative Pathogens



*Significant difference in NfL level between pneumococcal (N = 314) vs nonpneumococcal (N = 115) cases, after correction for age (respectively, 616 pg/mL [IQR 361–1,043 pg/mL] and 541 pg/mL [IQR 319–1,054 pg/mL], F[1,426] = 3.93, p = 0.048). **Significant difference in NfL level between *Listeria monocytogenes* (N = 21) vs non-*Listeria* (N = 408) cases, after correction for age (respectively, 1,049 pg/mL [IQR 741–2,219 pg/mL] and 572 pg/mL [IQR 342–1,007 pg/mL], F[1,426] = 6.29, p = 0.013). *Haemophilus influenzae* (N = 13) and *Staphylococcus aureus* (N = 11). Other pathogens: *Streptococcus agalactiae* (N = 7), *Streptococcus pyogenes* (N = 11), *Streptococcus suis* (N = 3), *Streptococcus salivarius* (N = 2), *Streptococcus anginosus* (N = 3), *Streptococcus dysgalactiae* (N = 1), *Streptococcus intermedius* (N = 2), *Streptococcus oralis* (N = 1), *Escherichia coli* (N = 2), *Klebsiella pneumoniae* (N = 1), *Campylobacter fetus* (N = 1), *Nocardia farcinica* (N = 1), Group C streptococcus not other specified (N = 1), viridans group streptococci not other specified (N = 1), and *Fusobacterium necrophorum* (N = 1). IQR = interquartile range; NfL = neurofilament light chain.

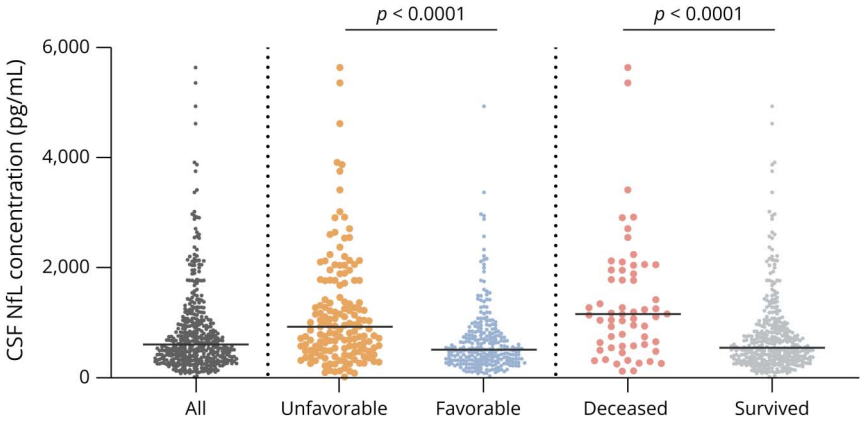
The median CSF NfL concentration was 600 pg/mL (IQR 348–1,047 pg/mL). A moderate correlation was found between CSF NfL concentrations and age (r = 0.6, p < 0.001), and a weak correlation between CSF NfL and CSF protein concentrations (r = 0.14, p = 0.009) and CSF NfL and CSF leukocyte counts (r = -0.2, p < 0.001). NfL concentrations were higher in patients presenting with focal cerebral deficits (717 pg/mL [416–1,401] vs 412 pg/mL [278–731] without focal cerebral deficits; p < 0.001) and those presenting with a GCS score <14 (NfL 654 pg/mL [IQR 397–1,083 pg/mL] vs 513 pg/mL [IQR 271–873 pg/mL] in those presenting with a GCS score of 14 and 15; p = 0.002). CSF NfL concentrations differed between causative pathogens (Figure 1). CSF NfL concentrations were higher in patients with pneumococcal meningitis compared with nonpneumococcal meningitis (median NfL 616 pg/mL [IQR 361–1,043 pg/mL] vs 541 pg/mL [IQR 319–1,054 pg/mL], after correcting for age p = 0.048).

CSF NfL concentrations in patients who died were more than 2-fold higher than in surviving patients (1,152 pg/mL [IQR 594–2043 pg/mL] vs 541 pg/mL [IQR 335–924 pg/mL], p < 0.001; Figure 2). CSF NfL concentrations were higher in patients with an unfavorable outcome (928 pg/mL [IQR 494–1765 pg/mL] vs 506 pg/mL [IQR 314–809 pg/mL], p < 0.001). In a multivariable analysis, older age, cranial nerve palsy, high serum C-reactive protein concentration, and high CSF NfL concentration were associated with an unfavorable outcome in bacterial meningitis due to any pathogen (Table 2). The association between CSF NfL concentration and outcome remained robust when including the causative pathogen (eTable 2, links.lww.com/NXI/A673). The area under the curve (AUC) for predicting unfavorable outcome in bacterial meningitis was 0.69 (95% CI 0.64–0.74). The optimal cutoff point in CSF NfL concentration according to the Youden index was 681 pg/mL (sensitivity 63% and specificity 67%). The AUC for predicting mortality in bacterial meningitis was 0.72 (95% CI 0.65–0.79), with an optimal cutoff point of 926 pg/mL (sensitivity 67% and specificity 75%).

Discussion

Our study shows that CSF NfL concentration independently predicts unfavorable outcome in adults with community-

Figure 2 Comparison of NfL Level Between Total Cohort (N = 429) and Different Outcome Groups (Median, Interquartile Range)



NfL level in deceased (N = 62) vs alive (N = 367) patients (respectively, 1,152 pg/mL [IQR 594–2043 pg/mL] and 541 pg/mL [IQR 335–924 pg/mL]; p < 0.001). NfL level in patients with unfavorable (N = 157) vs favorable outcome (N = 272) (respectively, 928 pg/mL [IQR 494–1765 pg/mL] and 506 pg/mL [IQR 314–809 pg/mL]; p < 0.001]. IQR = interquartile range; NfL = neurofilament light chain.

Table 2 Factors Associated With an Unfavorable Outcome

	Favorable outcome (N = 272)	Unfavorable outcome (N = 157)	Univariable OR unfavorable outcome (95% CI)	Multivariable OR unfavorable outcome (95% CI)	*p* Value multivariable analysis
NfL in CSF (pg/mL)[a]	506 (314–809)	928 (494–1765)	2.1 (1.6–2.7)	1.6 (1.2–2.2)	0.004
Age (y)[b]	59 (46–66)	66 (57–74)	1.04 (1.03–1.06)	1.03 (1.01–1.05)	0.007
Otitis or sinusitis	111/261 (43%)	52/144 (36%)	0.84 (0.53–1.3)	0.96 (0.6–1.6)	0.89
Pneumonia	14/263 (5%)	13/143 (9%)	2.1 (1–4.4)	1 (0.4–2.5)	1
Immunocompromised state	62/271 (23%)	49/156 (31%)	1.5 (1–2.2)	1.3 (0.8–2.2)	0.24
Rash	17/250 (6.8%)	9/129 (7%)	1.1 (0.5–2.6)	1.9 (0.6–6)	0.25
Cranial nerve palsy	9/244 (4%)	18/121 (15%)	4.6 (2.0–10.5)	4 (1.6–10.3)	0.004
Mono-, hemiparesis, or aphasia	44/227 (19%)	32/121 (26%)	2.5 (1.4–4.3)	1.7 (0.9–3.2)	0.14
Heart rate (per 10 bpm)[c]	97 (82–109)	104 (84–120)	1.2 (1.07–1.3)	1.1 (1.0–1.2)	0.10
Glasgow Coma Scale score[d]	13 (10–14)	10 (9–13)	0.84 (0.8–0.9)	0.9 (0.8–1.03)	0.16
C-reactive protein (mg/L)[e]	140 (62–250)	212 (117–337)	1.04 (1.03–1.05)	1.03 (1.01–1.05)	0.001
Thrombocyte count (*109/L)	198 (160–251)	183 (143–252)	—	—	—
<150	53/261 (20%)	41/140 (29%)	1.7 (1.07–2.7)	1.4 (0.8–2.5)	0.24
150–450	204/261 (78%)	98/140 (70%)	Reference	Reference	—
>450	4/261 (2%)	1/140 (1%)	0.6 (0.07–5.8)	0.6 (0.03–9.5)	0.71
White cell count in CSF (per μL)	2,448 (815–6,380)	1,667 (280–5,072)	—	—	—
<100	22/259 (8%)	25/153 (16%)	2.3 (1.2–4.4)	0.9 (0.4–2.2)	0.89
100–999	53/259 (20%)	37/153 (24%)	1.4 (0.9–2.4)	0.97 (0.5–1.7)	0.92
1,000–10,000	149/259 (55%)	74/153 (48%)	Reference	Reference	—
>10,000	35/259 (13%)	17/153 (11%)	1 (0.5–2)	0.7 (0.3–1.6)	0.45
CSF:blood glucose ratio[f]	0.1 (0.01–0.3)	0.02 (0.01–0.2)	0.2 (0.02–1.2)	0.5 (0.08–3.6)	0.51
Positive blood culture	174/235 (74%)	114/141 (81%)	1.5 (0.9–2.5)	1 (0.6–1.8)	0.97

Data are median (interquartile range) or n/N (%). The multivariable analysis used an imputed data set with 5 imputation rounds; all variables in the table were entered in the multivariable logistic regression model simultaneously.
[a] OR is for each increase in the natural logarithm in NfL (pg/mL).
[b] Age is known for all episodes.
[c] Heart rate is known for 403 episodes.
[d] Glasgow Coma Scale score known for 422 episodes.
[e] C-reactive protein is known for 415 episodes; OR is for a 10 mg/L increase.
[f] CSF:blood glucose ratio is known for 379 episodes.

acquired bacterial meningitis. Previous studies have identified several predictors for unfavorable outcome in bacterial meningitis[2,3,24,25]: a low level of consciousness on admission, cranial nerve palsy, a low CSF white cell count, factors predictive of pneumococcal infection (advanced age; presence of otitis or sinusitis, pneumonia, or immunocompromised status; and absence of rash) or systemic compromise (high heart rate and high serum C-reactive protein concentration), and infection by a penicillin-resistant *S. pneumoniae*.[26] As neuronal damage plays a central role in the pathophysiology of bacterial meningitis,[9] the use of a body fluid biomarker for neuronal damage such as NfL might provide clinicians with an additional tool for better prognostic assessment and could aid to identify those patients at risk for an unfavorable outcome.

In bacterial meningitis, outcome is in part determined by an excessive inflammation reaction of the host's immune system in reaction to the bacterial infection,[8,9] causing vascular and neuronal damage.[10] In previous studies, NfL was shown to predict outcome and disease progression in a wide variety of neurologic disorders such as Guillain-Barre syndrome,[27] amyotrophic lateral sclerosis,[28,29] critical illness neuropathy in intensive care patients,[30] Alzheimer disease,[31] FTD,[32] chronic inflammatory demyelinating polyneuropathy,[33] and MS.[34,35] Furthermore, plasma NfL concentrations demonstrated excellent prognostic accuracy in comatose patients after out-of-hospital cardiac arrest.[36,37] The prognostic value of neurofilaments in CNS infections has been studied previously. Two studies showed higher serum and CSF NfL levels in

patients with varicella zoster virus encephalitis compared with varicella zoster virus meningitis.[15,16] One study showed higher CSF concentrations of neurofilament heavy chain in 26 children with bacterial meningitis compared with controls.[17]

Results of this study show that the diagnostic accuracy of CSF NfL concentrations for predicting death or unfavorable outcome on an individual patient level is limited. Although NfL levels are higher in patients with an unfavorable outcome, the ranges overlap to an extent that makes it difficult to define a pathologic cutoff at the individual patient level, which is also reflected by the moderate AUC. Nevertheless, NfL in CSF might be a potential useful variable in a prediction model for unfavorable outcome in bacterial meningitis. Several previous studies have researched such prediction models and prognostics factors in bacterial meningitis.[38,39] Improving the stratification of patients with bacterial meningitis at presentation with respect to the risk for unfavorable outcome remains an important tool for physicians to predict clinical deterioration, but can also be a valuable tool for targeting intervention strategies, e.g., as stratification marker or outcome measure. The use of a marker for neuroaxonal damage such as NfL might be specifically interesting, as unfavorable outcome in bacterial meningitis is mainly caused by intracranial complications, and thus, the marker likely reflects downstream biological effects.[1,4,9] Future studies should therefore consider to evaluate the added value of NfL in predictor models for bacterial meningitis.

Our study has limitations. First, NfL was not measured in all patients included in the MeninGene cohort, but only in a limited number of samples. CSF samples from the diagnostic lumbar puncture are stored in about 60% of patients included in the cohort. However, baseline characteristics between episodes selected and not selected for the study were similar, indicating that the influence of selection bias on our results is limited. Second, NfL concentrations were measured in the CSF of the diagnostic lumbar puncture only. For better prognostic assessment, measuring several time points, for example, in plasma, might provide additional information on disease progression, as has been shown in some previous studies.[29,31,34,40] For several neurodegenerative diseases, a strong correlation between CSF and plasma NfL has been demonstrated.[14,35] Also, in an experimental pneumococcal meningitis model, CSF and plasma NfL showed strong correlation.[18] Future studies should therefore evaluate the prognostic value of serial plasma NfL measurement in bacterial meningitis.[17,18] Third, the exact time to clinical presentation from symptom onset in our cohort is not known, which would possibly be of interest as the level of NfL might differ over time.

In conclusion, CSF NfL concentrations are independently associated with unfavorable outcome in adults with community-acquired bacterial meningitis. Future studies should evaluate the added value of NfL in prediction models for bacterial meningitis.

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Disclosure

None. Go to Neurology.org/NN for full disclosures.

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Appendix Authors

Name	Location	Contribution
Nora Chekrouni, MD	Amsterdam UMC, University of Amsterdam, Department of Neurology, Amsterdam Neuroscience, Meibergdreef, Amsterdam, The Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
Thijs M. van Soest, MD	Amsterdam UMC, University of Amsterdam, Department of Neurology, Amsterdam Neuroscience, Meibergdreef, Amsterdam, The Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; and analysis or interpretation of data
Matthijs C. Brouwer, MD-PhD	Amsterdam UMC, University of Amsterdam, Department of Neurology, Amsterdam Neuroscience, Meibergdreef, Amsterdam, The Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
Eline A.J. Willemse, MSc	Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam Neuroscience, Neurochemistry Laboratory, Department of Clinical Chemistry, De Boelelaan 1117, Amsterdam, The Netherlands	Study concept or design and analysis or interpretation of data
Charlotte E. Teunissen, PhD	Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam Neuroscience, Neurochemistry Laboratory, Department of Clinical Chemistry, De Boelelaan 1117, Amsterdam, The Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; and analysis or interpretation of data
Diederik van de Beek, MD-PhD	Amsterdam UMC, University of Amsterdam, Department of Neurology, Amsterdam Neuroscience, Meibergdreef, Amsterdam, The Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data

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