

Neuron-specific enolase as a prognosticator in cardiac arrest patients: key considerations

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Neuron-specific enolase (NSE) is an “intracellular glycolytic enzyme” that is predominantly found in neurons and can be detected in serum and cerebrospinal fluid after neuronal injury. The estimation of NSE for diagnostic purposes has been in clinical practice for a long time. It is a valuable biomarker for various tumors and neuro pathologies.^[1] Importantly, NSE has also gained importance as a prognosticator in post-cardiac arrest patients. Nevertheless, there are some important concepts surrounding its application in this population. Therefore, we need to focus on those points carefully while using it for this purpose.

Correlating neuron-specific enolase levels in post-cardiac arrest patients

A recently published research article concluded that the prehospital administration of high-dose methylprednisolone resulted in a significant reduction of interleukin 6 (IL-6) levels 24 hours after admission, but NSE levels remained unchanged in out-of-hospital cardiac arrest (OHCA) patients.^[2] However, it merits further discussion on NSE. We must note that although NSE is the only recommended biomarker for predicting the neurological prognosis in cardiac arrest patients, various factors need to be considered as well.^[3] A multicenter study published in 2017 involving a total of 1053 patients of in-hospital cardiac arrest or OHCA treated with targeted temperature management (TTM) at 32–34 °C observed that the NSE threshold for poor outcome was >90 µg/L.^[4] In contrast, the cutoff value recommended for NSE was 60 ng/mL (60 µg/L) at 48 hours and/or 72 hours as per the 2021 European guidelines.^[5]

Additionally, another recently published study focusing on the difference in cutoff values for patients with an initial nonshockable versus shockable rhythm found a great margin of difference (69.3 vs. 102.7 ng/mL, respectively).^[6] I am not sure whether the value of 69.3 should be for the shockable rhythm group and

102.7 for the nonshockable group, and not vice versa. This is because the “median NSE level was significantly higher in the non-shockable group than in the shockable group (104.6 [40.6–228.4] vs. 25.9 [16.7–53.4] ng/mL).”^[6] Notably, all patients were treated with TTM in that study, although the temperature was not specified.^[6] Importantly, considering the fact that 94% of patients presented with an initial shockable rhythm in the study by Obling et al.,^[2] it is unsurprising that the maximum value of NSE observed was only 24.6 µg/L. Furthermore, the statement by them “there are no pharmacological intervention studies demonstrating reduced NSE levels in resuscitated OHCA patients”^[2] is incorrect, as no pharmacological intervention can directly lead to a reduction in NSE levels, unlike IL-6 levels.

Timing of the sampling

The timing of the sample taken for assessing the NSE level also plays a role in predicting the outcome. The poor outcome, as per the cerebral performance categories grading of 3–5 in OHCA subjects treated with TTM 33 °C, was observed when the NSE value was more than 50.2 µg/L on Day 4, with 100% specificity. The NSE level of more than 20.0 mcg/L on Day 4, along with a change of more than 0.0 mcg/L from Day 3 to Day 4, also predicted a poor outcome with 100% specificity. These observations could lead to conclusions that NSE levels are a useful predictor for neurological outcome at 1 month and long-term mortality, while the highest associations occurred mainly on Day 4 and Day 3.^[7]

Neuron-specific enolase ratio versus the absolute thresholds

The most fascinating thing is that we can learn a few more vital points if we analyze a study published in 2018. Notably, that study was planned with the background of variations of the threshold levels of NSE obtained for predicting poor outcomes with 100% specificity. In addition, the NSE levels had notable variations between laboratories. Hence, that study focused on the ratio of the NSE levels rather than “absolute value thresholds.”^[8] That study concluded that the NSE ratio is a distinctive method to quantify its changes over a period. The ratio of more than one reflects the probable evolving neuronal injury. Furthermore, an NSE ratio greater than 1.7 for 48:24 hours demonstrated 100% specificity for poor outcomes in this population.^[8]

Neuron-specific or nonspecific enolase?

In addition to the aforementioned factors, the major reason for the conflicting results between various studies could be due to the assessment of the incorrect isoenzyme (subunit) of the enolases. Initially, the γγ enolase was found in the neurons, while the αα enolase was found in the glial cells, also known

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Emergency and Critical Care Medicine (2026) 6:2

Received: 21 September 2025; Accepted: 3 November 2025

Published online: 3 January 2026

<http://dx.doi.org/10.1097/EC9.000000000000167>

as “non-neuronal enolase.” Their susceptibility to triggering factors such as temperature, chloride ions, and urea varies significantly.^[9] The $\gamma\gamma$ enolase and the hybrid form ($\alpha\gamma$ enolase) were found outside the brain too subsequently. Thus, measuring both $\gamma\gamma$ and $\alpha\gamma$ enolase happens while we measure the so-called “NSE,” leading to false conclusions.^[9] Furthermore, the hemolysis of the sample could introduce errors, as the $\alpha\gamma$ enolase is abundant in erythrocytes.

To conclude, although NSE is a good biomarker for predicting the neurological outcomes in post-cardiac arrest patients, it needs strong consideration of the important factors discussed here. Future studies focusing mainly on the ratio with accurate measurement of the exact isoenzyme of the NSE will guide us in a better direction. This requires the involvement of the pathologists and biochemists, besides the clinicians.

Conflict of interest statement

The author declares no conflict of interest.

Author contributions

Sethuraman RM wrote, reviewed, and edited the paper.

Funding

None.

Ethical approval of studies and informed consent

Not applicable.

Acknowledgements

None.

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How to cite this article: Sethuraman RM. Neuron-specific enolase as a prognosticator in cardiac arrest patients: key considerations. *Emerg Crit Care Med*. 2026;6(2):84–85. doi: 10.1097/EC9.0000000000000167