A Meta-Analysis of Observational Intra-Arterial Stroke Therapy Studies Using the Merci Device, Penumbra System, and Retrievable Stents

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ORIGINAL RESEARCH

A Meta-Analysis of Observational Intra-Arterial Stroke Therapy Studies Using the Merci Device, Penumbra System, and Retrievable Stents

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BACKGROUND AND PURPOSE: The time from arterial puncture to successful recanalization is an important milestone toward timely recanalization. With the significant improvement in recanalization rates by using thrombectomy devices, procedural time to recanalization is becoming a determinant factor in choosing among available devices. We aimed to assess the impact of time to recanalization on the outcome of intra-arterial stroke therapies.

MATERIALS AND METHODS: We conducted a meta-analysis of studies reporting procedural times in patients with stroke treated with the MD, PS, and RS.

RESULTS: We identified 16 eligible studies: 4 on the MD ($n = 357$), 8 on the PS ($n = 455$), and 4 on RS ($n = 113$). Merci device studies described total procedural duration, while PS and RS studies described puncture-to-recanalization times. With a random-effects model, mean procedural duration for the MD was 120 minutes (95% CI, 105.7–134.2 minutes). Mean puncture to recanalization time for the PS was 64.6 minutes (95% CI, 44.4–84.8 minutes) and 54.7 minutes for RS (95% CI, 47.3–62.2 minutes). Successful recanalization was achieved in 211 of 357 patients (59.1%) in the MD studies (95% CI, 49.3–77.7), 394 of 455 (86.6%) in the PS studies (95% CI, 84.1–93.8), and 105 of 113 (92.9%) in the RS studies (95% CI, 90.9–99.9). Functional independence (mRS ≤2) was achieved in 31.5% of patients in the MD studies, 36.6% in the PS studies, and 46.9% in the RS studies.

CONCLUSIONS: The use of the PS and RS was associated with comparable procedural time to recanalization. Available data did not allow this parameter to be determined for trials using the MD. Retrievable stents achieved the highest rate of successful recanalization and functional outcome and the lowest mortality.

ABBREVIATIONS: CI = confidence interval; MD = Merci retriever device; mRS = modified Rankin Scale; PS = Penumbra system, RS = retrievable stents; TICI = Thrombolysis in Cerebral Ischemia; TIMI = Thrombolysis in Myocardial Infarction

Early complete recanalization is a strong predictor of good outcome in stroke,[1] but the best means for achieving this remain uncertain.[2,3] Fewer than half of MCA occlusions achieve recanalization with IV tPA,[4,5] and even fewer in proximal occlusions.[2,6] In addition, 12%–34% of those who achieve recanalization with IV tPA have early reocclusion.[7,8]

The only randomized trials of intra-arterial thrombolytic therapy are Prolyse in Acute Cerebral Thromboembolism Trial I and II,[9,10] which randomized patients to prourokinase plus IV heparin versus IV heparin. Recanalization was achieved in 66% of the treatment group versus 18% in controls ($P < .001$).[10] With a mean time to start treatment of 5.3 hours, Prolyse in Acute Cerebral Thromboembolism Trial II combined a relatively higher recanalization rate with a favorable outcome and validated the interest in intra-arterial stroke therapy.[4,11]

Research led to the development of mechanical devices that await evidence from randomized trials to support their efficacy over IV tPA. Physicians performing intra-arterial stroke therapies rely on their experience to choose from these devices. Among the commonly used devices are the MD[12] (Concentric Medical, Mountain View, California), the PS[13] (Penumbra, Alameda, California), and RS[14] (Solitaire; ev3, Irvine, California; or Trevo; Concentric Medical). Many pooled analyses of recanalization rates with devices do not report procedural duration and intraprocedural complications.[13,15,16] These technical aspects reflect the device safety, ease of use, and speed of recanalization. This meta-analysis aims to compare the procedural time to recanalization of the MD, PS, and RS in the acute stroke setting.

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Materials and Methods

Search Strategy

We conducted a systematic review by using a predetermined protocol in accordance with the Meta-Analysis Of Observational Studies statement.[17] We identified English language articles by searching the following electronic data bases from the year of the first Mechanical Embolus Removal in Cerebral Ischemia trial publication[16]: MEDLINE (January 2004 to February 2011) and EMBASE (January 2004 to February 2011). We also scanned the bibliographies of key articles to identify additional studies.

We combined 3 search themes by using the Boolean operator "AND." These terms were searched in MEDLINE as both MeSH headings and text words:

1) Stroke or cerebrovascular accident

AND

2) Mechanical thrombolysis, thrombectomy, or endovascular intervention

AND

3) Device name (full and truncated)

Selection Criteria

The inclusion criteria were the following: 1) studies on humans; 2) published in full or as abstracts; 3) in the English language; 4) describing original data; 5) explicitly reporting the puncture-to-recanalization time or procedural duration; 6) using the MD, PS, or RS in the setting of acute ischemic stroke; and 7) in ≥10 patients. Studies exclusively reporting the use of devices other than the 3 devices of interest were excluded. Studies on nonretrievable stents were excluded.

Two of the authors (M.A.A., B.K.M.) screened the titles and abstracts and agreed on the included studies. Full text review of the articles retained from the primary screen was performed, and the data were extracted and summarized and the study quality was evaluated.

Data Extraction

Data were extracted by 1 author (M.A.A.). The data-extraction sheet included the following sections: 1) study characteristics, 2) baseline characteristics, 3) details of intra-arterial therapy, and 4) procedural and clinical outcome measures.

Study Characteristics

Data included single-institution or multicenter prospective or retrospective designs, year and journal of publication, and midyear of the study (median calendar year of treatment dates). The quality of included studies was judged on the basis of design, number of participating centers, presence of a nonhistorical comparative group, and adequacy of follow-up.

Baseline Characteristics of Patients

Baseline characteristics included number, mean age, stroke severity measured by the NIHSS score at presentation, time from stroke onset to presentation, extent of early ischemic changes on baseline imaging, treatment with IV tPA, and time from stroke onset to IV tPA administration.

Procedural Characteristics

Data included time from stroke onset to arterial puncture, site of occlusion, baseline TIMI/TICI scores, devices used, intra-arterial tPA use, procedural time to recanalization for the device studied, and final TIMI/TICI score. If the puncture-to-recanalization time was not stated, the reported "procedure duration" was used instead. Device-specific times were used if multiple devices were used. In only 1 study,[13] the procedural time to recanalization was not reported in the main publication but was later reported in an abstract by the same authors.[18] We have also investigated whether the procedural time-to-recanalization duration had changed during the years since 2004.

Outcomes

Outcomes included successful recanalization (TIMI grades 2 or 3, TICI grades 2b/3), procedural complications such as arterial perforation, device fracture or malfunction, and intracranial hemorrhage. Data on the duration of patient follow-up, mortality, and functional independence, defined as mRS ≤2 at 3 months, were collected. We assessed whether shorter procedural time to recanalization was associated with an mRS of ≤2.

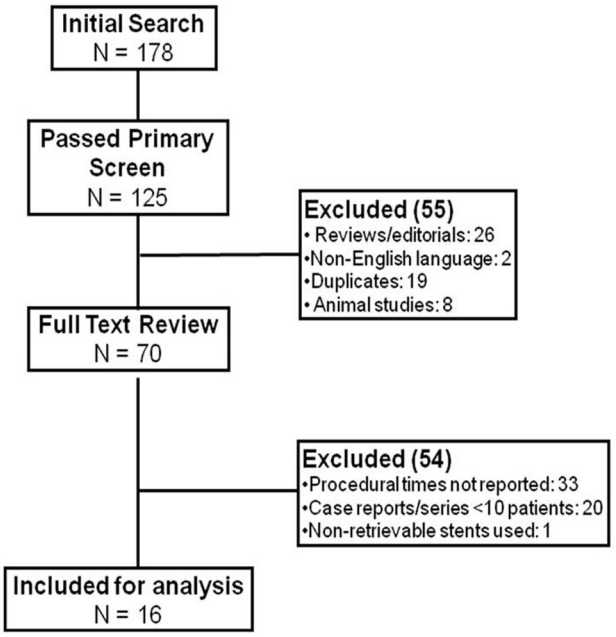

Fig 1. Outlines of the search and selection process.

Statistical Analysis

The mean procedural time to recanalization (in minutes) was recorded for each study along with a measure of variability. If the median time was reported, it was converted to the mean in studies reporting ≤25 patients by using the following formula: mean = $(A + 2 \times \text{median} + B) / 4$, where A and B represent the low and high ends of the range respectively.[19] In studies including >25 patients, the median was used as an estimate of the mean.[19] Similarly, in studies not reporting the SD, we derived standard errors on the basis of the study by Hozo et al[19] by using the range/4 for studies including ≤70 patients and range/6 for studies including >70 patients.

The proportion of patients experiencing adverse outcomes was recorded. Because the Q statistic indicated significant heterogeneity, a random-effects model was used to summarize the mean procedural time to recanalization across the studies stratified by the device used. For the test of trend, we used the Cuzick extension of the Wilcoxon rank sum test.[20] For all tests, a 2-sided P value ≤.05 was deemed significant. Sensitivity analyses were conducted in which the meta-analysis was restricted to published studies or to prospective-design studies. Analyses were performed by using STATA 10.0 (StataCorp, College Station, Texas).

Results

Study Characteristics

Figure 1 outlines the search and selection process. A total of 178 citations were retrieved, 125 of which passed the primary screen. A full-text review was performed for 70 studies, of which 16 were included in the final analysis. Those included 3 studies published in abstract form only.[18,21,22] Table 1 shows some characteristics of these studies. The studies were published between 2005 and 2011 and recruited a total of 925 patients. None of the studies had a randomized treatment al-

Table 1: Characteristics of the included studies

Author	Year	Centers	Design	Device Used	Size (Patients)	Mean Age (yr)	Median NIHSS Score
Aleu et al[21]	2011	Single	Retrospective	Ret stent	54	68	19
Castaño et al[24]	2010	Single	Retrospective	Ret stent	20	65.6	19
Devlin et al[37]	2007	Single	Retrospective	Merci	25	63	18
Frei et al[18]	2011	Multi	Prospective	Penumbra	53	63	18
Grunwald et al[38]	2009	Single	Retrospective	Penumbra	29	58.4	20
Kang et al[25]	2011	Multi	Retrospective	Penumbra	22	59	18.1
Kulcsár et al[26]	2010	Single	Prospective	Penumbra	27	66	14
Lee et al[39]	2009	Single	Retrospective	Merci	17	67	18
Menon et al[23]	2011	Single	Prospective	Penumbra	27	61.5	18
Menon et al[40]	2012	Single	Prospective	Ret stent	14	62.1	14
Pereira et al[22]	2011	Single	Prospective	Ret stent	25	66.3	18.7
Penumbra Pivotal Stroke Trial Investigators[13]	2009	Multi	Retrospective	Penumbra	125	63.5	20
Smith et al[12]	2005	Multi	Retrospective	Merci	151	67	20
Smith et al[16]	2008	Multi	Retrospective	Merci	164	68	19
Struffert et al[41]	2009	Single	Prospective	Penumbra	15	60.3	14
Tarr et al[42]	2010	Multi	Prospective	Penumbra	157	65	18.1

Note:—Multi indicates multiple; Ret stent, retrievable stent.

Table 2: Procedural outcomes

Author	Device Used	Mean/Median Puncture to Recanalization Time (min)	TIMI 2–3 Recanalization (No.) (%)
Aleu et al[21]	RS	51	50 of 54 (92.6)
Castaño et al[24]	RS	70	18 of 20 (90)[a]
Devlin et al[37]	MD	108[b]	14 of 25 (56)
Frei et al[18]	PS	52	47 of 53 (88.7)
Grunwald et al[38]	PS	51	25 of 29 (86.2)
Kang et al[25]	PS	40	22 of 22 (100)[a]
Kulcsár et al[26]	PS	97	25 of 27 (92.6)[a]
Lee et al[39]	MD	129.6[b]	13 of 17 (76.5)
Menon et al[23]	PS	80	23 of 27 (85.2)
Menon et al[40]	RS	84	12 of 14 (85.7)
Pereira et al[22]	RS	42[c]	25 of 25 (100)
Penumbra Pivotal Stroke Trial Investigators[13]	PS	97	103 of 125 (82.4)
Smith et al[12]	MD	126[b]	72 of 151 (47.7)
Smith et al[16]	MD	96[b]	112 of 164 (68.3)
Struffert et al[41]	PS	60[c]	12 of 15 (80)
Tarr et al[42]	PS	41	137 of 157 (87.3)

[a] TICI 2b/3.
[b] Procedural duration.
[c] Time from the first to last control series.

location, and 9 studies were prospective (607 patients). All studies except 1 reported their follow-up data.[18] All studies reported 3-month follow-up data except 1 that reported outcomes at 1-month follow-up.[5]

Baseline Characteristics

Table 1 shows demographic data. The mean age for each study ranged from 63 to 68 years for the MD trials, 58.4 to 66 years for the PS studies, and 62.1 to 68 years in RS studies. The median NIHSS score at the time of presentation for the MD- and PS-treated patients was 18 compared with 19 in RS studies. The median onset-to-groin puncture time was 4.3 hours for MD studies, 4.5 hours for PS studies, and 4.2 hours for RS studies.

The extent of early ischemic changes on the baseline CT scan was only reported in 1 study.[23] Intravenous tPA was administered in 51 of 357 (14.3%) patients in the MD studies, 144 of 455 (31.6%) in the PS studies, and 56 of 113 (49.6%) in the RS studies. The most frequent occlusion site across the studies was the MCA, accounting for 58%, 55%, and 59% in MD, PS, and RS studies, respectively.

Procedural Details and Outcomes

All identified studies reporting RS exclusively used the Solitaire stent except 1 study[21] that used both Solitaire and Trevo stents without indicating how many patients were treated with each stent. Intra-arterial tPA was used in 80 of 357 patients (22.4%) in MD studies compared with 140 of 387 (36.2%) in PS studies and 14 of 113 (20%) in the RS studies.

Use of other devices was reported in some studies. In studies on the MD, 2.8% of patients were treated with snares or other foreign-body retrieval devices, while 2.5% were treated by using balloon angioplasty at the site of occlusion. In PS studies, 1.3% of patients were treated with stent placement at the site of occlusion, while 1.3% of patients were treated with another device that was not specified. In RS studies, 2.7% were treated with the MD, 6.2% were treated with the PS, and 3.5% were treated with another device that was not specified.

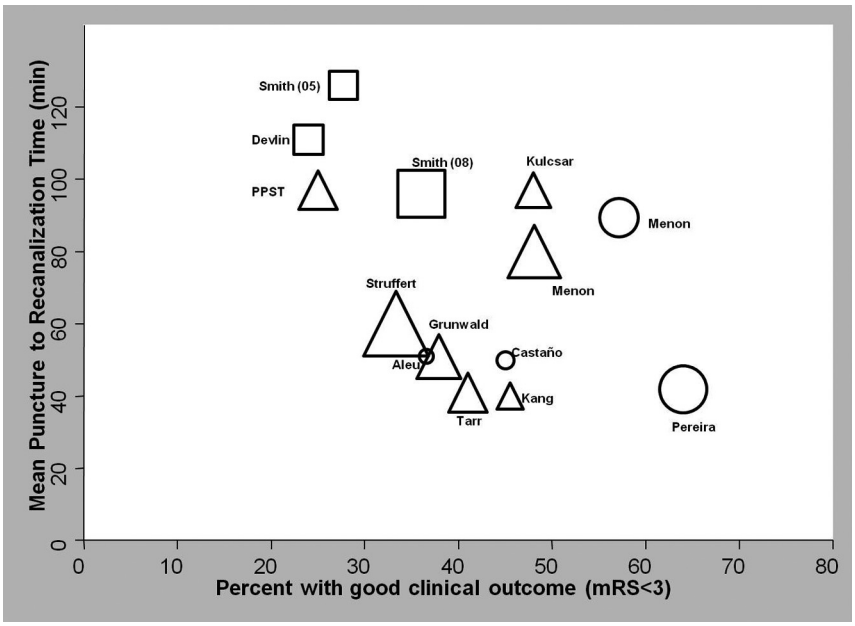

Fig 2. The relation (with 95% confidence limits) between the mean procedural time to recanalization and independent functional outcome (mRS ≤2) in the different studies. *P* value for the Cuzick test of trend is .06. The square indicates the MD; the triangle, the PS; and the circle, the RS.

The procedural time to recanalization was not always reported. All the included studies on the MD reported procedural durations, regardless of the recanalization outcome. With the random-effects model, mean procedural duration was 120 minutes for the MD (95% CI, 105.7–134.2 minutes). The procedural time to recanalization was 64.6 minutes in PS studies (95% CI, 44.4–84.8 minutes) and 54.7 minutes (95% CI, 47.3–62.2 minutes) in RS studies. There was a significant trend toward shorter mean procedural time to recanalization across the studies during the years 2004–2011 ($P = .012$).

Recanalization was reported according to TIMI in all studies except 3[24-26] that reported TICI scores. Successful recanalization (TIMI 2/3 or TICI 2b/3) was achieved in 59.1% (211 of 357) of patients in MD studies (95% CI, 49.3%–77.7%), in 86.6% (394 of 455) of patients in PS studies (95% CI, 84.1%–93.8%), and 92.9% (105 of 113) of patients in RS studies (95% CI, 90.9%–99.9%) (Table 2).

Procedural complications and device-related technical issues were not always reported. For the MD, all studies reported procedural complications, including vessel perforation in 6 of 357 cases (1.7%), dissection in 4 of 357 (1.1%), and device fractures in 13 of 357 (3.6%). In PS studies, procedural complications were reported in 6 of 8 studies. These included vessel perforations in 1.3% (5 of 380), dissection in 1.3% (5 of 380), and device fracture or malfunction in 1.1% (4 of 380). In studies of RS, 0.9% (5 of 113) of patients experienced in-stent thrombosis but no perforations, dissections, or other procedural complications or device malfunctions.

The mean incidence of postprocedure symptomatic intracranial hemorrhage was 8.7% with the MD (95% CI, 6.0–12.7), 2.5% (95% CI, 0.8–7.3) with the PS, and 9.9% with RS (95% CI, 5.1–19.2). The incidence of distal emboli was 1.1% in the MD trials, 4.4% in the PS studies, and 10.6% in RS studies.

Clinical Outcomes

All studies except 1 (using the PS) reported follow-up data. Mean follow-up duration was 3 months in all the studies except 1 that followed patients for 1 month.[5] The 3-month mortality rate was 37.8% in the MD studies, 20.7% in the PS studies, and 12.3% in RS studies. Functional independence (mRS ≤2) at 3 months was achieved in 31.5% of patients in the MD studies compared with 32% in the PS and 47.4% in RS studies. There was a suggestion of an inverse correlation between the procedural time to recanalization and the percentage of patients achieving functional independence in the included studies, irrespective of the device used ($P = .06$, Fig 2).

Sensitivity Analysis

A sensitivity analysis including only prospective studies did not significantly change the mean procedural time-to-recanalization results. For the MD, the mean time in the 4 prospective studies was 117 minutes (95% CI, 100.4–133.5 minutes), while in the 3 prospective studies using the PS, the mean time was 74.6 minutes (95% CI, 29.5–119.7 minutes), and in the 2 prospective studies using RS, the mean time was 57 minutes (95% CI, 39.7–74.3 minutes).

Analysis restricted to articles published in full yielded the same procedural time to recanalization for the MD. However, the mean time for the PS in the 7 studies published in full was 66.1 minutes (95% CI, 45.9–86.3 minutes), while for the 3 published studies on RS, the mean time was 71.5 minutes (95% CI, 53.9–89 minutes).

Discussion

In this meta-analysis, RS and PS studies reported equally short procedural times to recanalization, while RS had the best recanalization and favorable outcome among the 3 devices. Merci device studies reported only the total duration times for all patients, regardless of the recanalization result. While the

importance of recanalization in acute stroke cannot be overemphasized, the speed of achieving recanalization is also important.[27,28] Using this time interval to compare intra-arterial devices serves 2 goals. First, procedural time to recanalization reflects the technical feasibility of devices during the time constraints of stroke therapy. Second, shorter procedural time to recanalization results in shorter onset to recanalization times and thus higher chances of better outcome. Longer time in occlusion results in more tissue at risk of becoming infarcted core.[29] Long procedural time-to-recanalization might partly explain the dissociation between the high rate of successful recanalization and the disappointing rate of good outcome in intra-arterial trials. In the Penumbra Pivotal Trial, in which only a quarter of recanalized patients achieved functional independence,[13] a mean delay of 2 hours between emergency presentation and groin puncture[30] was described.

The time-dependent treatment benefit in acute ischemic stroke has been shown in IV thrombolysis studies. In a pooled analysis of 3670 patients from 8 randomized IV tPA trials,[31] the odds of good clinical outcome were 2.6 times higher in patients treated within 90 minutes of symptom onset compared with those treated with a placebo. Those treated within 91–180 minutes and 181–270 minutes had 1.64 and 1.34 odds ratios of achieving good clinical outcome, respectively. That analysis did not take into account successful recanalization, concluding that 5 patients need to be treated within 90 minutes of symptom onset for 1 of them to have an excellent outcome. If the high rates of successful recanalization with intra-arterial devices are combined with short procedural time-to-recanalization times, the number needed to treat to achieve good clinical outcome is likely to be lower.

Another important factor in deciding outcome is the extent of early ischemic changes on baseline brain imaging. Extensive changes on the Alberta Stroke Program Early CT Score[32] have contributed to the lack of efficacy with intra-arterial therapy.[33,34] In addition, the Alberta Stroke Program Early CT Score has been shown to reliably identify patients with stroke unlikely to make an independent recovery despite thrombolytic treatment.[32] In this meta-analysis, only 1 of 16 studies reported the extent of early ischemic changes on baseline imaging. Tissue-based decision-making in acute stroke therapy regardless of stroke onset time has been shown, in a retrospective study, to be associated with safety comparable to that in patients treated within the conventional time window.[35]

In this analysis, RS had an equivalent time to recanalization compared with the PS. However, a unique feature of RS not accounted for is the ability to restore flow, even if temporarily, when the stent is deployed, bypassing the occluded segment. Whether this "resets the ischemia clock" for the tissue at risk and helps salvage more brain is still to be shown. In addition, RS use was associated with the lowest mortality and highest functional independence rates in this analysis. A number of factors have potentially accounted for this outcome, including the high rate of IV tPA use, shorter onset-to-puncture times, improved operator learning curves, availability of other mechanical devices, and improved stroke care.

None of the MD studies reported procedural time to recanalization, but instead they reported procedural duration. This is an overestimate of the actual procedural time to recanalization because procedural duration encompasses cases that failed to recanalize, which are likely to last longer than successful recanalization cases. Therefore, puncture-to-recanalization times with the MD might still be comparable with those of the RS and the PS. We elected not to exclude the MD studies from this analysis, to provide an historical perspective by using the first FDA-approved device for stroke thrombectomy and to emphasize the importance of reporting procedural time to recanalization in future studies. This analysis should not be interpreted as showing shorter procedural times with the PS or RS over those of the MD.

This analysis has limitations. Meta-analyses of observational studies may generate falsely precise results due to biases and confounding in component studies. These nonrandomized studies are subject to biases, including during selection, analysis, or reporting. All the studies identified by our search had a nonrandomized patient allocation. While the value of an intra-arterial approach in acute stroke is apparent to many, evidence supporting its safety and efficacy over IV tPA from randomized trials is lacking, though some are ongoing. If even a fraction of patients described in the studies of our analysis were randomized in such trials, evidence on the use of these devices would have been available.

We could not adjust for the impact of important factors, including age and stroke severity, because individual patient data were not available. Nonetheless, patient characteristics in these studies were comparable on average. Retrievable stent studies reported the highest rate of IV tPA use, which could have contributed to the high successful recanalization rates observed. We could not adjust for this effect or for the positive effect of improved stroke care. Different interpretations exist for the TICI score among different observers,[36] which is a potential source of variability in defining recanalization. Some technical aspects that we attempted to extract were not always reported. It is difficult to hypothesize what impact this omission has on this analysis. We hope that this will draw attention to reporting these technical outcomes in future studies to enable a more generalizable comparison.

Conclusions

We aimed to summarize existing literature regarding the impact of procedural time to recanalization of 3 devices used in treating patients with ischemic stroke. The use of the PS and RS was associated with comparable procedural time to recanalization. Available data did not allow this parameter to be determined for trials using the Merci device. Retrievable stents achieved the highest rate of successful recanalization and functional outcome and the lowest mortality. The value of procedural time to recanalization and the effect it may have on functional outcome merit further exploration with ongoing prospective studies. One should interpret our findings, bearing in mind the limitations of available evidence.

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