



# Diagnostic Value of Serum Neuron-Specific Enolase Level in Patients With Acute Ischemic Stroke; A Systematic Review and Meta-Analysis

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## Abstract

**Background:** We aim to assess the predictive value of serum neuron-specific enolase (NSE) level in patients with acute ischemic stroke referring to the emergency department.

**Methods:** This systematic review and meta-analysis performed, considering the PRISMA and MOOSE statement guidelines. A computerized literature search of the known medical database conducted by using the relevant keywords. We included studies published before November 2016 in which stroke patients compared with non-stroke controls and also studies evaluating the serum levels of NSE in the study groups. Statistical analysis was pooled in a random effect model analysis using the Comprehensive Meta-Analysis software.

**Results:** We included 12 articles in the qualitative and quantitative analysis, that their quality acceptable based on the Newcastle Ottawa Scale (NOS scale). The pooled effect estimates showed that NSE is significantly higher in ischemic stroke patients in comparison with their controls with a high effect estimate [OR 9.68, 95% CI (3.06 to 30.6)]. The effect estimate remained statistically significant under the fixed and random effects model.

**Conclusion:** Our results show higher levels of NSE in patients with stroke than in the control group, indicating that NSE plays a role in the diagnosis of stroke. In terms of prognosis, there is evidence regarding the direct and indirect relationship; and it founded that serum levels of NSE is higher in larger stroke volume, which needs further research.

**Keywords:** Ischemia; Meta-analysis; Phosphopyruvate hydratase; Predictive value of tests; Stroke

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## Introduction

Acute ischemic stroke is one of the severe diseases, considering the fifth leading cause of mortality and morbidity in the United States. It reported that 1 of every 20 persons is dying due to this disease, and every 4 minutes, someone dies due to stroke.<sup>1-4</sup> Timely diagnosis results from proper history taking and neurological examinations, but still, there is an active role for para-clinical and radiological evaluation so can make the diagnosis, prognosis, and outcome prediction.<sup>5-9</sup>

Investigations have been conducted to assess the probable role of serum biomarkers for various aspects of stroke subject, from diagnosis to outcome prediction, and research is still on. Neuron-specific enolase (NSE) is the one, probably taken into consideration more than the others. It is a glycolytic catalyze enzyme, present in neuronal, neuroendocrine tissues, and cerebrospinal fluid (CSF).<sup>10</sup> Kansal et al reported that its measurement in CSF might assist in the diagnosis of neurodegenerative

diseases, such as Creutzfeldt-Jacob and ischemic stroke.<sup>11</sup> Recently, studies provide evidence regarding the possible correlation between ischemic stroke and elevation of serum NSE.<sup>12-14</sup> Anand et al. investigated time to increase the serum level of NSE in the case of middle cerebral artery occlusion.<sup>15</sup> Singh et al reported that NSE level is significantly high in patients with severe neurological deficit than the groups of mild or moderate.<sup>16</sup> Besides, the study of Lu et al demonstrates that after treatment of ischemic stroke, there is a strong correlation between the reduction of NSE serum level and good prognosis.<sup>17</sup>

It seems that the role of serum biomarkers, including NSE, for diagnosis of stroke has been previously taken into account; but it is still vague. In this systematic review and meta-analysis, we aim to assess the diagnostic value of serum NSE level in patients with acute ischemic stroke, to weigh whether its level could consider as a diagnostic factor or not?

## Methods

This systematic review and meta-analysis performed during 2017 with a team from Iranian and Egyptian researchers. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) statement guidelines during the preparation of this systematic review and meta-analysis.<sup>18,19</sup> All steps performed in line with the *Cochrane Handbook of Systematic Reviews and Meta-analysis* of interventions and all analyses were performed in line with the equations recommended by Borenstein et al in the introduction to meta-analysis.<sup>20,21</sup>

## Literature Search Strategy

A computerized literature search of the known medical database of PubMed, EMBASE, ISI Web of Sciences, CINAHL and Scopus using the following keywords: ((Phosphopyruvate Hydratase) OR (Neuron Specific Enolase)) AND "Stroke". We included studies published in English before November 2016 in which stroke patients compared with non-stroke controls and also studies evaluating the serum levels of NSE in the study groups.

## Study Selection

Two authors independently screened the literature search results for relevant studies. All studies published before November 2016 included. In the first step, titles and abstracts of the retrieved records screened, and then full-text articles of selected papers at the first step were evaluated. Any disagreement between the two reviewers resolved by discussion with a third reviewer.

## Eligibility Criteria

(1) Studies whose population was patients with stroke compared with non-stroke controls; (2) studies evaluating the serum levels of NSE in the study groups; (3) studies that were described as observational studies, whether prospective or retrospective, evaluating NSE in stroke and non-stroke patients. We excluded animal studies and also studies whose data were not reliable for analysis.

## Data Extraction

Data were extracted independently by 2 reviewers to a uniform data extraction sheet. The extracted data includes (1) characteristics of the study design of included studies, (2) characteristics of the study population, and (3) data of the study outcomes.

## Risk of Bias Across Studies

To explore the publication bias across studies, we constructed funnel plots to present the relationship between effect size and precision. Evidence of publication bias was assessed by (1) the Egger's regression test, and (2) the trim and fill method.

## Synthesis of Results

The prognostic value of NSE in stroke patients presented in observational studies in different formats. Studies reported their outcomes as (1) the mean difference and variance between the stroke group and the control group, (2) correlation coefficient between NSE and stroke, or (3) binary data as odds ratios with their 95% CI. The Cohen's (d) effect size and its variance computed from all studies according to equations provided in the Introduction to meta-analysis. Then the Cohen's (d) effect size was converted into the log point estimate (odds ratio) and its variance. Finally, the log (OR) and its variance were pooled in a random effect model analysis using the Comprehensive Meta-Analysis software. Heterogeneity assessed by the Cochrane Q test, chi-square test for the Q statistics distribution, and the I-square test. The trim and fill method was used to investigate small study effects and the possibility of publication bias.

## Results

### Study Selection

The primary literature search resulted in 1300 records, and finally, 12 articles with a total of 970 patients included in the meta-analysis.<sup>13,14,16,22-30</sup> Of the excluded studies, there were two relevant articles (Cunningham et al<sup>31</sup> and Wunderlich et al<sup>32</sup>) as they reported the effect estimates in figures whose data could not be extracted and were not reliable for analysis. The PRISMA flow diagram of the current study has shown in Figure 1.

### Characteristics and Quality of Included Studies

Baseline characteristics of these studies summarized in Table 1. The quality of included studies was acceptable, according to the Newcastle Ottawa Scale (NOS).

### The Correlation Between NSE and Stroke

Figure 2 shows the forest plot of the OR of NSE in stroke vs. control cases with 95% CI under the fixed and random effect models. The pooled effect estimates showed that NSE is significantly higher in ischemic stroke patients compared to their controls with a high effect estimate (OR 9.68, 95% CI [3.06 to 30.6]). The effect estimate remained statistically significant under the fixed and random effects model.

Figure 3 shows the funnel plot of standard error by point (log) of NSE in stroke vs. control cases with the standard error of under the random effect model. It showed no evidence of publication bias. The trim and fill method gave the same effect estimate suggesting no small study effects.

## Discussion

The current meta-analysis aimed to clarify whether there was any significant difference in NSE levels between stroke patients and control. Our findings show that NSE serum levels are considerably higher in stroke patients

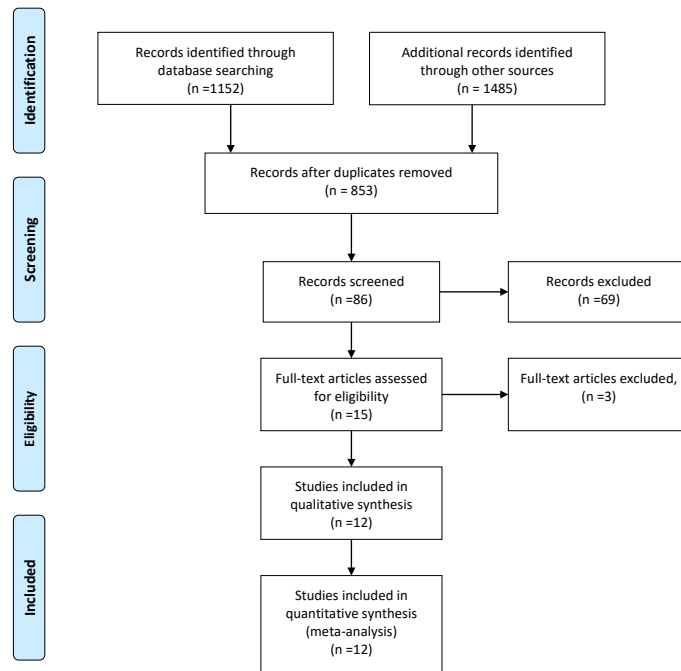


Figure 1: PRISMA Flow Diagram.

compared to their controls.

Stroke is an emergency medical condition which threatens the patient's life and causes high levels of disability and mortality all over the world. In response to stroke, brain cells produce particular changes, such as releasing specific neuronal markers into the circulation and increasing neuronal isoenzymes levels, which results in brain damage. The central nervous system insult is evaluated by several neurobiochemical markers which have a standard role in the diagnosis and management of stroke patients with neurological side effects. NSE a neuronal form of the intracytoplasmic glycolytic enzyme enolase is one of these markers. Several studies have verified that NSE can be discovered in the peripheral blood of stroke patients and could be a useful marker for acute ischemic stroke.

Likewise, the conclusion of our meta-analysis is in agreement with Anand et al<sup>15</sup> who conducted a systematic review in 2005 consisted of 597 patients, and reported that NSE was considerably higher in stroke patients in comparison with control. They also showed that NSE significantly correlated with infarct volume, however, it did not correlate with functional outcome, and there was no clear relationship between NSE and stroke severity. Also, a systematic review by Ahmed et al<sup>33</sup> confirmed that NSE positively correlated with subacute infarct volume.

These results are consistent with the findings of nine out of the 12 included studies in the current meta-analysis, which showed that NSE levels were meaningfully higher in stroke patients than in the control group while, other three included studies showed no significant difference between NSE and control.<sup>28,34,35</sup> This contrast might be

explained by the slow released of NSE from damaged tissue to peripheral blood.

In terms of functional outcomes, included studies used different methods to assess functional outcomes such as Barthel index, Lindley scale, modified Rankin Scale (mRS), Glasgow Outcome Score, and activities of daily living scale. Three studies<sup>22,32,35</sup> reported a notable correlation between NSE and functional outcome. Moreover, Pandey et al,<sup>14</sup> and Bharosay et al<sup>25</sup> concluded that the higher the NSE level, the more significant functional worsening. However, Shahrokhi et al showed no significant difference between NSE serum concentrations and clinical outcome.<sup>36</sup> Using different evaluation scales and the small sample size included might explain this contrast.

Nine included studies<sup>14,16,22-28</sup> used the National Institutes of Health Stroke Scale (NIHSS) to evaluate the neurological status and stroke severity. All of them reported a notable correlation between NIHSS scores and NSE levels.

Two studies reported on NSE levels at the onset of a stroke. Oh et al<sup>23</sup> found that the initial NSE was significantly higher in stroke patients than control within less than 24 hours. Wunderlich et al,<sup>32</sup> with a total of 66 patients, reported that NSE levels showed a first rise 2-3 hours after onset of the first stroke symptoms, but they did not compare that with control levels.

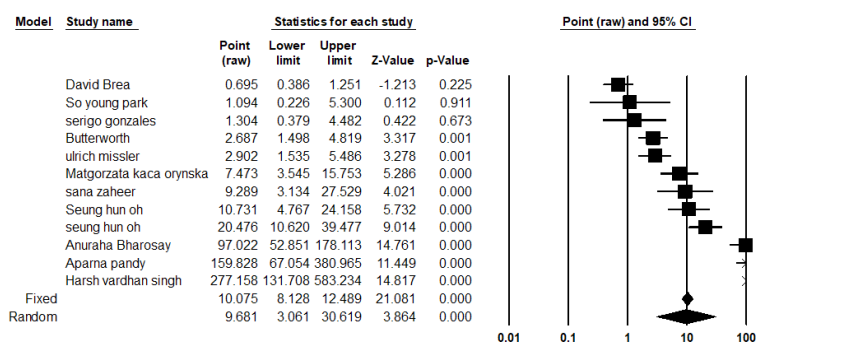
Regarding infarct volume, four included studies<sup>23,28,30,32</sup> demonstrated a significant correlation between NSE and infarct volume.

Brea et al<sup>28</sup> involved patients with acute ischemia and patients with intracerebral hemorrhage and showed that

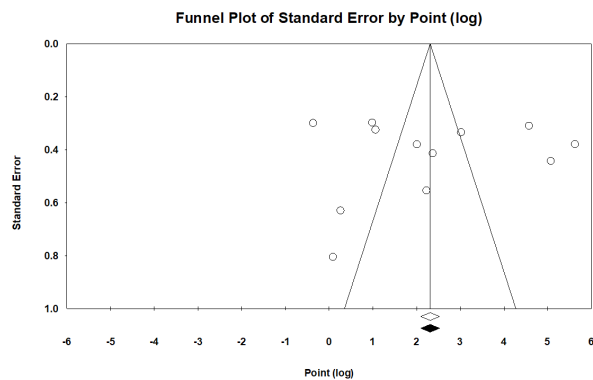
**Table 1.** Summary and Baseline Characteristics of the Final Included Studies

| Reference                       | Methodology  | Statistical Sample  | Prognosis Exploration Methodology                   | Description   |
|---------------------------------|--|---|---|---|
| Butterworth et al <sup>29</sup> | Hospitalized patients suffering from ischemic stroke were 103 that 51 of them were under control                     | The United Kingdom, # male: 63; # female: 40 age average: 73.6.           | Barthel index, mRS<br>Lindley score, Infarct volume | In this study, NSE correlated with ischemic stroke, but any correlation between first, second, and third days did not exist.  |
| Pandey et al <sup>14</sup>      | 200 patients suspected to ischemic and 50 of them were under control   | India<br># male: 82 above 21 years old<br># female: 38 above 21 years old | NIHSS   | In this study, the patient's NSE level in the seventh day for the severe group was higher.  |
| Hill et al <sup>22</sup>        | 38 patients hospitalized in 2 hospitals with an ischemic stroke diagnosis  | Canada;<br># male: 18, # female: 10                                       | NIHSS, mRS  | In this study, the NSE level for those suffering from AIS was higher, and it had a direct correlation with prognosis.   |
| Missler et al <sup>30</sup>     | Hospitalized patients for ischemic stroke check-in hospitals.  | Germany;<br># male: 32, # female: 12<br>Age average: 65.1                 | CT infarct volume<br>GCS at 6 months                | In this study, NSE and CVA volume correlated, but any correlation with outcome was not perceived.   |
| Zaheer et al <sup>13</sup>      | 75 visiting patients to check AIS, which approved in the second day by CT scan.                                      | Germany;<br># male: 47, # female: 28<br>Age average: 61.9                 | Arrival GCS<br>Thirtieth day mRS                    | In this study, NSE correlated with GCS and MRS of patients, and it is a prognosis factor.   |
| Oh et al <sup>23</sup>          | 109 visiting patients suspected to AIS that MRI approved their CVA.  | South Korea;<br># male: 42, # female: 21<br>Age average: 64.3             | NIHSS, mRS  | Arrival NSE of patients directly correlated with the outcome of patients.   |
| Oh et al <sup>24</sup>          | All visiting patients for AIS check  | South Korea;<br># male: 42, # female: 39<br>Age average: 66.7             | Lesion volume in MRI, NIHSS of the seventh-day      | Serum NSE level had a direct correlation with CVA volume and arrival NIHSS  |
| Bharosay et al <sup>25</sup>    | 251 suspected patients of CVA that 150 of them suffering patients, and the rest considered as the controlling group. | India;<br># male:95, # female: 55<br>Patients age: between 35 to 85       | NIHSS   | In this study; Serum NSE level of the severe group was higher than others   |
| Kaca et al <sup>26</sup>        | 71 patients suffering from AIS included in the study, and 41 of them considered as the controlling group             | Poland;<br># male: 42, # female: 29<br>Age average: 71                    | NIHSS, Barther score, mRS                           | In this study; NSE with stroke volume and patient's prognosis d not correlated.   |
| Gonzalez et al <sup>27</sup>    | 61 hospitalized patients with ischemic stroke diagnosis.   | Cuba;<br># male: 33, # female: 31<br>Age average: 65.6                    | NIHSS   | In this study; NSE correlated with patients' prognosis  |
| Brea et al <sup>28</sup>        | 224 hospitalized patients with ischemic stroke and hemorrhagic diagnosis   | Spain;<br># male: 114, # female: 110<br>Age average: 69.6                 | NIHSS, mRS  | In this study; it determined that serum NSE level in hemorrhagic patients is higher and also its level is correlated with ischemic and hemorrhagic patients prognosis |
| Singh et al <sup>16</sup>       | 100 patients suffering from CVA that their NSE checked 72 hours later.   | India   | NIHSS   | In this study; serum NSE level was correlated with NIHSS  |

Abbreviations: NSE, neuron-specific enolase; AIS, acute ischemic stroke; CVA, cerebrovascular accident; NIHSS, National Institutes of Health Stroke Scale; GCS, Glasgow coma scale; mRS, modified Rankin Scale.



**Figure 2.** Forest Plot of the Odds Ratio of NSE in Stroke vs. Control CASES With 95% CI Under the Fixed and Random Effect Models.



**Figure 3.** Funnel Plot of the Log (OR) of NSE in Stroke vs. Control Cases With The Standard Error of Under the Random Effect Model.

higher levels of NSE were associated with poor functional outcome in both acute ischemia and intracerebral hemorrhage patients. Pandey et al<sup>14</sup> stratified stroke into different subtypes and showed that patients with hemorrhagic stroke had higher levels of NSE than patients with ischemic stroke. These results are supported by the results of Andersen et al<sup>37</sup> who showed that NSE was more in patients with hemorrhagic stroke than infarct stroke.

### Strength Points

The present meta-analysis demonstrated no heterogeneity regarding the significant effect of NSE on stroke between the included studies. The effect estimate was consistent under the fixed and random effects model. Additionally, the funnel plot method showed no evidence of publication bias. The trim and fill method gave the same effect estimate of meta-analysis, suggesting no small study effects, this indicates that our results are highly consistent and reliable.

### Limitations

Study limitations come back to the variations between the included studies in defining the period of acute stroke, the measures of functional outcomes, the severity of stroke scales, and the methods of NSE concentrations. Also, 2 studies were excluded due to unreliable data extraction from them, as they reported the effect estimates in figures whose data could not be extracted and were unreliable for analysis.

### Conclusion

Our results show higher levels of NSE in patients with stroke than in the control group, indicating that NSE plays a role in the diagnosis of stroke. In terms of prognosis, there is evidence regarding the direct and indirect relationship; and it founded that serum levels of NSE is higher in larger stroke volume, which needs further research.

### Conflict of Interest Disclosures

The authors declare that they have no conflict of interests.

### Ethical Statement

The study protocol approved by the University review board (IR.TUMS.MEDICINE.REC.1396.3905).

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