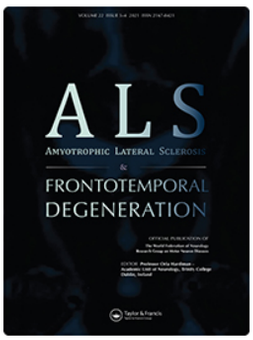

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RESEARCH ARTICLE

Cardiac troponin T is elevated and increases longitudinally in ALS patients

ULF KLÄPPE[1,2], SANHARIB CHAMOUN[1,2], QING SHEN[3], ANJA FINN[2], BJÖRN EVERTSSON[1,2], HENRIK ZETTERBERG[4,5,6,7], KAJ BLENNOW[4,5], RAYOMAND PRESS[1,2], KRISTIN SAMUELSSON[1,2], ANNA MÅNBERG[8], FANG FANG[9] & CAROLINE INGRE[1,2]

[1]Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden, [2]Department of Neurology, Karolinska University Hospital, Stockholm, Sweden, [3]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden, [4]Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden, [5]Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Psychology, Sahlgrenska Academy, University of Gothenburg, Mölndal, Sweden, [6]Department of Neurodegenerative Disease, UCL Institute of Neurology, Queen Square, London, UK, [7]UK Dementia Research Institute at UCL, London, UK, [8]Division of Affinity Proteomics, Department of Protein Science, KTH Royal Institute of Technology, Stockholm, Sweden, and [9]Unit of Integrative Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

Abstract

Objective: To test whether high-sensitivity cardiac troponin T (hs-cTnT) could act as a diagnostic or prognostic biomarker in ALS, comparing hs-cTnT to neurofilament light (NfL). *Methods:* We performed a case-control study, including 150 ALS patients, 28 ALS mimics, and 108 healthy controls, and a follow-up study of the ALS patients, during 2014–2020 in Stockholm, Sweden. We compared concentrations of hs-cTnT in plasma and NfL in the cerebrospinal fluid between cases and controls. To evaluate the diagnostic performance, we calculated the area under the curve (AUC). Hazard ratios (HRs) were estimated from Cox models to assess associations between hs-cTnT and NfL at ALS diagnosis and risk of death. The longitudinal analysis measured changes of hs-cTnT and NfL since ALS diagnosis. *Results:* We noted higher levels of hs-cTnT in ALS patients (median: 16.5 ng/L) than in ALS mimics (11 ng/L) and healthy controls (6 ng/L). Both hs-cTnT and NfL could distinguish ALS patients from ALS mimics, with higher AUC noted for NfL (AUC 0.88; 95%CI 0.79–0.97). Disease progression correlated weakly with hs-cTnT (Pearson's $r = 0.18$, $p = 0.04$) and moderately with NfL (Pearson's $r = 0.41$, $p < 0.001$). Shorter survival was associated with higher levels of NfL at diagnosis (HR 1.08, 95%CI 1.04–1.11), but not hs-cTnT. hs-cTnT increased (12.61 ng/L per year, 95%CI 7.14–18.06) whereas NfL decreased longitudinally since ALS diagnosis. *Conclusions:* NfL is a stronger diagnostic and prognostic biomarker than hs-cTnT for ALS. However, hs-cTnT might constitute a disease progression biomarker as it increases longitudinally. The underlying causes for this increase need to be investigated.

Keywords: *Case-control study, follow-up study, amyotrophic lateral sclerosis, cardiac troponin T, neurofilament proteins*

Introduction

Cardiac troponin T (cTnT) is commonly used as a biomarker for myocardial infarction (1). Several studies have detected elevated levels of cTnT in patients with neuromuscular disorders (2–8). The role of cTnT in ALS patients is, however, not fully understood as previous studies have reported largely inconsistent results. Elevated levels of cTnT were identified among ALS patients in two studies with 40 and 22 ALS patients, all free of cardiac disease (9,10). In contrast, normal cTnT levels were found in two other studies, including 28 and 60 ALS patients, respectively (11,12).

Correspondence: Caroline Ingre, MD, Ph.D., Department of Clinical Neuroscience, Karolinska Institutet, Tomtebodavägen 18A, 171 77 Stockholm, Sweden. Tel: +46 72-580 8725. E-mail: caroline.ingre@ki.se

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In the present study, we aimed to investigate the performance of high-sensitivity cTnT (hs-cTnT) in plasma as a diagnostic and prognostic biomarker for ALS, in comparison to NfL in CSF, which is currently one of the most promising biomarkers of ALS (13–21).

Materials and methods

We performed a case-control study and recruited patients who received a diagnosis of ALS between 1 January 2014 and 28 February 2020 at the Karolinska University Hospital neurology clinic that manages all ALS patients in Stockholm, Sweden ($n = 364$). Patients who met the revised El Escorial criteria for clinically definite, probable, and possible ALS were included ($n = 332$) (22). We excluded from the study patients without hs-cTnT in plasma and NfL in CSF measured at the time of diagnosis, leaving in the analysis 150 patients.

We recruited ALS mimics and healthy persons as controls. Individuals with signs of muscle weakness, who were referred to the clinic under initial suspicion of ALS but later diagnosed with other diseases, and had hs-cTnT measured, were recruited as mimics ($n = 28$; Supplementary Table 1). We reviewed the mimics in September 2020 again, to ensure their diagnosis. We included siblings and partners of ALS patients as healthy controls ($n = 108$).

We also performed a follow-up study of ALS patients. We followed patients from the date of diagnosis until the date of death or tracheostomy, or 28 February 2020, whichever came first. Among the 150 patients, 110 had at least one more measurement of hs-cTnT and 47 had at least one more measurement of NfL during follow-up (Supplementary Table 2). Thus, we defined a baseline cohort including 150 patients with a measurement at diagnosis and a longitudinal cohort including 110 patients with at least two measurements of hs-cTnT.

ALS patients were categorized as having bulbar or non-bulbar onset. We calculated diagnostic delay as the time interval between symptom onset and diagnosis. Disability was measured using the revised ALS Functional Rating Scale (ALSFRS-R). Disease progression rate was estimated by 48 minus ALSFRS-R score at diagnosis divided by diagnostic delay in months (23).

For ALS patients, CSF and blood were collected at diagnosis and repeatedly thereafter. Samples were collected from mimics during the diagnostic work-up, and from healthy controls shortly after the diagnosis of the index patient. The assessment of hs-cTnT was performed using Roche Diagnostics' Elecsys 5th generation assay (Rotkreuz, Switzerland). The measurement of NfL was based on UmanDiagnostics' sandwich enzyme-linked immunoassay (Umeå, Sweden; cat no 10-7001).

We used Kruskal-Wallis nonparametric test to compare differences in the distributions of age and sex, and the Mann–Whitney *U* test to compare hs-cTnT and NfL levels, between ALS patients and mimics as well as between ALS patients and healthy controls. To evaluate the diagnostic performance of hs-cTnT and NfL in separating ALS patients from mimics and healthy controls, we calculated Area Under the Curve (AUC) values and compared Receiver Operating Characteristic (ROC) curves (24). We compared AUC values by the Chi-square test.

Among ALS patients, we first calculated Spearman's rank correlation coefficients to measure the correlation between hs-cTnT and NfL. We then used Pearson's correlation coefficients and linear regression models to assess relationships between hs-cTnT and NfL at diagnosis and disease progression rate, adjusting for age at sampling, sex, site of onset, and diagnostic delay in linear regression. We used the Mann–Whitney *U* test to assess correlations between hs-cTnT and NfL, and site of onset.

We used the baseline cohort to assess associations between hs-cTnT and NfL at diagnosis and the risk of death after ALS diagnosis. We plotted Kaplan–Meier survival curves for patients with different levels of hs-cTnT and NfL. We used Cox models to estimate hazard ratios (HRs) and their 95% confidence intervals (CIs), with time since symptom onset as the underlying time scale. To assess the prognostic values independent of known prognostic indicators of ALS, we adjusted for sex, site of onset, age at onset, diagnostic delay, body mass index at diagnosis, disease progression rate at diagnosis, and *C9orf72* status in the analysis (25,26). hs-cTnT and NfL were mutually adjusted for one another.

We used the longitudinal cohort to present the temporal changes of hs-cTnT and NfL, using a linear regression model with cluster-robust standard errors adjusted for age and sex. We first analyzed all patients together and then according to sex, age at diagnosis (<65 and ≥ 65 years), onset type, and progression rate.

In all analyses, we considered $p < 0.05$ as a level of statistical significance. We performed the analyses in Stata software, version 16 (StataCorp, College Station, TX).

Protocol approvals and registrations

This study was approved by the Regional Ethical Review Board in Stockholm, Sweden, and followed the ethical principle as declared by the Declaration of Helsinki.

Results

The characteristics of study participants are summarized in Table 1. The ALS patients included in the study are the general representative of the entire population of ALS patients in Stockholm (Supplementary Table 3).

The median level of hs-cTnT in plasma was higher in ALS patients at baseline (16.5 ng/L) than in mimics (11 ng/L, $p < 0.001$) and healthy controls (6 ng/L, $p < 0.001$) (Figure 1 and Supplementary Table 4). 82 ALS patients (54.7%), six mimics (21.4%) and 12 healthy controls (11.1%) had hs-cTnT above the 99th percentile (1). ALS patients also had higher levels of NfL in CSF than controls.

Higher AUC was noted for NfL ($p = 0.02$) than cTnT in separating ALS patients from mimics (Table 2). Adding hs-cTnT to NfL did not increase the AUC ($p = 0.47$). The result was similar when comparing ALS patients to healthy controls. ROC curves are shown in Supplementary Figure 1. hs-cTnT did not correlate with NfL at baseline, in ALS patients (Spearman's rho −0.04; $p = 0.76$). There was a correlation between disease progression rate and hs-cTnT (Pearson's $r = 0.18$, $p = 0.04$; multivariable regression $p = 0.05$) and NfL (Pearson's $r = 0.41$, $p < 0.001$; multivariable regression $p = 0.001$). The median level of hs-cTnT was lower among ALS patients with bulbar onset (13 ng/L) than patients with non-bulbar onset (20 ng/L) ($p = 0.003$). There was no difference in the levels of NfL by type of onset.

We included in the survival analysis of the baseline cohort 125 ALS patients with baseline measures of hs-cTnT and NfL and all other prognostic factors ($n = 93$ including also *C9orf72* status; Supplementary Table 5). Supplementary Figure 2 depicts the Kaplan–Meier survival curves. After multivariable adjustment, a 1000-unit increase in NfL was associated with a higher risk of death (HR 1.08, 95% CI 1.04–1.11) (Table 3). The result was similar after further controlling for *C9orf72* status. Although increasing levels of hs-cTnT were suggested to be associated with a higher risk of death, the results were not statistically significant.

In the longitudinal cohort, after controlling for age and sex, hs-cTnT increased (12.61 ng/L per year, 95% CI 7.14–18.06; corresponding to

Table 1. Characteristics of ALS patients, ALS mimics and healthy controls, and the number of measurements of hs-cTnT in plasma and NfL in CSF.

	All ALS patients, ALS mimics, and healthy controls				ALS patients with at least one more measurement of hs-cTnT during follow-up
	ALS patients	ALS mimics	Healthy controls	*p* Value for difference	
No. of participants	150	28	108		110
No. of hs-cTnT measurements	150	28	108		110
No. of NfL measurements	150	28	13		47
Female, *n* (%)	70 (46.7)	9 (32.1)	67 (62.0)	0.006	49 (44.6)
Age at first sample, median (IQR), years	68.0 (60.4–74.1)	67.8 (51.8–75.1)	63.5 (57.4–70.2)	0.02	66.9 (60.2–73.8)
Age at onset, median (IQR), years	66.9 (59.6–73.0)	–	–	–	65.6 (58.9–72.3)
Type of onset, *n* (%)	Bulbar: 55 (36.7) Spinal: 89 (59.3) Other: 6 (4.0)	–	–	–	Bulbar: 42 (38.2) Spinal: 64 (58.2) Other: 4 (3.6)
Months from onset to diagnosis, median (IQR)	12.1 (7.5–18.2)	–	–	–	12.4 (8.6–18.3)
C9orf72 expansion[a]	10 (9.4%) out of 106 tested	–	–	–	9 (10.5%) out of 86 tested
SOD1 mutation[b]	3 (2.9%) out of 102 tested	–	–	–	3 (3.7%) out of 82 tested
BMI at diagnosis, median (IQR)	23.4 (21.3–26.9)	–	–	–	23.8 (21.2–27.1)
ALSFRS-R at diagnosis, median (IQR)	40 (35–43)	–	–	–	41 (36–43)
Disease progression rate at diagnosis, median (IQR)	0.64 (0.33–1.12)	–	–	–	0.57 (0.30–1.06)
Months of follow-up, median (IQR)	25.5 (16.7–34.5)	–	–	–	27.9 (19.6–37.4)
Death during follow-up, *n* (%)[c]	85 (56.7)	–	–	–	51 (46.4)
Months from onset to death, median (IQR)	25.0 (14.6–33.4), among 85 that died during follow–up	–	–	–	25.0 (16.8–33.4), among 51 that died during follow–up

Note. *p* Values were calculated using Kruskal–Wallis test. [a]The most common genetic risk factor for ALS. [b]The second most common genetic risk factor for ALS. [c]Death or invasive ventilation.
IQR: interquartile range; BMI: body mass index.

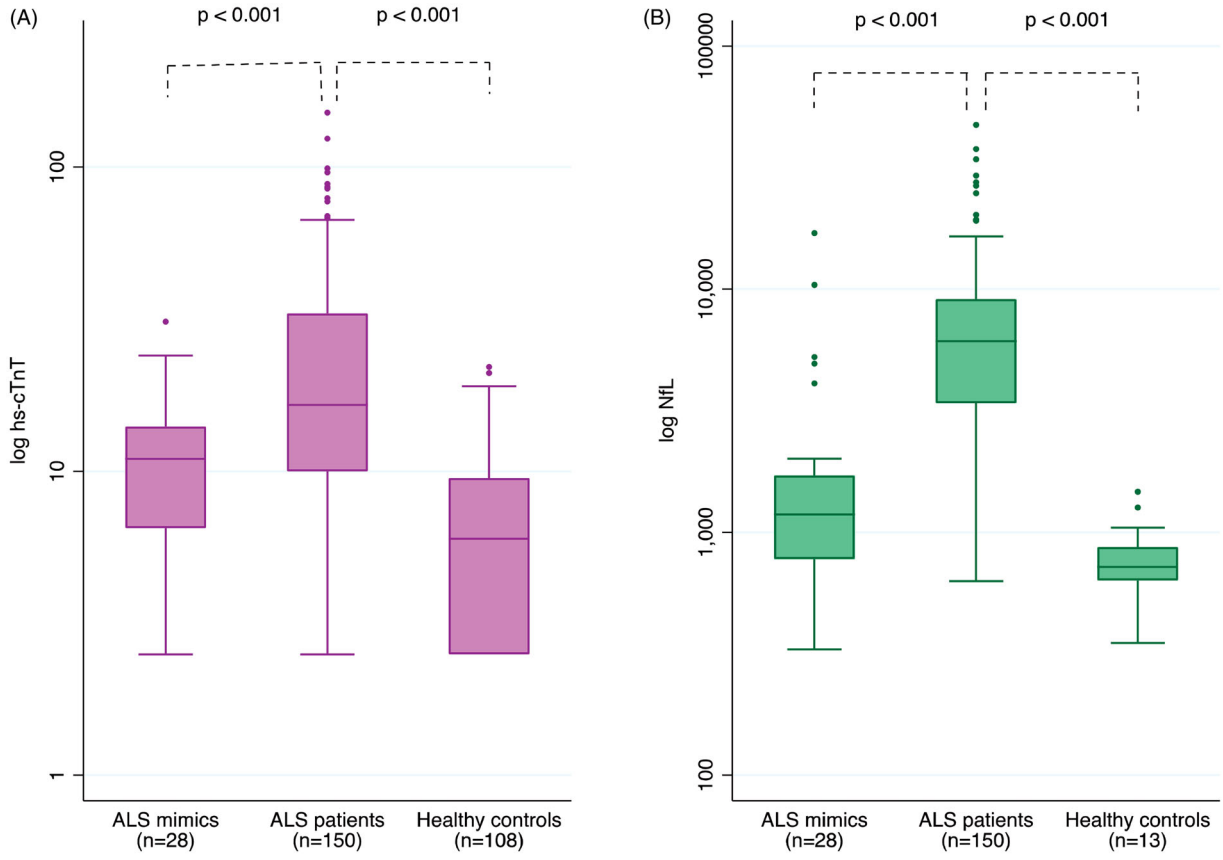

Figure 1. Boxplot on levels of (A) hs-cTnT in plasma, and (B) NfL in CSF, among ALS patients at baseline, ALS mimics, and healthy controls. All on a base 10 logarithmic scale. *p* Values were calculated using Mann–Whitney *U* test.

Table 2. Area under the curve (AUC) values with 95% CI for hs-cTnT in plasma, NfL in CSF, and combined, in separating ALS patients from ALS mimics and healthy controls.

	ALS ($n = 150$) vs ALS mimics ($n = 28$)	ALS ($n = 150$) vs healthy controls ($n = 13$)
hs-cTnT	0.70 (0.61–0.79)	0.88 (0.79–0.97)
NfL	0.88 (0.79–0.97)	0.98 (0.97–1.00)
hs-cTnT + NfL	0.89 (0.82–0.96)	0.99 (0.99–1.00)

68.7%increase per year) whereas NfL decreased (−1709 ng/L per year, 95% CI −1851 to −113; corresponding to 22.4% decrease per year) over time since diagnosis (Supplementary Table 6). The increasing hs-cTnT level was noted among all patients regardless of sex, age, type of onset, or progression rate. NfL decreased over time among patients younger than 65 years, patients with non-bulbar onset, and patients with the fastest progression rate. Figure 2 displays the temporal pattern of hs-cTnT and NfL for each ALS patient from diagnosis.

Discussion

In a case-control study of ALS supplemented with a longitudinal follow-up of the ALS patients, we found evidence of elevated hs-cTnT in ALS patients compared to mimics and healthy controls. We also demonstrated longitudinally increasing hs-cTnT levels in ALS patients after diagnosis, regardless of patient characteristics.

Previous studies have provided conflicting results on hs-cTnT levels in ALS patients compared to controls. Studies with negative findings did not directly study cTnT (11,12), whereas studies with positive findings, like our study, directly studied cTnT (9,10). We confirmed earlier studies in demonstrating elevated levels of NfL in CSF among ALS patients compared with mimics and healthy controls (14–16,18–21). In the analysis of diagnostic performance, hs-cTnT performed moderately well in distinguishing mimics from ALS patients. NfL, however, performed better, at a level similar to previous reports (15,16,18,20,21).

Elevated levels of hs-cTnT were found to correlate with faster disease progression, although weakly. Non-bulbar onset ALS patients had higher hs-cTnT levels compared to bulbar onset patients. Consistent with previous studies, NfL was found to correlate with a faster disease progression rate and was associated with a higher risk of death (15,16,18,20,21). No association was noted between the level of hs-cTnT and risk of death, however.

In our longitudinal analysis of ALS patients, hs-cTnT was found to increase over time. A

Table 3. Multivariable Cox proportional hazards regression models for hs-cTnT in plasma and NfL in CSF among ALS patients with and without adjustment for *C9orf72* repeat expansion.

	Cox regression adjusting for *C9orf72* ($n = 93$)			Cox regression not adjusting for *C9orf72* ($n = 125$)		
	HR	95% CI	*p* Value	HR	95% CI	*p* Value
hs-cTnT in plasma, per 1 unit increase	1.01	1.00–1.03	0.14	1.01	1.00–1.02	0.09
NfL in CSF, per 1000 units increase	1.08	1.03–1.14	0.001	1.08	1.04–1.11	<0.001
Female sex	0.93	0.50–1.74	0.82	0.89	0.54–1.46	0.65
Bulbar onset	1.92	0.97–3.81	0.06	1.75	1.02–3.00	0.04
Age at onset, per year increase	1.03	1.00–1.07	0.09	1.04	1.01–1.08	0.008
Diagnostic delay, per month decrease	1.05	1.01–1.09	0.01	1.03	0.99–1.06	0.15
BMI at diagnosis, per unit increase	0.98	0.88–1.09	0.72	0.99	0.93–1.06	0.82
Disease progression rate, per unit increase	2.02	1.07–3.81	0.03	1.90	1.41–2.57	<0.001
C9orf72 repeat expansion	0.68	0.14–3.20	0.62	–	–	–

Note. BMI: body mass index.

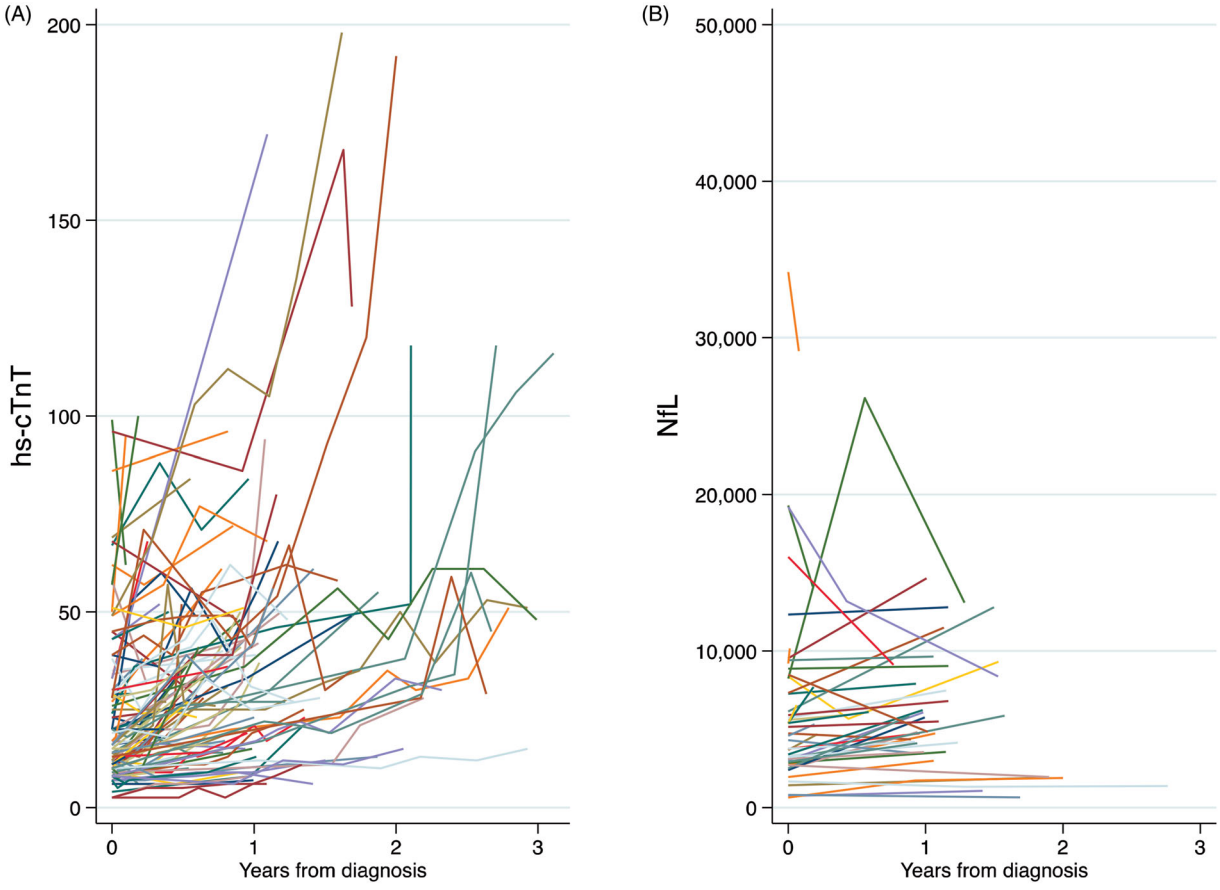

Figure 2. Temporal changes of (A) hs-cTnT in plasma ($n = 115$), and (B) NfL in CSF ($n = 47$), after ALS diagnosis.

similar pattern was noted by Mach et al., showing that ALS patients with elevated cTnT had a longer disease duration at sampling compared to those with normal cTnT levels (9). NfL slowly decreased over time, in contrast to prior studies that showed NfL to increase in early disease stages (16,27–29) and become stable thereafter (16,27,29–32). The contrasting temporal patterns of hs-cTnT and NfL indicate a potential use of hs-cTnT as an easily accessible and affordable disease progression

biomarker in clinical trials. The increasing levels over time in all subgroups of ALS patients also demonstrate its potential use.

The strengths of our study include the large sample size, the rich information on clinical characteristics, and the complete follow-up. It is to our knowledge the first study to examine the correlations between cTnT and NfL as well as clinical characteristics in ALS. There are some limitations. First, this study did not investigate the sources or pathophysiological mechanisms of the elevated and increasing levels of hs-cTnT in ALS patients. Myocardial injury (1) and defects (11), sympathetic dysfunction (33–36), cardiomyopathy (37,38), and chronic myocardia hypoxia due to respiratory failure in ALS (39), etc. might all contribute. In the present study, we had a measure of creatine kinase (CK) for 45 patients with ALS and found a moderate correlation between CK and hs-cTnT (Spearman's rho = 0.42; data not shown). Future studies should therefore examine the correlation between hs-cTnT and disease stage or number of body regions with involvement of upper or lower motor neurons, to better understand if hs-cTnT reflects central or peripheral damage. This applies to patients with ALS but also ALS mimics. Another limitation is the heterogeneous group of mimics.

In summary, we provide evidence that hs-cTnT in plasma is elevated in ALS patients compared to ALS mimics and healthy controls. However, NfL in CSF performs better than hs-cTnT, both as a diagnostic and prognostic biomarker. In contrast to NfL, hs-cTnT increases longitudinally as the disease progresses and might constitute a potential disease progression biomarker.

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Declaration of interest

- Ulf Kläppe reports no disclosures.
- Sanharib Chamoun reports no disclosures.
- Qing Shen reports no disclosures.
- Anja Finn reports no disclosures.
- Björn Evertsson reports no disclosures.
- Henrik Zetterberg has served at scientific advisory boards for Denali, Roche Diagnostics, Wave, Samumed, Siemens Healthineers, Pinteon Therapeutics and CogRx, has given lectures in symposia sponsored by Fujirebio, Alzecure and Biogen, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program; all outside the submitted work.
- Kaj Blennow has served as a consultant, at advisory boards, or at data monitoring committees for Abcam, Axon, Biogen, JOMDD/Shimadzu. Julius Clinical, Lilly, MagQu, Novartis, Roche Diagnostics, and Siemens Healthineers, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program; all outside the submitted work.
- Rayomand Press has received grants from Pfizer and CSL Behring; all outside the submitted work.
- Kristin Samuelsson has served as a member at scientific advisory boards for Alnylam Pharmaceuticals and Akcea Therapeutics; all outside the submitted work.
- Anna Månberg reports no disclosures.
- Fang Fang reports no disclosures.
- Caroline Ingre serves as a member of the ALS Advisory Board EU for Biogen, a member of the Publication Steering Committee for Cytokinetics, a board member of the data monitoring committee of APL-ALS 206 for Apellis Pharmaceutical, a board member of the Stiching TRICALS Foundation and has received grants from Pfizer; all outside the submitted work.

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ORCID

Henrik Zetterberg http://orcid.org/0000-0003-3930-4354
Caroline Ingre http://orcid.org/0000-0001-5327-7204

Data availability statement

Anonymized data will be made available upon reasonable requests to the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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