Evaluation of Neurofilaments as a Prognostic Biomarkers in Amyotrophic Lateral Sclerosis

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Synopsis

Neurofilaments are markers of axonal injury and are considered promising biomarkers in Amyotrophic lateral sclerosis (ALS) disease. This study supported the role of neurofilaments as a prognostic biomarker for ALS disease based on the meta-analysis of literature.

Introduction

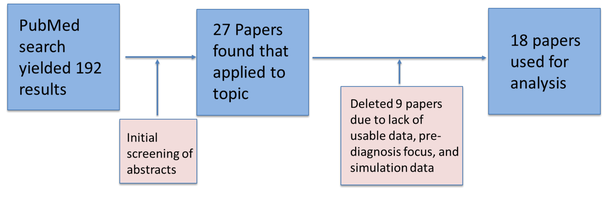
The ALS is a fatal neurodegenerative disease characterized by a progressive degeneration of upper and lower motor neurons, resulting in muscle wasting and typically leading to death from respiratory failure within 3 to 5 years of onset. As per the FDA Guidance for Industry 2019 on Developing Drugs for Treatment in ALS, the FDA encourages sponsors to incorporate exploratory biomarkers in all phases of drug development. Among various biomarkers studied for ALS, neurofilaments, a marker of axonal injury and neurodegeneration, are considered promising biomarkers of ALS because of their significantly elevated levels in patients with ALS. Both light (NfL) and heavy (pNfH) chain neurofilaments present in cerebrospinal fluid (CSF) and plasma have been studied in the literature as a potential prognostic biomarker for ALS

Objective

The objective of this study is to determine the role of neurofilaments in the prognosis of ALS.

Materials and Methods

Data Collection:
A PubMed search was used to collect studies evaluating the neurofilament levels in ALS patients. Relationships between neurofilaments (both NfL and pNfH in CSF and plasma) and clinical endpoints were collected. Clinical endpoints included ALS Function Rating Scale-revised (ALSFRS-R), disease progression (DP) slope and mortality. Correlation coefficients were collected to examine the association between neurofilament levels and ALSFRS-R, as well as between neurofilament and DP slope. To evaluate the association between neurofilaments and mortality, hazard ratios with 95% confidence intervals were collected.



Data Analysis:
Heterogeneity analysis was assessed using the Cochran's Q test and the I2 statistic. A random-effects model was chosen for the analysis considering substantial heterogeneity (I2 > 50%) in the data. The statistical analysis was conducted using 'metafor' package version 3.4.0 in R version 4.1.3.

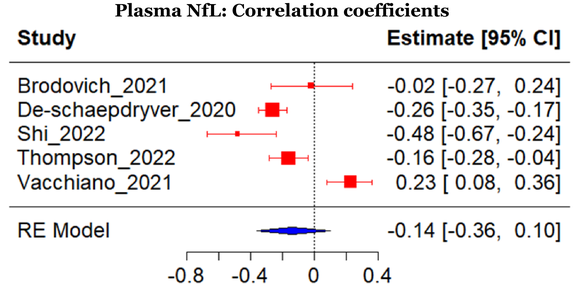
Results and Discussion

Study	Study Type	Region	Data Collection
Brodovich 2021	Prospective	France	--
De-schaepdryver 2020	Retrospective	Italy	2009 - 2018
Gille 2019	Prospective	Belgium	2016 - 2017
Lu 2015	Prospective	UK	--
Steinacker 2017	Prospective	Germany	2012 - 2015
Thompson 2022	Prospective	UK	2017 - 2020
Abu-rumeileh 2020	Prospective	Italy	2009 - 2019
Boylan 2012	Prospective	USA	--
Gaiani 2017	Retrospective	Italy	2010 - 2016
Illan-gala 2018	Prospective	Spain	--
Shi 2022	Prospective	China	--
Menke 2015	Prospective	UK	2009 - 2013
Schaeodryver 2019	Retrospective	Belgium	2007 - 2018
Steinacker 2015	Prospective	Germany	2010 - 2014
Benatar 2020	Prospective	USA	2015 - 2017
Thouvenot 2020	Prospective	France	--
Vacchiano 2021	Prospective	Italy	2014 - 2021
Verde 2019	Prospective	Germany	2010 - 2016

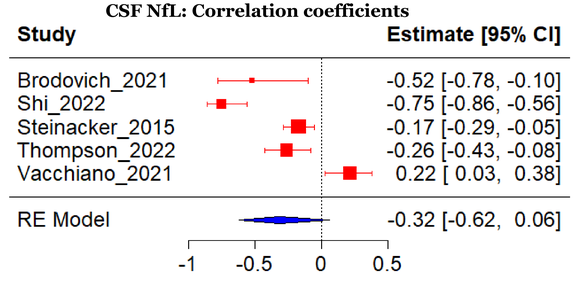
- Higher levels of neurofilaments have been observed in ALS subjects.
- Plasma and CSF neurofilaments were positively correlated.
- Relationships between neurofilaments and clinical endpoints are shown here:

1. ALSFRS-R total score: Higher neurofilament levels may be linked to low ASLFRS-R total scores, or a decline in physical function.

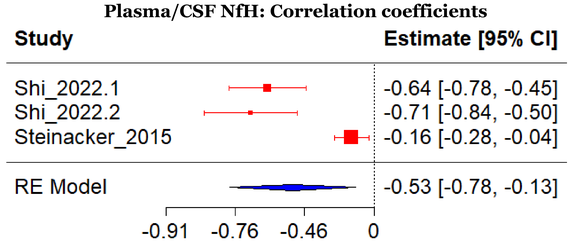
Plasma NfL: Correlation coefficients



CSF NfL: Correlation coefficients



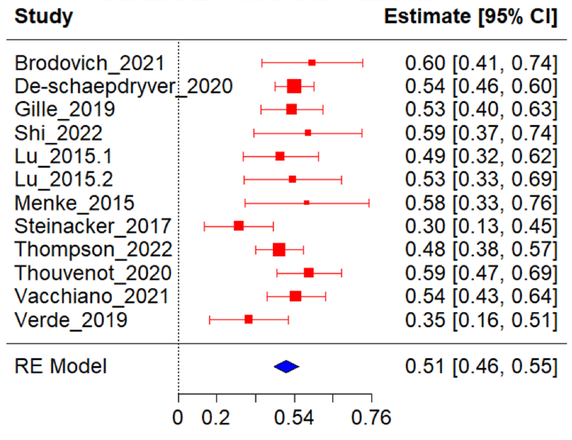
Plasma/CSF NfH: Correlation coefficients



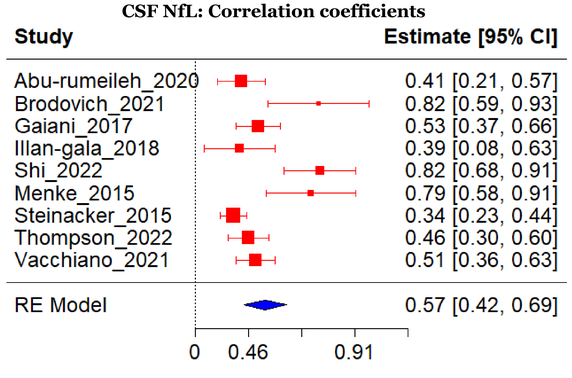
2. Disease Progression Slope: Both NfL and pNfH in plasma and CSF were positively correlated with DP slope.

$$DP\ slope = \frac{48 - ALSFRS\ total\ score}{months\ from\ symptom\ onset\ at\ first\ sampling}$$

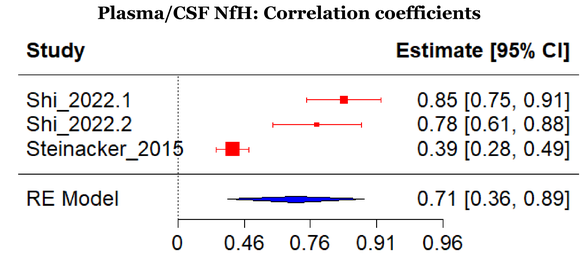
Plasma NfL: Correlation coefficients



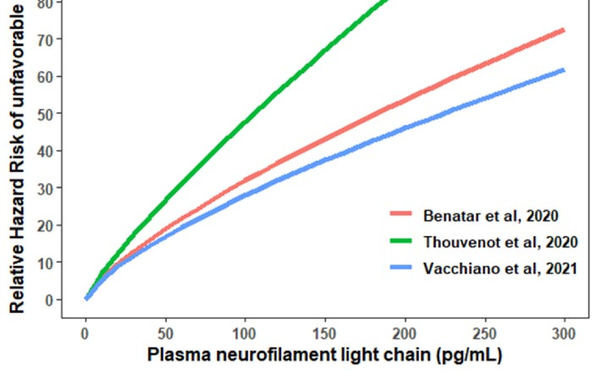
CSF NfL: Correlation coefficients



Plasma/CSF NfH: Correlation coefficients



3. Mortality: Higher plasma/CSF neurofilament levels were associated with a higher risk of unfavorable clinical outcomes (death, tracheostomy and/or permanent assisted ventilation) in ALS patients.



Conclusion

- Higher neurofilament levels were associated with lower ALSFRS-R total score and faster disease progression (DP slope).
- Higher neurofilament levels were associated with a higher risk of unfavorable clinical outcomes in ALS patients.
- The applicability of these findings in randomized controlled trials is being investigated using existing database at FDA and may provide valuable insights in evaluating neurofilaments role as a potential surrogate endpoint.

References:

- Understanding ALS. The ALS Association. https://www.als.org/understanding-als. Published 2022. Accessed July 13, 2022.
- Food and Drug Administration. Amyotrophic Lateral Sclerosis: Developing Drugs for Treatment Guidance for Industry. 2019. Accessed July 13, 2022. https://www.fda.gov/media/130964/download