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Serum Neurofilament Light Chain Levels Correlate with Poor Prognosis in Ischemic Stroke: an Updated Systematic Review and Meta-Analysis

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ADMINISTRATIVE INFORMATION

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Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 12 November 2024 and was last updated on12 November 2024.

INTRODUCTION

Review question / Objective The neurofilament light chain (NfL) is a neuronal cytoplasmic protein with high expression in myelinated axons and has a significant role in the diagnosis and prognosis of primary neurological disorders. However, whether serum neurofilament light chain (sNfL) levels are associated with poor prognosis in ischemic stroke (IS) patients has been controversial. Here, we present an updated systematic review and meta-analysis that aims to thoroughly assess the correlation between sNfL levels and poor prognosis in ischemic stroke.

Condition being studied Up to September 28, 2024, we comprehensively searched the databases of PubMed, Web of Science, Embase, and the Cochrane Library to identify observational studies evaluating the association of sNfL levels on poor functional outcomes (modified Rankin Scale [mRS] score of 3-6), infarct volume, and mortality in patients with IS. The combination was evaluated by including as many studies as possible that reported the association between sNfL levels and outcomes as adjusted ratios, and the quality of the included studies was assessed using the Newcastle-Ottawa scale. A random-effects meta-analysis was performed with Review Manager 5.4, with subgroup analyses based on different times of blood sampling, detection methods, and locations, and the I2Test and Funnel plots were used to assess heterogeneity and publication bias. Finally, a cut-and-paste method was used to adjust for potential publication bias.

METHODS

Search strategy Pubmed ("Neurofilament light chain proteins" [All Fields] OR "Neurofilament light chain"[All Fields] OR "NfL" [All Fields]) AND (stroke OR (cerebrovascular AND (event OR disease OR accident))) AND (outcome OR outcomes OR consequence OR consequences OR endpoint* OR

end-point* OR dementia OR cognitive OR cognition OR executive OR memory OR attention OR "processing speed" OR visuospatial OR language OR disability OR gait OR motor OR functional OR mrs OR "modified Rankin scale" OR dependency OR IADL OR Barthel OR mortality OR death OR recurrence OR recurrent OR functionality OR survival OR depression OR depressive OR depressed OR "quality of life" OR
QoL)
Web of science TS = ("Neurofilament light chain proteins" OR "Neurofilament light chain" OR "NfL") AND TS = (stroke OR (cerebrovascular AND (event OR disease OR accident))) AND TS=(outcome OR outcomes OR consequence OR consequences OR endpoint* OR end-point* OR dementia OR cognitive OR cognition OR executive OR memory OR attention OR "processing speed" OR visuospatial OR language OR disability OR gait OR motor OR functional OR mrs OR "modified Rankin scale" OR dependency OR IADL OR Barthel OR mortality OR death OR recurrence OR recurrent OR functionality OR survival OR depression OR depressive OR depressed OR "quality of life" OR QoL)
Embase ("Neurofilament light chain proteins" OR "Neurofilament light chain" OR "NfL") AND (stroke OR (cerebrovascular AND (event OR disease OR accident))) AND (outcome OR outcomes OR consequence OR consequences OR endpoint* OR end-point* OR dementia OR cognitive OR cognition OR executive OR memory OR attention OR "processing speed" OR visuo spatial OR language OR disability OR gait OR motor OR functional OR mrs OR "modified Rankin scale" OR dependency OR IADL OR Barthel OR mortality OR death OR recurrence OR recurrent OR functionality OR survival OR depression OR depressive OR depressed OR "quality of life" OR QoL)
Cochrane Library ID Search Hits
#1 MeSH descriptor: [Stroke] explode all trees
#2 "Neurofilament light chain proteins" OR "Neurofilament light chain" OR "NfL"
#3 outcome OR outcomes OR consequence OR consequences OR endpoint* OR end-point* OR
dementia OR cognitive OR cognition OR executive OR memory OR attention OR "processing speed" OR
visuo spatial OR language OR disability OR gait OR motor OR functional OR mrs OR "modified
Rankin scale" OR dependency OR IADL OR Barthel OR mortality OR death OR recurrence OR recurrent
OR functionality OR survival OR depression OR depressive OR depressed OR "quality of life" OR QoL
#4 #1 AND #2 AND#3.

Participant or population Table 1 summarizes the basic characteristics of the studies included in the Meta-analysis, all of which were observation studies. They were published over a 9-year period from 2015 to 2024. European studies predominated, with three studies from Germany , two from Sweden two from Switzerland and one from Finland. The remaining studies were from China,Korea,Taiwan,United States.The combined sample size of all studies was 3441 cases.

Intervention No intervention.

Comparator No.

Study designs to be included Observational studies evaluating the association of sNfL levels on poor functional outcomes (modified Rankin Scale [mRS] score of 3-6), infarct volume, and mortality in patients with IS. The combination was evaluated by including as many studies as possible that reported the association between sNfL levels and outcomes as adjusted ratios, and the quality of the included studies was assessed using the Newcastle-Ottawa scale.observational study.

Eligibility criteria Inclusion criteria: (1) published in English; (2) prospective or retrospective cohort studies of patients with IS or transient ischemic attack (TIA) or reporting IS or TIA as a subgroup of all stroke patients; (3) association between sNfL and poor functional outcome (modified Rankin Scale [mRS] score of 3-6), infarct volume, or mortality after stroke was reported during any follow-up; (4) association between sNfL level and stroke outcome was reported as a multivariable-adjusted effect size with 95% confidence interval (CI). We excluded (1) non-English language articles, (2) duplicate studies, (3) animal experiments, and (4) reviews, case reports, conference abstracts, and articles for which relevant data were not available. When study populations overlapped across multiple publications, we included the most recent or complete publication.

Information sources PubMed, Web of Science, Embase, and the Cochrane Library.

Main outcome(s) The association of sNfL levels on poor functional outcomes (modified Rankin Scale [mRS] score of 3-6)in patients with IS . （follow-up 3 months）.

Additional outcome(s) The association of sNfL levels on infarct volume and mortality in patients with IS.

Data management A standardized data extraction form was used to extract basic data, including first author, year of publication, country, total population, method of stroke or TIA determination, time of blood sampling, method of sNfL detection, definition of outcome, duration of follow-up, and reported correlation factors and adjusted covariates. The quality of the literature was assessed using the three criteria of selection, comparability, and outcome according to the guidelines of the Newcastle-Ottawa Scale (NOS).

Quality assessment / Risk of bias analysis The quality of the literature was assessed using the three criteria of selection, comparability, and outcome according to the guidelines of the Newcastle-Ottawa Scale (NOS).In addition, publication bias was assessed using funnel plots and the Egger test, a statistical tool used to quantitatively assess whether funnel plots are symmetrical. $P < 0.05$ was considered statistically significant, indicating publication bias.Finally, a cut-and-paste method was used to adjust for potential publication bias.

Strategy of data synthesis This Meta-analysis was performed using the software "Review Manager" (RevMan, version 5.4). All extracted numerical data are presented as absolute numbers or proportions. Effect sizes for the association between sNfL and outcome were combined using the ratio of ratios (OR) and 95% CI, with P 50 percent[32]. If significant heterogeneity was detected, a random effects model should be used. When significant between-study heterogeneity existed, we performed sensitivity analyses to assess its effect on the combined outcome by systematically excluding each study. We also conducted subgroup analyses based on the time of blood sampling, the method of sNfL detection, and the subject area of the participants. In addition, publication bias was assessed using funnel plots and the Egger test, a statistical tool used to quantitatively assess whether funnel plots are symmetrical. $P < 0.05$ was considered statistically significant, indicating publication bias.

Subgroup analysis In the included 11 studies, meta-analysis was performed based on time of blood sampling , detection method , and location; the results are shown in Table 2. In the subgroup analysis based on the time of blood sampling, there was a significant difference in the results of the heterogeneity test (time of blood sampling within 24 hours of stroke: $I2 = 78\%$, $P < 0.01$, and time of blood sampling 24 hours after stroke: $I2 = 0\%$, $P = 0.99$). Meanwhile, the heterogeneity between the two groups was statistically significantly different ($I2 = 82\%$, $P = 0.02$). Thus, the time of blood sampling was an important source of heterogeneity. Subgroup analysis based on the sNfL detection method showed no heterogeneity among the three groups ($I2 = 0\%$, $P = 0.75$), suggesting that the detection method did not affect the results of the Meta-analysis. However, we found that three studies using the ECLIA assay did not show an association with poor function (OR = 1.71 95% CI: 0.90-3.26; P=0.10), and similarly, two studies using the ELISA assay did not conclude an association (OR = 1.59 95% CI: 0.63-4.02; P = 0.33). According to subgroup analysis based on geographic location, there was no heterogeneity among the three groups ($I2 = 0\%$, P=0.53), suggesting that geographic location does not influence the results of Meta-analysis.

Sensitivity analysis We performed a sensitivity analysis to assess the robustness of the results with state software. When a study included in the meta-analysis was removed one at a time, the results of the meta-analysis remained generally constant, which suggests that the current meta-analysis is stable.

Country(ies) involved China.

Keywords neurofilament light chain; ischemic stroke; outcome; meta-analysis.

Contributions of each author

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