Stroke

CLINICAL AND POPULATION SCIENCES

Association of Plasma Neurofilament Light With Small Vessel Disease Burden in Nondemented Elderly

A Longitudinal Study

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BACKGROUND AND PURPOSE: Neurofilament light chain (NfL) is a promising predictive biomarker of active axonal injury and neuronal degeneration diseases. We aimed to evaluate if an increase in plasma NfL levels could play a monitoring role in the progression of cerebral small vessel disease (CSVD) among the nondemented elders, which are highly prevalent in elderly individuals and associated with an increased risk of stroke and dementia.

METHODS: The study included 496 nondemented participants from the Alzheimer disease neuroimaging initiative database. All participants underwent plasma NfL measurements and 3.0-Tesla magnetic resonance imaging of the brain; 387 (78.0%) underwent longitudinal measurements. The number of cerebral microbleeds, lacunar infarcts, and volumetric white matter hyperintensities, as well as Fazekas scores, were measured. Cross-sectional and longitudinal associations between CSVD burden and NfL levels were evaluated using multivariable-adjusted models.

RESULTS: Plasma NfL was higher in the moderate-severe CSVD burden group (45.2±16.0 pg/mL) than in the nonburden group (34.3±15.1 pg/mL; odds ratio [OR]=1.71 [95% CI, 1.24–2.35]) at baseline. NfL was positively associated with the presence of cerebral microbleeds (OR=1.29 [95% CI, 1.01–1.64]), lacunar infarcts (OR=1.43 [95% CI, 1.06–1.93]), and moderate-severe white matter hyperintensities (OR=1.67 [95% CI, 1.24–2.25]). Longitudinally, a higher change rate of NfL could predict more progression of CSVD burden (OR=1.38 [95% CI, 1.08–1.76]), white matter hyperintensities (OR=1.41 [95% CI, 1.10–1.79]), and lacunar infarcts (OR=1.99 [95% CI, 1.42–2.77]).

CONCLUSIONS: Plasma NfL level is a valuable noninvasive biomarker that supplements magnetic resonance imaging scans and possibly reflects the severity of CSVD burden. Furthermore, high plasma NfL levels tend to represent an increased CSVD risk, and dynamic increases in NfL levels might predict a greater progression of CSVD.

Key Words: biomarkers ■ cerebral small vessel diseases ■ magnetic resonance imaging ■ plasma ■ stroke, lacunar ■ white matter

Cerebral small vessel disease (CSVD), a common heterogeneous disease, affects small leptomeningeal and intraparenchymal arteries, arterioles, capillaries, and venules in the brain stemming from the subarachnoid or large intraparenchymal arterial circulations.[1] Neuroimaging CSVD markers include small subcortical infarcts, lacunar infarcts (LIs), white matter hyperintensities (WMHs), enlarged perivascular spaces,

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†A list of all Alzheimer Disease Neuroimaging Initiative participants is given in the Data Supplement.

The Data Supplement is available with this article at https://www.ahajournals.org/doi/suppl/10.1161/STROKEAHA.120.030302.

For Sources of Funding and Disclosures, see page 903.

Stroke is available at www.ahajournals.org/journal/str

Nonstandard Abbreviations and Acronyms

ADNI	Alzheimer disease neuroimaging initiative
CMB	cerebral microbleed
CN	cognitively normal
CSF	cerebrospinal fluid
CSVD	cerebral small vessel disease
LI	lacunar infarct
LR	logistic regression
MRI	magnetic resonance imaging
NfL	neurofilament light chain
OR	odds ratio
WMH	white matter hyperintensities
WMHV	WMH volume

cerebral microbleeds (CMBs), and brain atrophy.[2] CSVD recently has been recognized as a dynamic whole-brain disease because of its common microvascular pathology, diffuse nature, as well as the varying progression of its lesion types.[3] Furthermore, it has been identified as the common cause of stroke and the major subtype of vascular cognitive impairment.[4] Magnetic resonance imaging (MRI), which serves as one of the most effective methods to monitor the dynamic changes and progression of CSVD, has several limitations; it is expensive, time consuming, and unsuitable for patients with contraindications.[2,5] Longitudinal tracking of CSVD and early interventions using MRI are limited by its unavailability in many primary health centers.

Neurofilament light chain (NfL) is a primary intermediate component of the axonal cytoskeleton that offers mechanical support and regulates the axonal size.[6,7] It is released into the extracellular space and subsequently into cerebrospinal fluid (CSF) and blood during axonal damage; thus, it is a potential marker for subcortical large-caliber axonal degeneration and neuronal damage.[8] Increased NfL levels in the blood and CSF of patients indicate its role as a nonspecific predictive or diagnostic biomarker of neurodegenerative neuroaxonal damage in a variety of acute and chronic neurological disorders,[9] such as Alzheimer disease,[10] frontotemporal dementia,[11] multiple scleroses,[12] and traumatic brain injury.[13] As lumbar puncture is an invasive procedure, monitoring longitudinal changes of CSF NfL levels is rare and not systematically performed. Therefore, measurement of plasma NfL has been considered a convenient and relatively noninvasive tool to provide valid information about neuroaxonal damage in the central nervous system at a low cost compared with imaging examination.[14] Recent studies have verified NfL as a blood biomarker for CSVD MRI markers,[15–17] suggesting a potential role of NfL in CSVD monitoring.

Based on the above-mentioned findings, we speculate that plasma NfL plays specific roles in predicting and monitoring CSVD progression. Considering the significant clinical and societal implications as well as prevalence of CSVD, large prospective cohort studies are urgently needed to verify whether plasma NfL can be a blood biomarker for patients with newly diagnosed CSVD. Therefore, we aimed to investigate the cross-sectional and longitudinal associations between plasma NfL and CSVD burden among nondemented elders in the Alzheimer disease neuroimaging initiative (ADNI) database.

METHODS

ADNI Database

Data were obtained from the ADNI database (http://adni.loni.usc.edu). ADNI was launched in 2003 as a public-private partnership, led by Michael W. Weiner, MD, the Principal Investigator. In this study, informed consent was obtained from study participants, and the study was approved by the local institutional review board at each participating site.

Study Participants

Medical records of 787 participants showing both plasma NfL and CSVD data were initially included. According to ADNI inclusion criteria, all participants were 55 to 90 years old and had no significant neurological diseases. To avoid the influence of complex Alzheimer disease status on the results, only individuals showing cognitively normal (CN) function and early mild cognitive impairment were considered for inclusion. Finally, a total of 496 individuals (248 CN and 248 early mild cognitive impairment individuals) were included, among whom 387 participants (response rate 78.0%) had available follow-up information. The average follow-up time of the study population was 26.5 months (range, 0–51.8 months), and the mean time between blood sample collection and MRI scan was 5.4 days (range, −120 to 176 days). CN participants had a mini-mental state examination score of >24 and a clinical dementia rating score of 0. Patients with early mild cognitive impairment had a mini-mental state examination score of ≥24, a clinical dementia rating score of 0.5, preserved activities of daily living, and absence of dementia. Their objective memory loss was tested using logical memory II (delayed-recall test) of the Wechsler Memory Scale.

Measurement of Plasma NfL

Blood samples were collected, processed, aliquoted, and frozen at −80 °C following the normalized processes, and plasma samples were analyzed using the ultrasensitive single-molecule array technique as described previously.[18] With regard to each calibrator, the relative error was <20% for measured blank concentrations, measurement repeated 3 times, with the upper and lower limits of quantification at 1620 and 2.2 pg/mL, respectively. All samples were measured within the limits of quantifications. The sensitivity of analysis was <1.0 pg/mL, and the NfL level for each tested sample surpassed the limit of detection. Besides, the NfL change rates were determined longitudinally.

Impacts of possible extreme outliers on the final statistics were reduced through additional quality control.

MRI Data Acquisition

All subjects were examined using 3.0-Tesla MRI scanner, and the procedure was described in a previous report.[19,20] Details of the parameters are shown in the ADNI website (http://adni.loni.usc.edu/methods/mri-tool/mri-analysis).

Assessment of CMBs

CMBs were considered as homogenous hypointense lesions with a diameter of up to 10 mm on T2*-weighted MRI images.[2,21] The number and locations of CMBs were identified by trained image analysts and further confirmed by radiologists experienced in reading T2* images. Typically, only the CMBs with definite status were selected and counted for analyses. CMBs were recorded as present if there was at least 1 visible CMB, or absent if there was no visible CMBs. Furthermore, CMBs of multifactorial causes were categorized by location: (1) lobar CMBs; (2) deep CMBs; and (3) mixed CMBs that involved both deep and lobar regions.

WMHs Measurement

WMHs were measured using the Bayesian approach for the segmentation of high-resolution 3-dimensional magnetization prepared rapid gradient echo T1-weighted and T2-FLAIR sequences, with specific methods being reported in a previous study.[22] WMHs were evaluated using the Fazekas rating scale, which is used to rate separately periventricular and deep WMHs. Fazekas score was calculated as the sum of periventricular and deep WMH scores, ranging from 0 to 6, by 2 experienced neurologists. The severity of WMHs was categorized as 0 to 1 (Fazekas scale score, 0–2) and 2 to 3 (Fazekas scale score, 3–6).[23,24] Both Fazekas score and WMH volume (WMHV) were analyzed in the present study.

Assessment of LIs

LIs were defined as CSF-like hypointensities with a diameter of 3 to 15 mm surrounded by rims of hyperintensities on T2 FLAIR.[25] We deemed the severity of LIs as none-mild (0–2 counts) and moderate-severe (≥3 counts).[26]

Assessment of CSVD Burden

In this study, CSVD burdens were quantitatively assessed using the neuroimaging markers CMBs, WMHs, and LIs. As for simple MRI score, one point each was scored for the presence of CMBs, a Fazekas score of ≥2, and a LI count of ≥3, resulting in a minimum score of 0 and a maximum score of 3.[26] As for CSVD amended score, one point was assigned for the presence of CMBs, 3 point each for Fazekas score and LIs, resulting in a score among 0 to 7. Total CSVD burden scores were then categorized into 3 groups according to the simple CSVD score: none (0 points), mild (1 point), and moderate-severe CSVD (2-3 points) groups. The progression of CSVD burden and markers were defined as if there was an increase in simple MRI score, CMB counts, Fazekas score, and LIs counts during follow-up.[27]

Statistical Analysis

Statistical analyses were conducted using R, SPSS, and Python. The statistical significance threshold was set at a 2-tailed $P<0.05$.

Differences in demographic characteristics between CSVD burden groups were assessed using the Kruskal-Wallis and the χ^2 test, and associations between demographic characteristics and plasma NfL were tested using the Spearman rank correlation. Logistic regression (LR) models were used to evaluate the effect of baseline NfL levels on CSVD burden and CSVD markers, as well as 1-way ANOVA and Bonferroni corrections for multiple comparisons ($P<0.017$). The associations of plasma NfL levels with CSVD risk were analyzed by entering these variables as linear terms (per SD). Interaction terms for cognitive status and *APOE ε4* status were used to find whether the effect existed ($P<0.100$) after subgroup analyses. Besides, multiple linear regression models were used to explore the associations of baseline NfL with WMHV. The 3 regression models for LR and multiple linear regression were multivariable adjusted. With regard to evaluation of the NfL predictive performance, the leave-one-out cross-validation method was adopted in all models to measure the coefficient of determination (R^2), successively leaving one sample out from a training data set and estimating regression parameters based on the remaining n-1 samples.

Longitudinal plasma NfL concentration and WMHV were evaluated by calculating Spearman rank correlations between slopes from mixed-effects linear models of NfL concentration and WMHV. Slopes were calculated using a separate mixed-effects linear model controlled for age, sex, education levels, mini-mental state examination, and ICV using the lme4 package. LRs were used to estimate the odds of progressions of CSVD burden and CSVD markers based on plasma NfL levels. Moreover, mixed-effects linear models were used to assess the associations of baseline NfL and changes in plasma NfL levels with longitudinal changes in WMHV. The model included random intercepts and slopes for time and an unstructured covariance matrix for the random effects it regarded as predictors in the interactions between time and dependent variables. Baseline and longitudinal NfL concentrations and WMHVs in the models were natural log-transformed to ensure normality using the car package. These models were adjusted for the same variables as were the baseline models.

The receiver operator characteristic curve, as well as the area under the curve of NfL, was used to determine the best diagnostic abilities for plasma NfL levels. LR models were formulated to determine the predictive probability between NfL and demographic characteristics, and new receiver operator characteristic curves were built.[28]

RESULTS

Participant Characteristics

The baseline and longitudinal characteristics of study participants were shown in Table 1 and Table I in the Data Supplement, respectively. Briefly, 496 nondemented subjects aged 72.0 years (SD=6.7; 242 females) were enrolled at baseline, and 387 subjects were included during the follow-up from the ADNI cohort. Plasma NfL levels were associated with age (Spearman $\rho=0.517$, $P<0.001$) and mini-mental state examination ($\rho=-0.170$, $P=0.002$), but not with sex, education levels, *APOE ε4* carrier status, or vascular risk factors at baseline.

Table 1. Demographic Characteristics of Participants at Baseline

Characteristics	All participants (n=496)	CSVD burden*			*P* value
		0 (n=304)	1 (n=134)	2–3 (n=58)	
Demographic characteristics					
Age (SD), y	72.0 (6.7)	70.2 (6.5)	73.6 (6.2)	77.6 (4.8)	<0.001†
Female, n (%)	242 (48.8)	160 (52.6)	59 (44.0)	23 (39.7)	0.084
Education (SD), y	16.3 (2.6)	16.5 (2.6)	16.0 (2.6)	15.7 (2.8)	0.091
MMSE	28.7 (1.5)	28.8 (1.4)	28.6 (1.5)	28.7 (1.5)	0.258
APOE ε4 carrier status, n (%)	177 (35.7)	108 (35.5)	50 (37.3)	19 (32.8)	0.829
Vascular risk factors					
Hypertension, n (%)	230 (46.4)	130 (42.8)	55 (49.3)	34 (58.6)	0.063
Hyperlipidemia, n (%)	250 (50.4)	147 (48.4)	69 (51.5)	34 (58.6)	0.343
Coronary heart disease, n (%)	32 (6.5)	14 (4.6)	12 (9.0)	6 (10.3)	0.102
Diabetes, n (%)	50 (10.1)	30 (9.9)	17 (12.7)	3 (5.2)	0.278
Smoking, n (%)	147 (29.6)	101 (33.2)	32 (23.9)	14 (24.1)	0.089
Alcohol consumption, n (%)	10 (2.0)	6 (2.0)	3 (2.2)	1 (1.7)	0.970
MRI findings					
CMBs, n (%)	125 (25.2)	0 (0)	82 (61.2)	43 (74.1)	<0.001†
WMHV (SD), cm^3	6.2 (8.7)	3.4 (3.1)	7.6 (9.5)	17.8 (14.1)	<0.001†
LIs, n (%)	68 (13.7)	6 (2.0)	28 (20.9)	34 (58.6)	<0.001†
ICV (SD), cm^3	1406.4 (184.0)	1384.1 (195.7)	1452.4 (166.0)	1419.0 (134.7)	0.118
Plasma NfL levels (SD), pg/mL	34.3 (15.1)	31.5 (13.7)	36.0 (15.2)	45.2 (16.0)	<0.001†

APOE ε4 indicates apolipoprotein E *ε4*; CMBs, cerebral microbleeds; CSVD, cerebral small vessel disease; ICV, intracranial volume; LIs, lacunar infarcts; MMSE, mini-mental state examination; MRI, magnetic resonance imaging; NfL, neurofilament light; and WMHV, white matter hyperintensities volume.

*CSVD burden: CSVD burden score was evaluated at baseline.

†*P*<0.001.

Baseline Associations of Plasma NfL With CSVD Burden

Plasma NfL level was higher in the moderate-severe CSVD burden group (45.2±16.0 pg/mL) than in the nonburden group (34.3±15.1 pg/mL). Baseline associations between plasma NfL levels and CSVD burden in multivariable-adjusted LR models were shown in Table 2. Higher levels of plasma NfL were correlated with moderate-severe CSVD burden (odds ratio [OR]=1.71 [95% CI, 1.24–2.35], *P*=0.001, Figure 1A), presence of CMBs (OR=1.29 [95% CI, 1.01–1.64], *P*=0.041, Figure 1B), WMHs (OR=1.67 [95% CI, 1.24–2.25], *P*=0.001, Figure 1B), and LIs (OR=1.52 [95% CI, 1.12–2.06], *P*=0.008, Figure 1B) but not with mild CSVD burden (*P*=0.296, Figure 1A). Detailly, higher NfL levels were associated with 2 to 3 points Fazekas score (*P*=0.008, Figure 1C), 1 to 2 counts LIs (*P*=0.024, Figure 1C), and >3 LIs (*P*=0.006, Figure 1C). There was a significant association between increased NfL levels and higher CSVD amended score. All these significant associations existed even after Bonferroni corrections (Figure I and Tables II and III in the Data Supplement). Besides, multiple linear regression models showed that NfL levels were positively associated with WMHV (β=0.400, *P*=0.016, Figure 2A, Table IV in the Data Supplement).

The diagnostic accuracies of plasma NfL were shown in Table V and Figure II in the Data Supplement. The area under the curves (95% CI) of combined indices (NfL, age, sex, *APOE ε4*, and cognition) were 0.71 (0.67–0.76), 0.69 (0.63–0.74), 0.75 (0.70–0.81), and 0.720 (0.65–0.79) for CSVD burden, CMBs, WMHs, and LIs, respectively.

Longitudinal Associations of Plasma NfL With CSVD Burden and Markers

No significant associations were found with progressive outcomes of CSVD burden nor progression of CMBs, WMHs, or LIs (Table VI in the Data Supplement). Moreover, Spearman rank correlation indicated that higher levels of plasma NfL were associated with accelerated changes in WMHV (ρ=0.147, *P*=0.004, Figure 2B).

Increased change rates of plasma NfL levels might predict accelerated increases in CSVD burden (OR=1.38 [95% CI, 1.08–1.76], *P*=0.011) and progression of WMHs (OR=1.41 [95% CI, 1.10–1.79], *P*=0.006) and LIs (OR=1.57 [95% CI, 1.42–2.77], *P*=0.001; Table 3). Spearman rank correlation and mixed-effects linear model also demonstrated that change rates of NfL levels were associated with accelerated changes in WMHV (ρ=0.164, *P*=0.001, Figure 2C; β=0.005, *P*<0.001, Table IV in the Data Supplement).

Table 2. The Association Between Baseline Plasma NfL and CSVD

	Baseline plasma NfL 1-SD increase						
	Model 1		Model 2		Model 3		
Variables	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	R^{2*}
CSVD burden							
0	Reference		Reference		Reference		
1	1.13 (0.90–1.44)	0.297	1.15 (0.90–1.46)	0.276	1.14 (0.89–1.46)	0.296	0.4200
2–3	1.67 (1.24–2.25)‡	0.001	1.72 (1.26–2.34)‡	0.001	1.71 (1.24–2.35)‡	0.001	
CSVD markers							
CMBs counts							
0	Reference		Reference		Reference		
≥1	1.29 (1.02–1.62)†	0.035	1.29 (1.01–1.63)†	0.039	1.29 (1.01–1.64)†	0.041	0.3259
Deep	1.02 (0.36–2.85)	0.977	0.98 (0.36–2.65)	0.967	1.01 (0.33–2.56)	0.862	
Lobar	1.25 (0.97–1.62)	0.089	1.27 (0.98–1.65)	0.074	1.27 (0.98–1.66)	0.074	
Mixed	1.49 (0.97–2.28)	0.069	1.42 (0.92–2.19)	0.112	1.43 (0.93–2.22)	0.106	
WMHs (Fazekas score)							
0	Reference		Reference		Reference		
1	1.34 (1.06–1.71)†	0.017	1.27 (0.99–1.63)	0.057	1.27 (0.99–1.62)	0.064	0.2159
2–3	1.71 (1.29–2.27)§	< 0.001	1.69 (1.26–2.27)‡	0.001	1.67 (1.24–2.25)‡	0.001	
LIs counts							
0	Reference		Reference		Reference		
1–2	1.64 (1.11–2.42)†	0.012	1.74 (1.16–2.63)‡	0.008	1.77 (1.17–2.68)‡	0.007	0.3053
≥3	1.49 (1.12–2.00)‡	0.007	1.53 (1.13–2.07)‡	0.005	1.52 (1.12–2.06)‡	0.008	

Model 1: Adjusted for age. Model 2: Model 1+adjustment for sex, education levels, MMSE, ICV, and *APOE ε4* carrier status. Model 3: Model 2+adjustment for hypertension, diabetes, hyperlipidemia, coronary heart disease, smoking status, and alcohol drinking status. *APOE ε4* indicates apolipoprotein E *ε4*; CMBs, cerebral microbleeds; CSVD, cerebral small vessel disease; ICV, intracranial volume; LIs, lacunar infarcts; MMSE, mini-mental state examination; NfL, neurofilament light; OR, odds ratio; and WMH, white matter hyperintensities.

*R^2 was calculated using the leave-one-out cross validation.

†*P*<0.05.

‡*P*<0.01.

§*P*<0.001.

Subgroups Analyses Between Plasma NfL and CSVD

The interaction effects by cognitive or *APOE ε4* status were revealed (Table VII in the Data Supplement). At baseline, there were no significant differences stratified by cognition and *APOE ε4* carrier on the association of plasma NfL level with CSVD, WMHs, and LIs. CMBs in the early mild cognitive impairment and *APOE ε4* (+) group showed a clear correlation with NfL (Tables VIII through IX and Figure III in the Data Supplement).

Longitudinally, the rates of plasma NfL changes were more associated with the progression of CSVD, CMBs, and WMHs in CN participants (Table X in the Data Supplement). On the contrary, an increase in the change of plasma NfL level was associated with a more progression of CSVD, WMHs, and LIs in *APOE ε4* (–) individuals rather than in *APOE ε4* (+) individuals (Table XI and Figure IV in the Data Supplement).

DISCUSSION

Our study comprehensively evaluated the associations of plasma NfL levels on baseline and progressive CSVD. The primary results showed that increased plasma NfL concentration was linked to higher risk of CSVD prevalence at baseline and CSVD progression at follow-up. In all participants, increased plasma NfL was significantly associated with a higher CSVD burden and higher prevalence of CSVD markers at baseline. Furthermore, faster change rates of NfL levels were significantly correlated with the progression of CSVD burden and MRI markers. These findings indicate that plasma NfL is a dynamic biomarker of CSVD progression in nondemented elders, especially those with normal cognitive function. Therefore, our study offers an available noninvasive blood-based tool to monitor longitudinal CSVD change and understand the future trend of CSVD change.

The novelty of this study was to demonstrate the association of plasma NfL with CSVD burden and uncover the essential roles of longitudinal plasma NfL changes by dynamically monitoring long-term CSVD development. Two main forms of sporadic CSVD have been described before, namely, arteriolosclerosis and cerebral amyloid angiopathy.[29] Therein, CMBs, WMHs, and LIs are the primary reported manifestations in MRI CSVD assessment, with WMHs being the most extensively defined radiological finding of CSVD.[30] NfL is a marker of subcortical

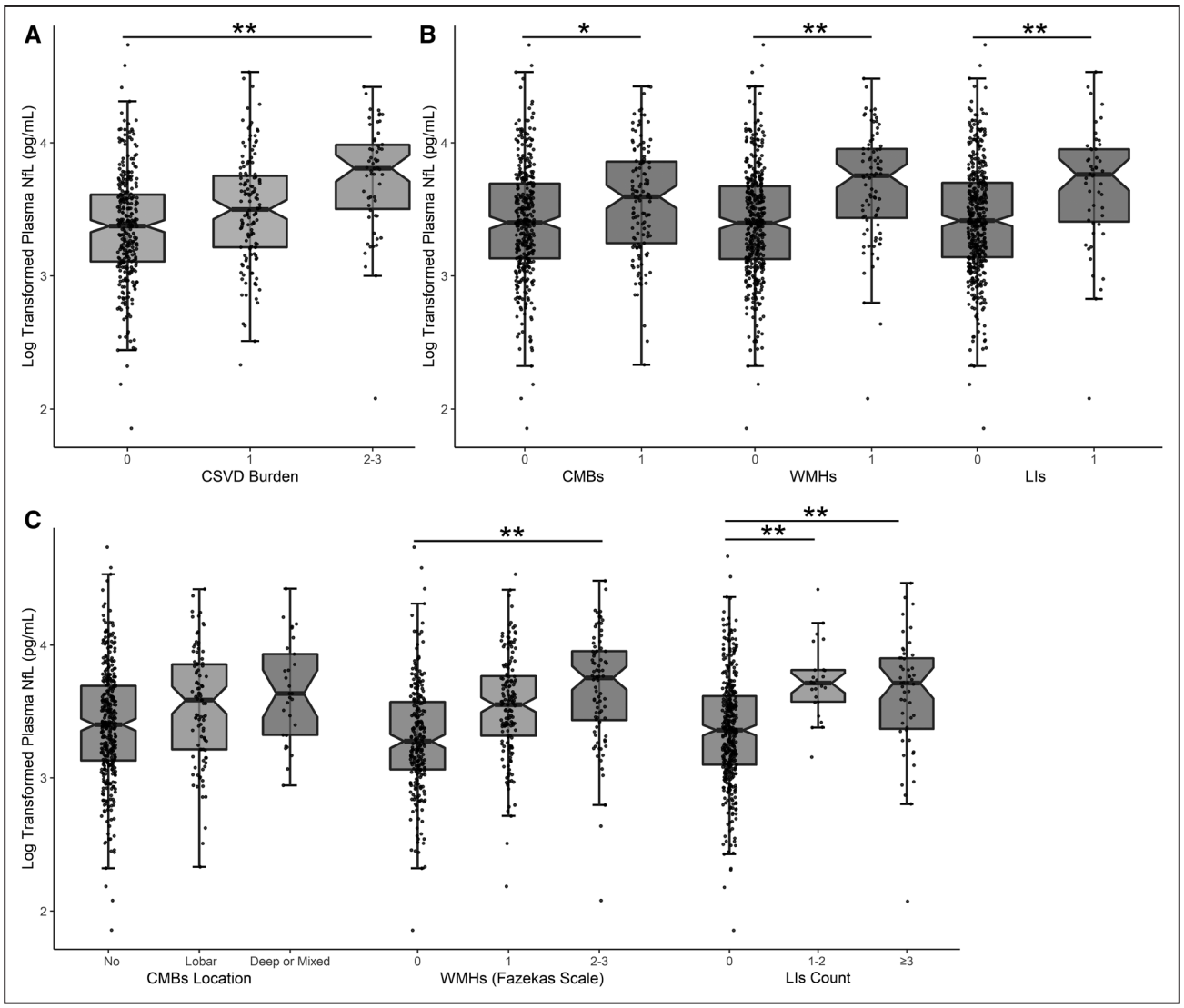

Figure 1. The cross-sectional association between baseline plasma neurofilament light chain (NfL) and cerebral small vessel disease (CSVD) burden.

A, Higher levels of plasma NfL were correlated with moderate-severe CSVD burden (*P*=0.001) but was not related to mild CSVD burden (*P*=0.296) compared with non-CSVD group. **B**, As for CSVD markers, higher levels of NfL were associated with the presence of cerebral microbleeds (CMBs; *P*=0.041) and white matter hyperintensities (WMHs; *P*=0.001) and lacunar infarcts (LIs; *P*=0.008). **C**, Detailly, higher NfL levels were associated with 2–3 points Fazekas score (*P*=0.008), 1–2 counts LIs (*P*=0.024), and >3 LIs (*P*=0.006). The *P* values were calculated using logistic regression models.

large-caliber axonal degeneration, and recent studies noted the loss of white matter microstructural integrity as a good indicator of axonal injury.[9,31] Therefore, paying attention to longitudinal WMHs changes could help better evaluate the risk of CSVD. Meanwhile, as a hemorrhagic event of chronic CSVD, CMBs play a vital part in neurodegenerative and vascular disorders.[32] The mechanism underlying the associations between CSVD burden progression and plasma NfL was linked to acute and chronic neuroaxonal damage.[15,33] Besides, the presumed vessel-originating LIs were recognized as the second most frequently reported cerebral ischemic lesions via radiological imaging after WMHs, as well as one-fourth pathogenesis of all acute ischemic stroke.[29] A previous study showed that serum NfL was a sensitive biomarker of tissue damage in recent small subcortical infarcts, resulting in ongoing axonal damage after post-ischemic immunologic or inflammatory processes.[15,34,35] Our study revealed that higher burden of chronic LIs was also associated with increased levels of NfL reflecting progressive CSVD.

Increased plasma NfL concentrations were also found in several other neurodegenerative disorders, meaning that NfL lacks specificity for CSVD diagnosis. Therefore, plasma NfL cannot be used as a tool to differentiate Alzheimer disease from other neurodegenerative diseases. Instead, it could be valuable biomarker of neurodegeneration. However, because of the moderate

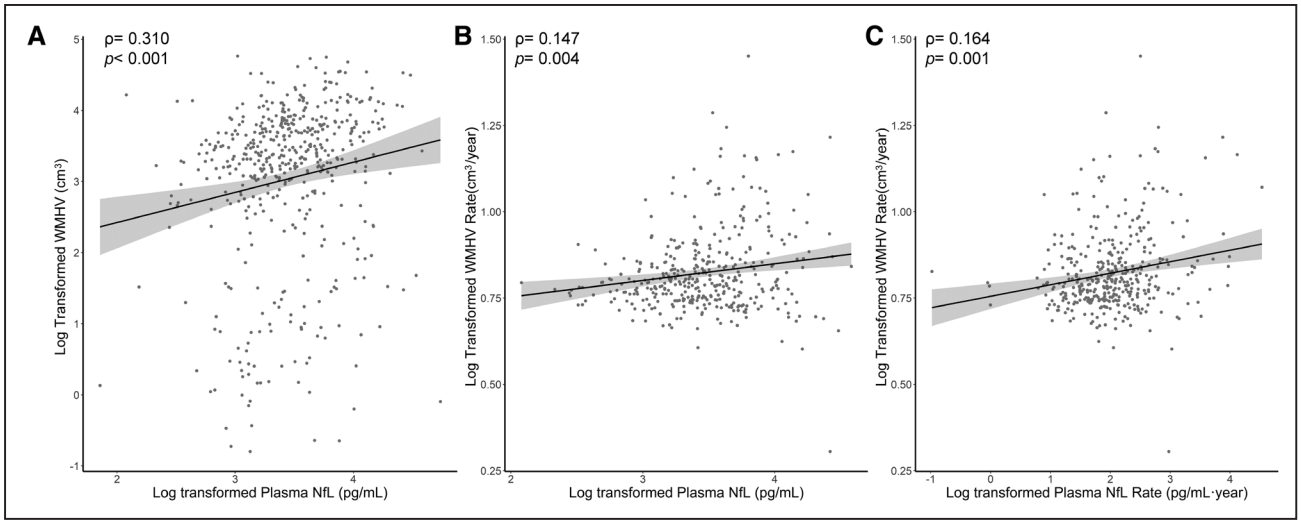

Figure 2. The correlation analyses of baseline and change rate in white matter hyperintensities volume (WMHV) with baseline and change rate of plasma neurofilament light (NfL).
A, Higher levels of plasma NfL were associated with increased baseline WMHV (ρ=0.310, P<0.001) and (**B**) accelerated changes of WMHV (ρ=0.147, P=0.004) and (**C**) change rates of NfL were associated with increased WMHV (ρ=0.164, P=0.001). The ρ and P values were calculated using the Spearman rank correlation.

results yielded by the receiver operator characteristic curve, plasma NfL would be a prognostic biomarker rather than a diagnostic biomarker according to FDA BEST biomarker categories.[36] Therefore, NfL could be used to identify the likelihood of CSVD and progression in patients with CSVD risk.

With regard to monitoring the progression of diseases, plasma biomarkers have advantageous such as noninvasiveness and easy accessibility relative to CSF biomarkers. Studies showed that plasma NfL has comparable specificities and sensitivities,[37,38] suggesting that both measures reflect similar physiological processes.[39] Blood collection is cheaper and more time efficient than MRI, which also allows for good repeatability in longitudinal studies. Plasma NfL can thus serve as a complementary tool MRI for the assessment of CSVD progression and monitoring of treatment responses and prognosis.[9]

Prevention and treatment of CSVD are limited by the incomplete understanding of its pathogenesis.[1,29] First, reducing blood pressure is the most important modifiable risk factor for CSVD.[40] Second, antiplatelet therapy, thrombolytic strategies, and statins are effective in CSVD treatment.[1,30,41] A previous study has elucidated the utility of NfL measurements in monitoring treatment effects,[42] and we speculate that NfL will play a critical role in CSVD treatment monitoring, which is urgently needed.

A few limitations of our study should be noted. Although significant associations of baseline levels and change rates of plasma NfL with CSVD progression were detected, there was a lack of data about some markers (enlarged perivascular spaces and brain atrophy) in the

Table 3. The Association Between Change Rate of Plasma NfL and CSVD Progression

	Plasma NfL rate 1-SD increase						
	Model 1		Model 2		Model 3		
Variables	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	R^{2*}
CSVD burden	1.36 (1.07–1.73)†	0.013	1.35 (1.06–1.73)†	0.015	1.38 (1.08–1.76)†	0.011	0.187
CSVD markers							
CMBs	1.14 (0.86–1.44)	0.417	1.12 (0.86–1.47)	0.391	1.15 (0.88–1.51)	0.313	0.141
WMHs (Fazekas score)	1.39 (1.10–1.75)‡	0.006	1.40 (1.10–1.78)‡	0.006	1.41 (1.10–1.79)‡	0.006	0.101
LIs	1.96 (1.42–2.72)§	<0.001	1.9 (1.39–2.64)§	<0.001	1.99 (1.42–2.77)§	<0.001	0.060

Model 1: Adjusted for age. Model 2: Model 1+adjustment for sex, education levels, MMSE, ICV, and *APOE ε4* carrier status. Model 3: Model 2+adjustment for hypertension, diabetes, hyperlipidemia, coronary heart disease, smoking status, and alcohol drinking status. *APOE ε4* indicates apolipoprotein E *ε4*; CMBs, cerebral microbleeds; CSVD, cerebral small vessel disease; ICV, intracranial volume; LIs, lacunar infarcts; MMSE, mini-mental state examination; NfL, neurofilament light; OR, odds ratio; and WMH, white matter hyperintensities.
*R^2 was calculated using the leave-one-out cross validation.
†P<0.05.
‡P<0.01.
§P<0.001.

ADNI database; associations with such markers should be further verified in the future studies. Besides, a higher proportion of *APOE ε4* carriers was found in ADNI CN participants compared with community population, the 4-year follow-up period was insufficient, and the longitudinal associations between plasma NfL and CSVD progression were not significant because most participants showed no progression of CSVD. Consequently, these findings should be verified in larger populations and cohorts with longer follow-up periods.

CONCLUSIONS

Collectively, our findings suggest that plasma NfL is a valuable noninvasive biomarker to monitor the severity of CSVD burden and CSVD markers in nondemented individuals. Furthermore, change in plasma NfL level could be a supplementary biomarker to those established MRI markers for assessing CSVD burden and tracking CSVD progression. It is worth noting that a higher plasma NfL level tends to represent a higher risk of CSVD, and a dynamic increase in NfL level might predict a greater progression of CSVD in nondemented elders.

ARTICLE INFORMATION

Received April 17, 2020; final revision received October 20, 2020; accepted November 23, 2020.

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Acknowledgments

Drs Yu, Tan, and Dong conceptualized the study, analyzed, and interpreted the data, and drafted and revised the article. Drs Qu, Tan, Shen, and Li analyzed and interpreted the data, drafted, and revised the article, did the statistical analysis, and prepared all the figures. Drs Tan, Cui, Dong, and Yu interpretation of the data and revision of the article. All authors contributed to the writing and revisions of the article and approved the final version.

Sources of Funding

This study was supported by grants from the National Natural Science Foundation of China (91849126, 81571245, and 81771148), the National Key R&D Program of China (2018YFC1314700), Shanghai Municipal Science and Technology Major Project (No.2018SHZDZX01) and ZHANGJIANG LAB, Tianqiao and Chrissy Chen Institute, and the State Key Laboratory of Neurobiology and Frontiers Center for Brain Science of Ministry of Education, Fudan University. Data collection and sharing for this project was funded by the Alzheimer disease neuroimaging initiative (ADNI; National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer Association; Alzheimer Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc; Cogstate; Eisai Inc; Elan Pharmaceuticals, Inc; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc; Fujirebio; GE Healthcare; IXICO Ltd; Janssen Alzheimer Immunotherapy Research & Development, LLC; Johnson & Johnson Pharmaceutical Research & Development LLC; Lumosity; Lundbeck; Merck & Co, Inc; Meso Scale Diagnostics, LLC; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California. Data used in preparation of this article were obtained from the Alzheimer Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

Disclosures

None.

Supplemental Materials

Tables I–XI
Figures I–IV

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