



Early neurological improvement as a predictor of outcomes after endovascular thrombectomy for stroke: a systematic review and meta-analysis

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ABSTRACT

Background Early neurological improvement (ENI) is a potential predictor for 90-day outcomes following mechanical thrombectomy for acute ischemic stroke (AIS). We performed a systematic review and meta-analysis to better understand whether ENI can be used as a surrogate for long-term outcomes following mechanical thrombectomy for AIS.

Methods Following the PRISMA guidelines, a systematic literature review of the English language literature was conducted using PubMed, MEDLINE, and Embase. ENI definition, including timing and degree of improvement on the National Institutes of Health Stroke Scale (NIHSS), was catalogued for each included study. Outcomes of interest included 90-day modified Rankin Scale (mRS) 0–2, symptomatic intracranial hemorrhage (sICH), and mortality. We calculated pooled ORs and their corresponding 95% confidence intervals (CI) for all definitions of ENI.

Results We included nine studies with 2355 patients in our analysis. ENI definitions included improvement in NIHSS of 8 points, 4 points, 12%, and 30% or greater. There was a significant association between ENI and mRS 0–2 rates (OR 8.62, 95% CI 4.86 to 15.29; $p < 0.001$). Significance of the association was maintained across all definitions ($p < 0.001$). Moreover, achieving ENI was a significant predictor of reduced odds for reported sICH rates (OR 0.11, 95% CI 0.06 to 0.21; $p < 0.001$). There was a significant association between ENI and reduction in mortality rates (OR 0.09, 95% CI 0.05 to 0.15; $p < 0.001$).

Conclusions Broadly defined, ENI is a promising predictor of good functional outcome at 90 days and is associated with lower rates of mortality and sICH.

INTRODUCTION

Stroke is a widespread medical event that impacts patients' lives, often resulting in reduced independence.¹ Assessing outcomes following treatment for acute ischemic stroke (AIS) traditionally includes a multitude of measurements. A good outcome is commonly defined as a modified Rankin Scale (mRS) score of 0–2 at 90 days post-treatment.² The mRS is typically measured at 90 days after treatment and is used to assess the degree of disability in patients who have suffered a stroke. The National Institutes of Health Stroke Scale (NIHSS) is a parameter which can be measured sooner than 90

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Early neurological improvement has thus far been used to assess the clinical improvement in patients 24 hours after stroke treatment.

WHAT THIS STUDY ADDS

⇒ This study examines the literature on early neurological improvement and its predictive value for long-term outcomes.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

⇒ Our systematic review and meta-analysis indicates that early neurological improvement is a promising predictor for 90-day outcomes following mechanical thrombectomy for acute ischemic stroke.
⇒ Our study also compares different definitions of early neurological improvement and highlights the need for a consistent definition of the term.

days post-treatment, most commonly at admission and after 24 hours as a deficit rating scale, and can be used as a predictor of functional outcome and mortality.^{3,4}

Early neurological improvement (ENI) has been used as a 24-hour measurement to assess a change in NIHSS score.⁵ ENI has been defined in several different ways, most commonly as an integer improvement in the NIHSS score after 24 hours of 8, but also as a percentage change in the NIHSS score and as an improvement of 4, 6, and 10 in the NIHSS score after 24 hours.^{6–8} If it can be validated as a reliable early predictor of long-term outcome, ENI will be a valuable tool for informing patients and their families of their prognosis in a timely manner. To our knowledge, a meta-analysis and systematic review of the literature addressing ENI as a predictor of 90-day outcomes has not yet been performed. To assess whether ENI can be used as a reliable predictor of good functional outcome following mechanical thrombectomy treatment for AIS, we performed a systematic review and meta-analysis of studies that reported on ENI and 90-day functional outcome, including a comparison of different definitions of ENI.

METHODS

Search strategy

On 28 January 2022, following the PRISMA guidelines for performing systematic reviews, a systematic literature review of the English language literature was conducted within the Nested Knowledge Autolit software per the drafted protocol from inception, using PubMed, Embase, Web of Science, and Scopus.⁹ Based on each database, different combinations of possible keywords and/or MeSH terms were used for that purpose. Keywords and MeSH terms included: “stroke”, “cerebral infarction”, “thrombectomy”, “NIHSS”, “National Institutes of Health Stroke Scale”, “early”, “neurological improvement”, “neurological outcome”, “functional outcome”, “functional independence”, “clinical outcome”, “clinical improvement”. Moreover, we did an extensive manual search through the references of the included articles to retrieve any missed papers.

Screening process

We included all original studies fulfilling our pre-determined PICO: Population was patients with AIS with reported ENI, Intervention was thrombectomy, there was no Control group, the Outcomes of interest were the modified Rankin Scale (mRS) 0–2, mortality, and symptomatic intracerebral hemorrhage (sICH). We excluded papers where the ENI was not described, review articles, duplicate studies including the same patients presented in another included paper, case reports, case series with fewer than five patients, and conference abstracts. We did not pose any limitations regarding sample size, study design, or patients’ characteristics.

Two authors carried out the title and abstract screening against the pre-defined criteria. This was followed by a full text screening of any retained studies of the first screening step. In both stages, the senior author was consulted to resolve any conflicts in the decisions.

Data extraction

Following a pilot extraction, an extraction sheet was built and the extraction was performed by at least two authors. The extracted data included study characteristics, baseline data of the included patients, and the aforementioned outcomes of interest. After performing the extraction, a third author carried out an extensive revision of the extracted data to avoid any prior mistakes.

Risk of bias

We assessed the risk of bias using ROBINS-I, a tool for assessing risk of bias in non-randomised studies of interventions.¹⁰ Two authors evaluated the quality of each study, which was adjudicated by a third author when needed.

Statistical analysis

Using R software version 4.1.2, we calculated pooled ORs and their corresponding 95% CIs. A random model was adopted to pool all data due to heterogeneity among the included studies in defining ENI. Heterogeneity was assessed using Q statistics and the I^2 test, where $I^2 > 50\%$ or $p < 0.05$ were considered significant.¹¹ Among the performed analysis, the number of studies was < 10 so publication bias (Egger’s regression test) and the impact of sample size (meta-regression) were not tested.¹² Since the included studies used different definitions of ENI, we used subgroup analyses to investigate different definitions and test for statistical differences among them.

RESULTS

Search and screening results

Following the removal of 1586 duplicate records, we retrieved 800 papers for further screening. We excluded 776 records at the title and abstract screening stage, thus retaining 24 records for full-text screening. Finally, nine papers were determined to satisfy our inclusion criteria with the appropriate report of outcomes of interest (see online supplemental figure S1).

Study characteristics and risk of bias

Of the nine included studies, six used a retrospective design and five were multicenter studies. The sample size of the included studies ranged from 91 individuals to 568, with reported outcomes at 3 months of follow-up for all studies. The median NIHSS score at baseline and patients’ characteristics/comorbidities are shown in table 1. Five papers included in the meta-analysis defined ENI as a reduction in NIHSS score of 8 or more,^{13–17} Weyland *et al* defined ENI as any improvement in the NIHSS score in 24 hours,¹⁸ Soize *et al* defined ENI as a reduction in NIHSS score of 4 or more,¹⁹ Pu *et al* defined ENI as a 12% or greater reduction in NIHSS score,²⁰ and Cao *et al* defined ENI as a 30% or greater improvement in NIHSS score.²¹ Definitions of both ENI and sICH are shown in online supplemental table S1. All definitions of ENI focused on improvement of score from baseline to 24 hours after baseline.

For all included studies there was no high risk of bias among all assessed domains. However, certain specific bias risk was identified in specific study aspects. A detailed assessment of risk of bias is shown in online supplemental table S2.

Functional independence (mRS 0–2)

Nine studies with 2355 patients reported the functional independence rates in relation to ENI. Overall, there was a significant association between ENI and mRS 0–2 rates (OR 8.62, 95% CI 4.86 to 15.29; $p < 0.001$); however, a significant heterogeneity was observed among the included studies ($I^2 = 84\%$, $p < 0.001$). On further stratification of studies based on their definition of ENI, the significance of the association was maintained across all definitions ($p < 0.001$; figure 1). Moreover, the residual heterogeneity dropped to an insignificant level between studies ($I^2 = 37\%$, $p = 0.171$), confirming the different definition as the main source of the overall heterogeneity. Nevertheless, the odds of achieving functional independence were significantly variable among different ENI subgroups/definitions, as shown by the test for subgroup differences ($p < 0.001$).

Incidence of sICH

Three studies of 1208 patients reported the incidence rates of sICH as associated with ENI. Overall, having ENI was a significant predictor of reduced odds for the reported sICH rates (OR 0.11, 95% CI 0.06 to 0.21; $p < 0.001$), with no heterogeneity among the included studies ($I^2 = 0\%$, $p = 0.694$). This significance was present across different ENI definitions, except for ≥ 8 NIHSS points¹³ (OR 0.16, 95% CI 0.01 to 2.99; $p = 0.220$); however, there was no significant variability across different ENI subgroups ($p = 0.694$; figure 2).

Mortality rates

Five studies with 1161 patients reported the association between ENI and subsequent mortality. There was a significant association between ENI and the reduction in mortality rates (OR 0.09, 95% CI 0.05 to 0.15; $p < 0.001$), with no significant heterogeneity among the included studies ($I^2 = 18\%$, $p = 0.302$). This

Table 1 Characteristics of the included studies

Study	Design	Setting	Sample size	Follow-up duration (months)	Baseline NIHSS (IQR): ENI achieved	Baseline NIHSS (IQR): ENI not achieved	Mean (SD) age, years: ENI achieved	Mean (SD) age, years: ENI not achieved	Median (IQR) age, years: ENI achieved	Median (IQR) age, years: ENI not achieved	Male (%): ENI achieved	Male (%): ENI not achieved	HTN (%): ENI achieved	HTN (%): ENI not achieved	DM (%): ENI achieved	DM (%): ENI not achieved	Smoking (%): ENI achieved	Smoking (%): ENI not achieved	CAD (%): ENI achieved	CAD (%): ENI not achieved
Weyland ¹⁸	Retrospective	Single center	549	3	15 (1–41)	18 (0–38)	75 (28–99)	67.5 (49–91)	47	59	81	77	22	31	14	14	27	35		
Guengo ¹⁴	Retrospective	Multicenter	237	3	15 (9–23)	17 (9–39)	68 (53–78)	64 (55–76)	53	64	53	60	16	25	19	26			12.9	10.4
Sun ¹⁵	Prospective	Single center	187	3	28 (16–34)	17 (9–34)	60 (11)	59 (10)	75.8	88	66.1	73.6	22.6	29.6					25.2	
Wirtz ¹⁶	Retrospective	Single center	155	3	18 (14–24)		71.5 (61–82)	48.1	48.1	76.7		26.4								
Heit ¹³	Prospective	Multicenter	91	3	17 (13–21)	15.5 (9.5–20)	68 (61–76)	71 (59–81)	48	52	74	80	26	33						
Soize ¹⁹	Retrospective	Single center	244	3	17 (14–21)	19 (14–23)	65.5 (51.5–76)	69.0 (58.5–78)	44.5	53.4	44.5	44.1	11.8	16.1	28.3	22.5			20.5	24.6
Pu ²⁰	Retrospective	Multicenter	568	3	16 (11–19)	16 (12–21)	64 (54–72)	65 (55–73)	63.7	61.3	60.6	65.5	17.3	19.7	28.9	26.4				
Cao ²¹	Retrospective	Multicenter	97	3	14 (11–17)	17 (12–20)	60.8 (9.2)	62.9 (10.7)	71.4	56.4	66.7	61.8	23.8	16.4	40.5	29.1				
Cal ¹⁷	Prospective	Multicenter	227	3	15.5 (10.5–20.5)	14 (7–21)	62.86 (13.93)	67.65 (11.64)	60	56	56	57	10	14	16	24	12	19		

¹Wirtz et al did not stratify characteristics by ENI status; relevant characteristics for the entire study are listed in the "ENI achieved" column

²MD, coronary artery disease; DM, diabetes mellitus; ENI, early neurological improvement; HTN, hypertension; NIHSS, National Institutes of Health Stroke Scale.

*Write et al did not stratify characteristics by ENI status; relevant characteristics for the entire study are listed in the "ENI achieved" column. CAD, coronary artery disease; DM, diabetes mellitus; ENI, early neurological improvement; HTN, hypertension; NIHSS, National Institutes of Health Stroke Scale.

significance persisted among the different definitions of ENI, with no significant variability among the definitions ($p=0.296$; figure 3).

DISCUSSION

In this meta-analysis and systematic review we have shown that ENI of various definitions is correlated with 90-day outcomes following thrombectomy for AIS. These findings are important because it will allow clinicians to inform patients and their families about the likelihood of long-term outcomes without the need to wait the full 90 days. Additionally, we found that patients who achieve ENI had a significantly lower rate of mortality at 90 days and lower rates of sICH compared with those who did not achieve ENI. This association between ENI and good outcomes is likely due to the fact that patients who demonstrate a significant improvement in the NIHSS score at 24 hours are poised to improve further until the clinical course for recovery from their stroke stabilizes at day 4.^{8 22}

We found that, although there were multiple definitions of ENI, all definitions were associated with good functional outcomes at 90 days. This holds true for safety outcomes (mortality, sICH), except in the study by Heit *et al* in which no significant association between sICH and ENI was found.

Using retrospective analyses, previous authors have found that ENI is significantly correlated with 90-day outcomes.^{6 23 24} These previous studies, however, had small patient cohorts, making it difficult to extrapolate the results to broader patient populations. However, even though previous studies have had small cohorts, the association between ENI and good outcomes has been consistent with the present study.⁸ Our study adds to the current literature by increasing the power of these studies with a larger cohort of 2355 patients in the form of a systematic review and meta-analysis. With this larger patient population, we achieved results consistent with the smaller studies that were analyzed. Additionally, our study examined the value of using different definitions of ENI, with results showing that all definitions of ENI were significantly correlated with good functional and safety outcomes.

Our meta-analysis has a number of limitations. The major limitation that must be noted is the heterogeneity in the definitions of ENI. Most of the studies analyzed did not agree on a definition of ENI, and definitions ranged from any improvement in NIHSS score at 24 hours to an 8-point improvement in NIHSS score at 24 hours. Other studies used percentage thresholds ranging from 12% to 30% improvement in NIHSS at 24 hours. This meant that we were not able to pool together these studies under a single definition of ENI, thereby decreasing the power of our study. Similarly, NIHSS scores trend towards being higher for left hemisphere strokes than for right hemisphere strokes, and this bias must be considered when using the NIHSS score.²⁵

Another limitation which must be noted is that we did not have access to patient-level data. It has been shown that underlying pathologies such as increased blood pressure and increased mean glucose levels, and varying treatment modalities such as pretreatment with intravenous thrombolysis are associated with outcomes.^{26–28} We were unable to control for these factors since we did not have access to data that detailed individual patient characteristics and treatment. Furthermore, there were several studies which would have otherwise been eligible for our analysis but did not include patient data. Instead, these studies only reported on the analysis of their data without providing the raw data for our analysis. Despite these limitations, we were able

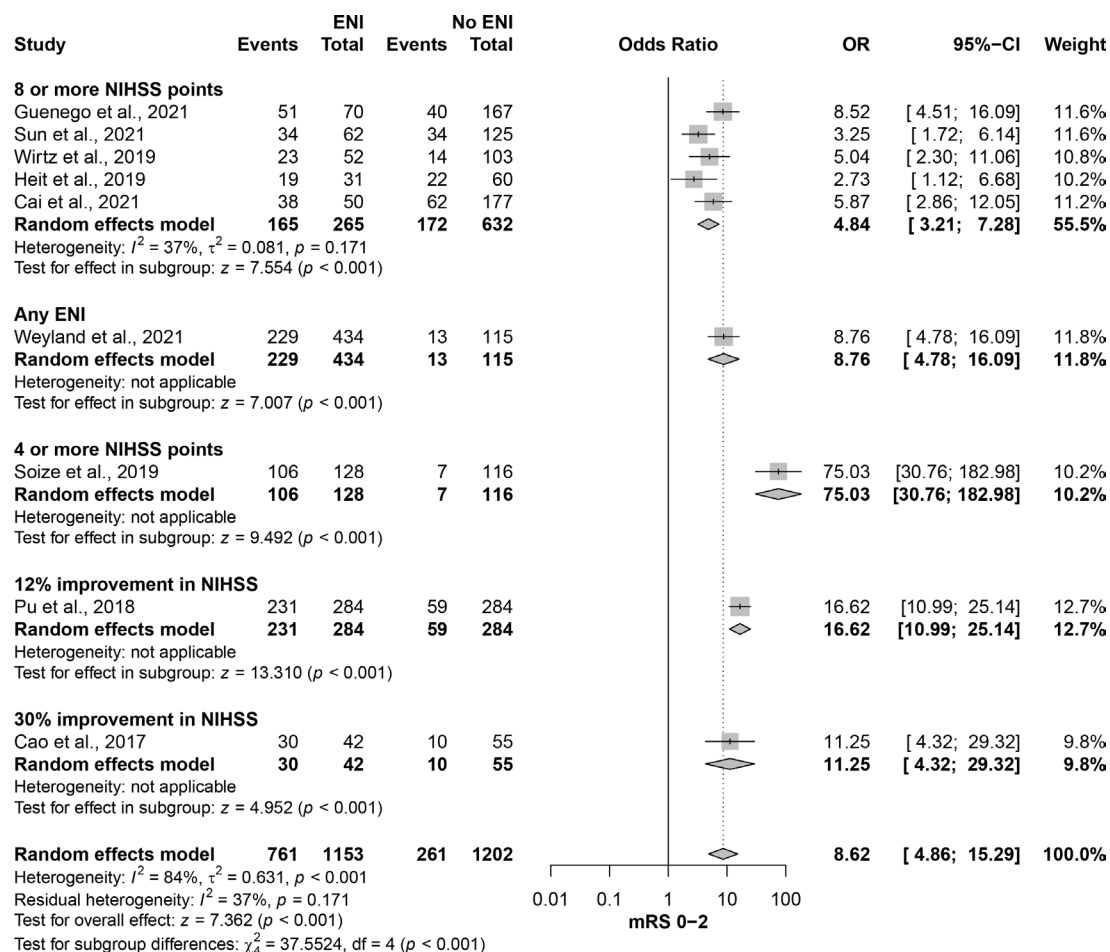


Figure 1 Forest plot of modified Rankin Scale score (mRS) of 0-2 at 90 days. Results were stratified by definition of early neurological improvement (ENI).

to obtain statistically significant results with low heterogeneity between studies.

It is important to note that integer changes in NIHSS scores at 24 hours have their own limitations. For example, a patient

who has a 5-point improvement in the NIHSS score from 15 to 10 (33%) may fare worse than a patient who has a 4-point improvement in the NIHSS score from 7 to 3 (57%). Though the former 5-point improvement had a greater absolute change

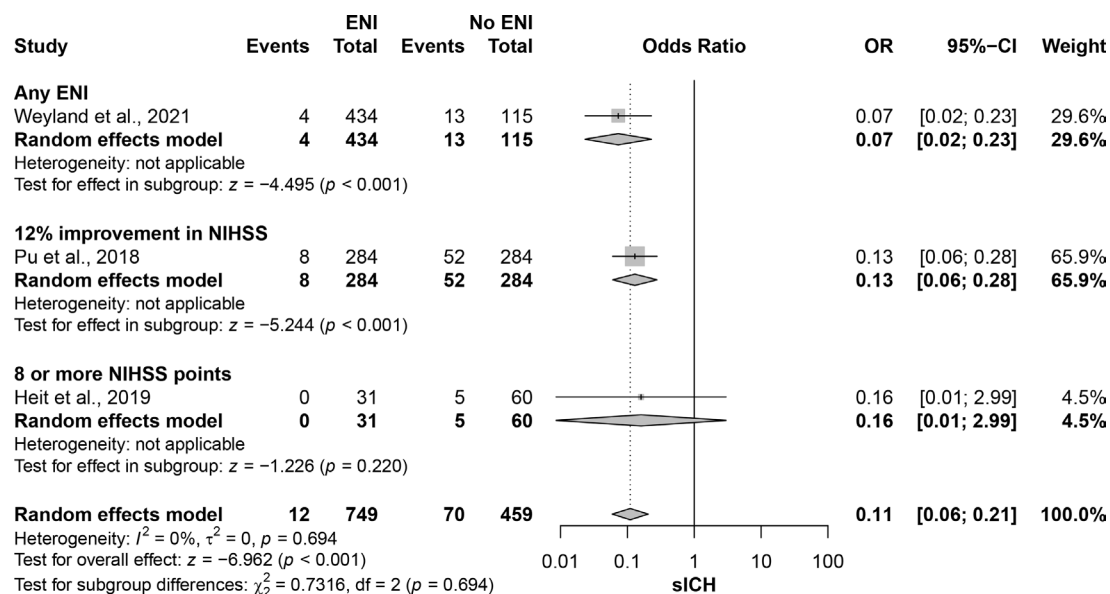


Figure 2 Forest plot of symptomatic intracranial hemorrhage (sICH). Results were stratified by definition of early neurological improvement (ENI). NIHSS, National Institutes of Health Stroke Scale.

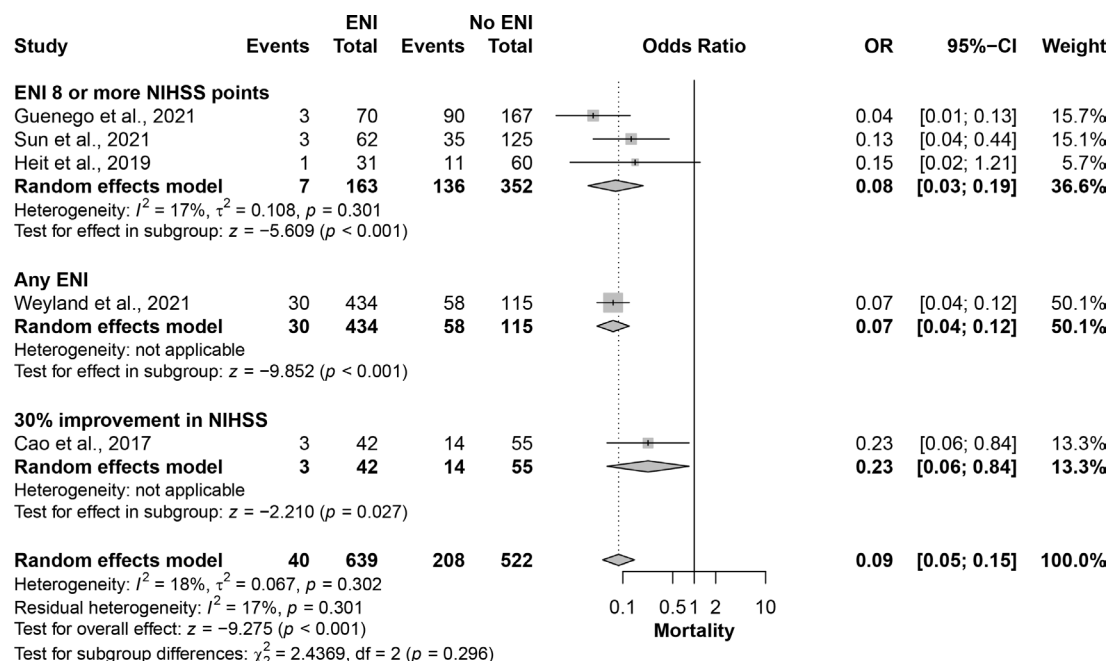


Figure 3 Forest plot of mortality at 90 days. Results were stratified by definition of early neurological improvement (ENI). NIHSS, National Institutes of Health Stroke Scale.

in the NIHSS score, the latter may have better outcomes due to both their final NIHSS score and greater percentage change.²⁹ Future papers could assess early NIHSS as a percentage versus an integer in order to determine the optimal threshold for ENI as it correlates with functional outcomes, as current literature supports the use of an absolute 24-hour NIHSS adjusted for baseline.³⁰ Furthermore, both baseline NIHSS at presentation and final NIHSS at 24 hours likely correlate with good outcomes following treatment. Based on existing literature, it is difficult to ascertain whether these NIHSS values hold a better predictive value than ENI.

Our study, while important, demonstrates the need for a unified definition of ENI. This would allow a higher-powered analysis of studies to be carried out to better assess the predictive value of ENI as a surrogate for long-term outcomes. As more data regarding ENI and long-term outcomes are published, clinicians will be able to better inform patients and their families about their prognosis following thrombectomy treatment for AIS.

CONCLUSIONS

In this meta-analysis of a systematic review of nine studies, ENI was shown to be a promising predictor of long-term functional outcomes in patients treated with mechanical thrombectomy for AIS. Additionally, ENI was found to be significantly associated with lower rates of sICH and mortality. Future prospective studies are needed to further validate the association and to investigate if it is clinically meaningful.

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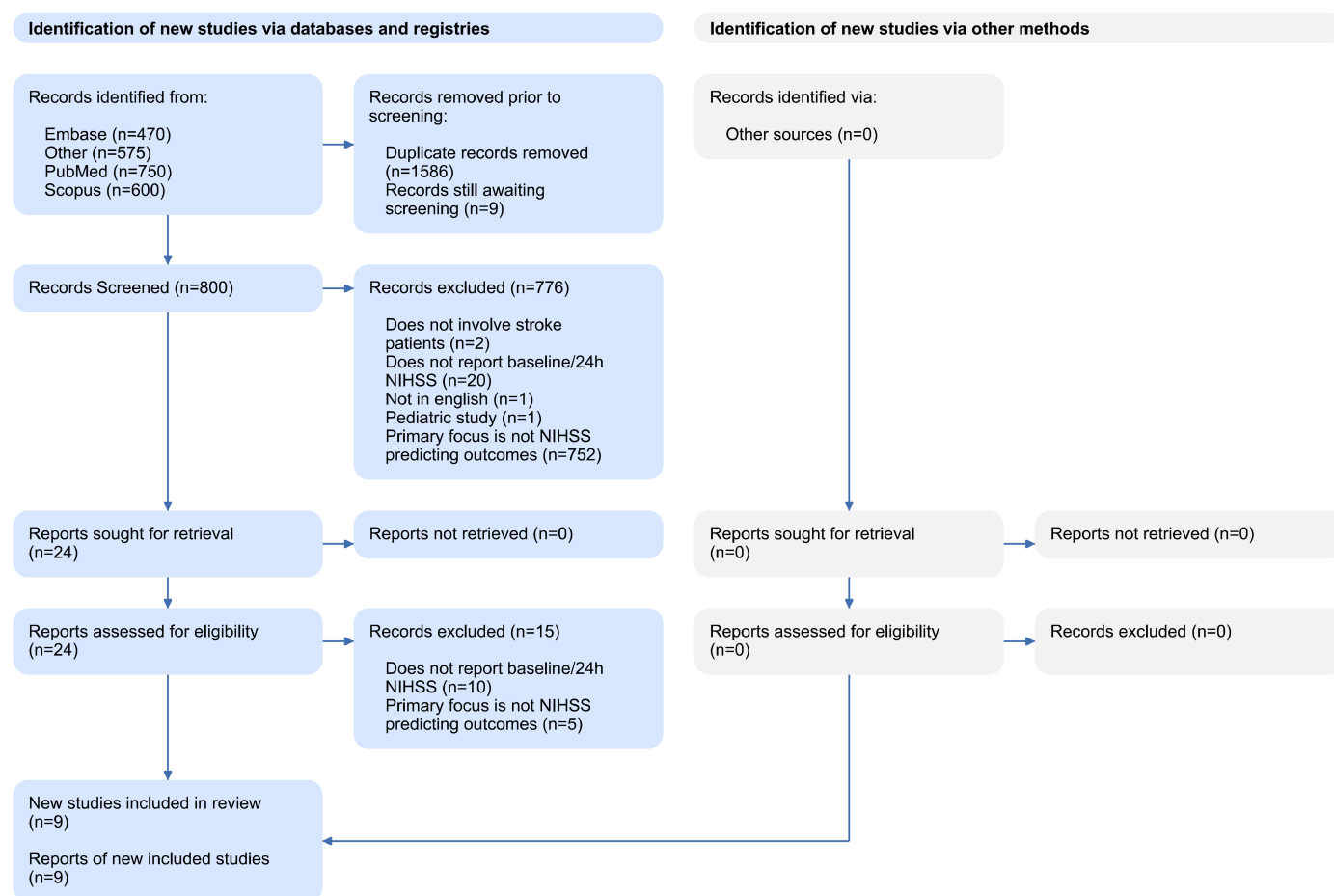
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Study	Definition of ENI	Definition of sICH
Weyland, 2021	Any improvement in NIHSS	Heidelberg Bleeding Classification
Guenego, 2020	Improvement of 8 or more points in NIHSS	N/A
Sun, 2021	Improvement of 8 or more points in NIHSS	N/A
Wirtz, 2019	Improvement of 8 or more points in NIHSS	N/A
Heit, 2019	Improvement of 8 or more points in NIHSS	Increase of at least 4 points in NIHSS or intracranial hemorrhage on imaging within 36 hours
Soize, 2019	Improvement of 4 or more points in NIHSS	N/A
Pu, 2018	Improvement of 12% or greater in NIHSS	Heidelberg Bleeding Classification
Cao, 2017	Improvement of 30% or greater in NIHSS	N/A
Cai, 2021	Improvement of 8 or more points in NIHSS	N/A

Supplementary Table S1. Definitions of ENI and sICH of the included studies

Supplementary Table S2 Risk of bias assessment. Risk of bias was assessed using “ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions”.

Study	D1	D2	D3	D4	D5	D6	D7	Overall
Weyland, 2021	Moderate	Low	Low	No information	Low	Moderate	Low	Moderate
Guenego, 2020	Moderate	Low	Moderate	No information	Low	Moderate	Low	Moderate
Sun, 2021	Low	Low	Moderate	No information	Low	Low	Low	Low
Wirtz, 2019	Moderate	Low	Low	No information	Low	Moderate	Low	Moderate
Heit, 2019	Low	Low	Low	No information	Low	Low	Low	Low
Soize, 2019	Moderate	Low	Moderate	No information	Low	Moderate	Low	Moderate
Pu, 2018	Moderate	Low	Moderate	No information	Low	Moderate	Low	Moderate
Cao, 2017	Moderate	Low	Low	No information	Low	Moderate	Low	Moderate
Cai, 2021	Low	Low	Low	No information	Low	Low	Low	Low

Supplementary Figure S1 PRISMA flow diagram showing the review process.

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Time frame: Since the initial planning of the work								
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) No time limit for this item.	<input type="checkbox"/> None <table border="1"> <tr> <td>Nested Knowledge, LLC</td> <td>Access to software</td> </tr> <tr> <td></td> <td>Click the tab key to add additional rows.</td> </tr> </table>	Nested Knowledge, LLC	Access to software		Click the tab key to add additional rows.		
Nested Knowledge, LLC	Access to software							
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Time frame: past 36 months								
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3	Royalties or licenses	<input checked="" type="checkbox"/> None <table border="1"> <tr> <td></td> <td></td> </tr> <tr> <td></td> <td></td> </tr> <tr> <td></td> <td></td> </tr> </table>						

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Please place an "X" next to the following statement to indicate your agreement:

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Date:4/3/2022

Your Name:Sherief Ghozy

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11	Stock or stock options	<input checked="" type="checkbox"/> None <div> <div></div> <div></div> <div></div> </div>	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	<input checked="" type="checkbox"/> None <div> <div></div> <div></div> <div></div> </div>	
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Date:3/30/2022

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Manuscript Title:Early neurological improvement as a predictor of outcomes after endovascular thrombectomy for stroke: A systematic review and meta-analysis

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3	<input type="checkbox"/> None <div> <div>Medtronic</div> <div>Royalties</div> </div>	

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		<input type="checkbox"/> None			
		Nested Knowledge, LLC		Stockholder	
		Superior Medical Experts, LLC		Founder/stockholder	
		Marblehead Medical, LLC		Founder/stockholder	
		Conway Medical, LLC		Founder/stockholder	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	<input type="checkbox"/> None			
		Brainomix		Software use	
13	Other financial or non-financial interests	<input checked="" type="checkbox"/> None			
<p>Please place an "X" next to the following statement to indicate your agreement:</p> <p><input checked="" type="checkbox"/> I certify that I have answered every question and have not altered the wording of any of the questions on this form.</p>					