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RESEARCH

Cerebrolysin after Endovascular Thrombectomy in Stroke: 12-Month Functional Outcomes in a Propensity-Matched Cohort

Jacek Staszewski[1,7] · Aleksander Dębiec[1] · Katarzyna Gniadek-Olejniczak[2] · Adam Stępień[1] · Renata Piusinska-Macoch[1] · Stefan Strilciuc[4] · David Balo[3] · George Harston[3,6] · Krzysztof Brzozowski[5] · Piotr Zięcina[5,7] · Jerzy Narloch[5] · Marek Wierzbicki[5] · Piotr Piasecki[5]

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Abstract

Background Long-term outcomes after endovascular thrombectomy (EVT) and the role of adjunctive neuroprotection to achieve post-stroke independence remain incompletely characterized. In this hypothesis-generating target-trial emulation, we assessed 12-month functional outcomes in a prespecified extension of a propensity score–matched cohort of rigorously selected EVT patients treated with adjunctive Cerebrolysin, a multimodal neuroprotective agent. Methods Consecutive EVT patients were prospectively enrolled and treated with Cerebrolysin 30 mL/day for 21 days starting immediately post-EVT, with a second 21-day course at 69–90 days. Outcomes were compared with historical controls using 1:1 nearest-neighbor propensity score matching on ten prespecified covariates. The primary endpoint was functional independence (modified Rankin Scale [mRS] 0–2) at 12 months. Secondary endpoints included 12-month mRS shift, Barthel Index (BI), and need for institutional care. Multivariable regression models were used to estimate adjusted associations, with prespecified sensitivity analyses including calendar time and key EVT predictors. Results Cerebrolysin use was associated with higher odds of 12-month functional independence after adjustment for potential confounders (aOR 6.10, 95% CI 1.64–22.66; p<0.01) and a favorable shift toward lower disability across the 12-month mRS distribution (common OR for favorable shift 3.57, 95% CI 1.42–8.93; p<0.01). Cumulative 12-month mortality was similar between groups (both 18%). Among survivors, 6% of the Cerebrolysin group versus 19% of controls required institutional care (unadjusted OR 0.26; 95% CI 0.07–0.99; NNT 8). BI scores were higher in the Cerebrolysin group than in controls (median (Q1–Q3) 92 (82–100) vs 83 (73–93); p=0.01). In multivariable models, Cerebrolysin remained associated with 12-month independence alongside complete reperfusion (mTICI 3), lower post-EVT NIHSS, fewer device passes, and absence of symptomatic intracranial hemorrhage. Conclusions In EVT-treated patients selected for a small infarct core, robust collaterals, and high-quality reperfusion, adjunctive Cerebrolysin showed a potential benefit toward better 12-month functional outcomes. These exploratory findings require confirmation in multicenter randomized trials to establish efficacy and refine patient selection.

Keywords Ischemic stroke · Endovascular thrombectomy · Cerebrolysin · Neuroprotection · Neurorecovery · Modified Rankin Scale · Long-term outcome

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✉ Jacek Staszewski
jstaszewski@wim.mil.pl

[1] Clinic of Neurology, Military Institute of Medicine, Szaserow 128, Warsaw 04-141, Poland

[2] Neurorehabilitation Clinic, Military Institute of Medicine, Warsaw, Poland

[3] Brainomix Ltd., and Oxford University Hospitals NHSFT, Oxford, United Kingdom

[4] Department of Genomics, MEDFUTURE Institute for Biomedical Research, Iuliu Haţieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

[5] Department of Radiology, Military Institute of Medicine, Warsaw, Poland

[6] Oxford University Hospitals NHSFT, Oxford, United Kingdom

[7] Faculty of Medicine, Warsaw University, Warsaw, Poland

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Introduction

Mechanical thrombectomy (EVT) has re-defined the management of anterior-circulation large-vessel-occlusion (LVO) acute ischemic stroke (AIS), delivering reperfusion rates that routinely exceed 80%. Despite high angiographic success, real-world registries show that fewer than half of EVT-treated patients achieve 90-day functional independence (e.g., ≈42% in the nationwide Swedish RSEVAS cohort), reflecting overlapping pathomechanisms: no-reflow, reperfusion injury, secondary symptomatic intracerebral hemorrhage (sICH), chronic neuroinflammation and neurodegeneration [1]. Adjunct strategies that stabilize the neurovascular unit (NVU), reduce reperfusion-related injury, reestablish neurovascular coupling and support network-level plasticity during subacute and chronic recovery are therefore of interest [2].

Most pivotal AIS trials halt follow-up at 3 months, leaving a knowledge gap about longer-term trajectories. Some randomized studies with prespecified 12-month analyses confirm that EVT benefit persists over 90 days, but results are still below expected. For patients treated in the early window (< 6 h), the best available randomized evidence showed that the 90-day benefits of EVT persist at 12 months with higher rates of independence vs. controls (44% vs. 30%, respectively), but with no clear mortality separation (23% vs. 24%) [3]. Independent predictors of long-term functional independence after EVT also remain poorly explored, but these known include younger age, lower baseline NIHSS, higher Thrombolysis In Cerebral Infarction (mTICI) grade and early (3-month) independence [4].

Stroke recovery is dynamic and individualized: early gains may fade due to secondary neurodegeneration and comorbidities, whereas sustained, targeted rehabilitation leverages neuroplasticity to support continued improvement. Adjunct neuroprotection in the acute and post-acute phases may help translate early reperfusion and the heightened plasticity window into durable functional benefits by supporting cerebroprotection, neuromodulation, brain repair, and neuropsychiatric recovery; however, in the current endovascular era, clinical evidence remains mixed and inconclusive [5].We recently reported that Cerebrolysin - a peptide preparation with multimodal blood-brain-barrier (BBB)–stabilizing and neurotrophic properties - administered in two 21-day cycles (immediately after endovascular thrombectomy and again between days 69 and 90) – significantly reduced risk of any secondary ICH (RR 0.37), improved early NIHSS at Day 7 (median 3 vs. 6) and 90-day functional independence from 44% to 68% in our single-center pilot add-on study [6]. Our protocol prespecified a favorable profile for effective neuroprotection in the EVT population: a small ischemic core, robust collaterals, and successful recanalization - with Cerebrolysin dosing designed to cover both the acute injury phase and the subsequent period of neural plasticity, based on biological rationale and prior evidence [7]. Importantly, to our knowledge, randomized or prospective studies of adjunct neuroprotective agents administered with EVT have reported outcomes only up to 90 days; dedicated 12-month functional results have not yet been published. Additionally, no studies to date have examined the effects of Cerebrolysin on long-term functional independence when administered in two treatment cycles after EVT: immediately following reperfusion and again during the chronic phase. A repeat course of Cerebrolysin, combined with EVT and rehabilitation, may enhance training-dependent neuroplasticity thereby improving function even beyond the early post-stroke window. We hypothesized that:

1) In patients with successful EVT, adjunct Cerebrolysin would enhance both early and late neurological recovery (motor or language), resulting in superior 12-month outcomes compared with standard care alone;
2) A second, time-limited course of Cerebrolysin combined with task-specific rehabilitation at 3 months would promote additional functional gains beyond those achieved with rehabilitation alone.

Therefore, the present analysis extends previous observations to 12 months, assessing whether early gains translate into sustained functional independence and improved activities of daily living, and examining whether treatment remains independently associated with outcome after adjustment for established EVT predictors [6].

Aim

The primary objective was to assess whether adjunct Cerebrolysin was associated with a higher proportion of functional independence (mRS 0–2) at 12 months compared with propensity score–matched (PSM) historical EVT-only controls, in adjusted analyses.

Secondary objectives were to compare 12-month outcomes between groups, including the full mRS distribution, excellent outcome (mRS 0–1), mortality, and institutionalization, and to describe delayed safety events and Cerebrolysin tolerability. We also aimed to identify variables independently associated with 12-month functional independence (including age, baseline NIHSS, collateral grade, final reperfusion grade [mTICI], sICH, and Cerebrolysin exposure) in an exploratory analysis, and to assess the robustness of findings in prespecified sensitivity analyses using alternative covariate specifications.

Materials and methods

Study Design and Target-Trial Emulation

We framed this observational comparative-effectiveness study as a target-trial emulation and report it in accordance with the TARGET Statement (see Supplementary Materials) [8]. This analysis represents a prespecified 12-month extension of a prospective, single-center, open-label, non-randomized pilot study with blinded outcome assessment; the protocol and 90-day results were reported previously [6, 9]. The target trial we sought to emulate would enroll consecutive adults with acute anterior-circulation LVO undergoing EVT and meeting prespecified clinical and imaging eligibility criteria. After reaching successful reperfusion and confirmation of eligibility, participants would be assigned at baseline to one of two strategies: adjunctive Cerebrolysin initiated within the protocol-defined time window after stroke onset versus EVT-only (no Cerebrolysin). Follow-up would extend to 12 months, with the primary outcome defined as functional independence (mRS 0–2) at 12 months and key secondary outcomes including the ordinal 12-month mRS distribution, mortality, and institutionalization. The causal estimand corresponds to the effect of assignment to adjunct Cerebrolysin versus EVT-only on these outcomes.

The study prospectively enrolled 50 consecutive patients with AIS who received Cerebrolysin following EVT (Cerebrolysin group) and compared their outcomes with those of 50 historical controls (Control group) matched for baseline characteristics known to influence stroke prognosis: age, sex, stroke laterality and occlusion site, CT angiography collateral score (CTA-CS 2–3), pre-stroke mRS (0–1), use of bridging r-tPA, and post-EVT variables including mTICI (2b, 2c or 3), onset-to-reperfusion time, and NIHSS immediately following EVT. Prospective Cerebrolysin patients and historical controls were required to fulfill key eligibility criteria which reflect standard EVT practice and study protocol requirements. These included adults with anterior circulation LVO treated within 6 h of symptom onset by aspiration and/or stent-retriever thrombectomy; ASPECTS $\geq$ 6; CTA-CS $\geq$ 2; successful reperfusion (mTICI $\geq$ 2b); pre-stroke mRS $\leq$ 1; and a target mismatch profile on CTP (ischemic core volume $<$ 70 ml, mismatch ratio $>$ 1.8, and mismatch volume $>$ 15 ml) (Table 1S). All patients received care in the Neurointensive Stroke Care Unit and received the treatment according to AHA/ASA and ESO-ESMINT guidelines [10, 11].

Automated processing of NCCT, CTA, and CTP scans was routinely performed for all directly admitted patients using the latest CE-marked version of the e-Stroke software (Brainomix, Oxford, UK) as a clinical decision-support tool. In the present study, e-Stroke was used to assist in adjudicating inclusion criteria for both prospective participants and historical controls. The study protocol was reviewed and approved by the Institutional Review Board of the Military Institute of Medicine, Warsaw, Poland (53/WIM/2020), registered at ClinicalTrials.gov (NCT04904341), and conducted in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines [12]. All patient data were anonymized to ensure confidentiality. Written informed consent was obtained from all participants in the Cerebrolysin group, whereas for the historical control group, informed consent was not required because only de-identified retrospective data were analyzed.

Intervention

Cerebrolysin was administered per protocol to all consecutive EVT patients meeting the clinical and imaging inclusion criteria summarized in Table 1S, without additional physician-level discretion. The Cerebrolysin cohort was enrolled between June 2021 and December 2023. Fifty consecutive patients fulfilling study criteria received Cerebrolysin within 8 h of onset (median 250 min). Cerebrolysin 30 mL/day (intravenous) was initiated immediately after EVT (not later than 8 h after stroke onset) and continued for 21 days, with a second 21-day course during weeks 10–13 (day 69–90), to couple acute neuroprotection with a later neurorecovery phase.

Comparator

Controls were historical EVT-only patients selected from our prospectively maintained registry from the period preceding initiation of the Cerebrolysin observational study (June 2018–May 2021), i.e., before adjunct Cerebrolysin was administered at our center. They were managed under the same imaging workflow, periprocedural care pathway and treated by the same team of three experienced operators (P.P., P.Z., K.B.) achieving high rates of successful reperfusion (e.g., mTICI $\geq$ 2b in $\geq$ 85% of cases) with low complication rates as the Cerebrolysin group.

The registry is based on a comprehensive, formalized, and audited database required for financial settlements with the National Health Fund. Among 342 registry patients screened, 50 meeting the same clinical and imaging eligibility criteria as the Cerebrolysin group were selected (15%) (Fig. 1S).

Patients were matched 1:1 using nearest-neighbour propensity score matching based on 10 prespecified variables: age, sex, stroke laterality, occlusion location (MCA M1 vs. MCA M2), CT angiography collateral score (CTA-CS 2–3), pre-stroke mRS (0–1), bridging IV thrombolysis,

Table 1 Baseline characteristics of the studied groups after matching

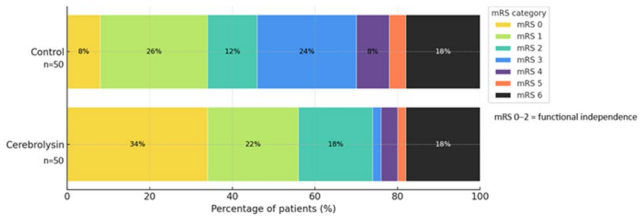
Characteristics	Cerebrolysin group	Control Group	*p*-value	Std diff
N	50	50		
Demographic and clinical factors				
Age, years, median (Q1-Q3) *	72 (60–77)	71 (61–78)	0.9	0.077
Sex (male, n (%)*	28 (56)	29 (58)	0.8	-0.04
Hypertension	41 (82)	43 (86)	0.6	-0.109
Atrial fibrillation	19 (48)	22 (44)	0.5	-0.122
Anticoagulation treatment	13 (26)	13 (26)	0.9	0
Hyperlipidemia	27 (54)	24 (48)	0.5	0.12
Diabetes mellitus	12 (24)	13 (26)	0.8	-0.046
History of TIA or stroke	4 (8)	7 (14)	0.3	-0.193
Active smoking	22 (44)	19 (48)	0.7	0.122
CAD	15 (30)	20 (40)	0.3	-0.211
Bridging r-tPA *	20 (40)	21 (42)	0.8	-0.041
Periprocedural and radiological				
Vessel occlusion site*				
MCA M1	40 (80)	38 (76)	0.6	0.097
MCA M2	10 (20)	12 (24)		-0.097
CTA-CS = 3 *	28 (56)	25 (51)	0.4	0.12
ASPECTS baseline	9 (8–10)	10 (9–10)	0.02	-0.853
ASPECTS < 10	31 (62)	19 (38)		
9#	13 (42)	11 (58)	0.01	0.494
8#	11 (36)	4 (21)		
7#	7 (22)	4 (21)		
Core volume, ml	10 ml (8–24)	7 ml (5–15)	0.2	0.185
Mismatch volume, ml	90 ml (52–109)	100 ml (52–149)	0.5	-0.131
TICI *				
3	28 (56)	21 (43)		0.283
2c	8 (16)	16 (32)	0.18	0.37
2b	14 (28)	13 (25)		0.05
Onset to TICI, minutes *	217 (149–317)	228 (150–358)	0.8	-0.078
Onset to groin, min	170 (124–293)	161 (121–278)	0.9	0.077
Onset to needle, min	179 (89–250)	160 (59–280)	0.7	0.223
Method of EVT				
Aspiration	39 (81)	41 (87)	0.3	-0.1
Thrombectomy	31 (65)	26 (55)		0.203
Number of passes	2 (1–3)	2 (1–3)	0.9	0
General anesthesia during EVT	14 (28)	17 (34)	0.9	-0.148
Onset to Cerebrolysin, minutes	250 (140–360)	-	-	
Stroke characteristics				
TOAST subtype				
ICAS	28 (46)	25 (50)		0.12
CE	19 (48)	22 (44)	0.6	-0.122
Other	3 (6)	3 (6)		0
Pre-stroke mRS = 0*	45 (90)	43 (86)	0.4	0.123
Left hemisphere stroke *	22 (44)	25 (50)	0.6	-0.12
NIHSS pre-EVT	12 (7–15)	14 (9–17)	0.3	-0.337
NIHSS post-EVT *	7 (5–13)	8 (5–12)	0.9	-0.169
Length of ICU stay, days	4 (2–6)	5 (2–8)	0.8	-0.529

Data are presented as median (Q1–Q3) for continuous variables and n (%) for categorical variables. Q1 and Q3 denote the 25th and 75th percentiles, respectively. Std diff: standardized difference (absolute values ≥ 0.1 considered potentially meaningful, ≥ 0.8 large)

ICA internal carotid artery sclerosis, *CE* cardiac embolism, *NIHSS* National Institutes of Health Stroke Scale, *MCA M1* −2, middle cerebral artery segment 1, −2

* matching variables

\# calculation based within the ASPECTS < 10 subset



* Adjusted treatment effects are reported separately using multivariable logistic regression (mRS 0–2) and proportional-odds ordinal regression (mRS 0–6).

Fig. 1 Unadjusted distribution of 12-month modified Rankin Scale (mRS) scores in EVT patients treated with Cerebrolysin versus controls

and post-EVT variables including final reperfusion grade (mTICI 2b/2c/3), onset-to-reperfusion time, and NIHSS on admission to the stroke unit after EVT [6, 9].

Rehabilitation

Patients in both the Cerebrolysin and control groups received a standardized, protocolized multidisciplinary rehabilitation program consistent with national guidelines. In-hospital rehabilitation was initiated within 24 h after reperfusion (≥45 min/day, 5 days/week) and, after discharge, continued in a rehabilitation unit (approximately 150 min/day, 6 days/week). The typical rehabilitation course lasts ~ 3 months after stroke, with a maximum reimbursed duration of 4 months per year.

Outcomes Assessment

The primary outcome was functional independence at 12 months, defined as mRS 0–2. Secondary outcomes included the 12-month mRS score assessed on the full ordinal scale, excellent outcome (mRS 0–1) at 12 months, BI, institutional care status at 12 months, and all-cause mortality. Neurological assessments followed a standardized routine protocol in both groups and were performed by a senior neurologist masked to treatment allocation and EVT procedural outcomes. Functional outcome was assessed using the mRS at four prespecified time points: day 7, day 30, 3 months (±3 days), and 12 months (±14 days) after stroke. When an in-person visit was not possible, outcomes were obtained via a structured telephone interview; if the patient could not be reached, the family/caregiver was contacted to ascertain functional status and vital status. The Barthel Index was recorded at 30 days, 90 days, and 12 months. Adverse events (AEs) were actively monitored at each assessment point and documented from clinical visits and medical record review using a standardized form capturing vascular events, infections, cardiac complications, and suspected drug-related reactions.

Statistical Analysis

Analyses were conducted on an intention-to-treat basis. The Shapiro-Wilk test was used to assess the normality of the variables. Continuous variables were non-normally distributed and are reported as median (Q1–Q3), where Q1 and Q3 denote the 25th and 75th percentiles; between-group comparisons were performed using the Mann–Whitney U test. Categorical variables are reported as counts and percentages and were compared using the χ^2 test.

We evaluated functional independence at 12 months (primary endpoint) as a binary outcome defined as mRS 0–2 versus 3–6 and estimated the association between Cerebrolysin use and 12-month functional independence using multivariable logistic regression. Prespecified covariates included age, NIHSS immediately after EVT, baseline ASPECTS, CTA-CS, final reperfusion status (TICI 3 vs. < 3), symptomatic intracranial hemorrhage, bridging IV thrombolysis, and CT perfusion parameters (ischemic core volume and mismatch volume. Results are reported as adjusted odds ratios (OR) with 95% confidence intervals (CI) and number needed to treat (NNT). We additionally performed an adjusted ordinal ("shift") analysis of 12-month mRS (0–6) using proportional-odds ordinal logistic regression with the same covariates, reporting a common OR for a shift toward lower disability. To address potential secular trends in stroke care, a calendar time (treatment year) was additionally evaluated in sensitivity analyses as well as other variables of interest: pre-EVT NIHSS (instead of post-EVT NIHSS) and clinical data (AF, diabetes).

Standardized differences were calculated to quantify the magnitude of between-group differences, with absolute values ≥ 0.1 considered potentially meaningful and ≥ 0.8 indicating large effects. Variables with $p < 0.1$ in univariate analysis or of established clinical relevance were entered into a multivariate logistic regression model to identify independent predictors of functional independence at 12 months. To prevent multicollinearity, only one variable was retained among highly correlated metrics of early recovery. The final model included treatment with Cerebrolysin, age, NIHSS score immediately post-thrombectomy (0 h), final TICI = 3, CTA-CS = 3, presence of sICH according to ECAS-3 criteria, and number of thrombectomy passes. Model discrimination and calibration were assessed with the area under the receiver-operating-characteristic curve (AUC), the Nagelkerke R^2 statistic, and the Hosmer–Lemeshow goodness-of-fit test. In addition to traditional endpoint analyses, we conducted an exploratory trajectory-based analysis to characterize within-patient recovery patterns and their temporal evolution over 12 months [13, 14]. We analyzed longitudinal mRS trajectories at D7, D30, D90, and 12 months. Following prior work using repeated-measures

mRS to classify interval change, we defined improvement as any≥1-point decrease and worsening as any≥1-point increase between successive assessments. From these operational definitions, we derived trajectory classes (monotonic improvement, monotonic worsening, fluctuating, deterioration after improvement). We further defined early improvement as a≥1-point improvement from D7 to D30 and late improvement as a≥1-point improvement from D30 to D90 or from D90 to 12 months. Functional independence was mRS 0–2 per consensus nomenclature; sustained independence required mRS 0–2 at both D90 and 12 months; and conversion categories captured transitions between D90 and 12 months. The trajectory definitions used are presented in Table 2S. The frequency of each trajectory category was summarized by treatment arm. Between-group comparisons for categorical variables (e.g., monotonic improvement, sustained independence) were performed using χ^2 test with Yates correction where appropriate. Ordinal mRS distributions at 12 months were compared using the Mann–Whitney U test, which also served as a global shift analysis across the mRS range. Continuous or ordinal change scores (Δ mRS) were expressed as median and analyzed using nonparametric methods. Barthel Index (BI) was not scored in deceased patients; BI was recorded as missing and a death indicator was retained. NIHSS was assigned the maximum score of 42 for deceased patients. Missing data (<5%) were handled using multiple imputations by chained equations. Statistical significance was defined as two-sided $p<0.05$. All statistical procedures were performed using PQStat Software (version 1.8.6.122, PQStat, Poznań, Poland, 2024). This was an academic, investigator-initiated study designed to address clinically relevant questions applicable to routine stroke care.

Table 2 Characteristics of the study cohort by functional independence at 12 months

Characteristic	mRS 0–2	mRS 3–6	*p*-value	Std diff
N	60	40		
Study group: Cerebrolysin n/N (%)	37/60 (62%)	13/40 (32%)	<0.01	0.58
Demographics and clinical characteristics				
Age, years median (Q1-Q3)	69.0 (56–74)	74.5 (63–80)	<0.01	−0.48
Male sex	36/60 (60%)	21/40 (52%)	0.45	0.15
Hypertension	48/60 (80%)	36/40 (90%)	0.26	−0.28
Atrial fibrillation	21/60 (35.0%)	20/40 (50.0%)	0.13	0.21
Anticoagulation treatment	13/60 (22%)	13/40 (32%)	0.22	−0.24
Hyperlipidemia	29/60 (48%)	22/40 (55%)	0.51	−0.13
Diabetes mellitus	18/60 (30%)	7/40 (18%)	0.15	0.29
History of stroke/TIA	8/60 (13%)	3/40 (8%)	0.51	0.19
Coronary artery disease	18/60 (30%)	17/40 (42%)	0.19	−0.26
Periprocedural and radiological factors				
Bridging r-tPA	28/60 (47%)	13/40 (32%)	0.15	0.29
CTA-CS = 3	40/60 (66%)	15/40 (38%)	<0.01	0.53
ASPECTS baseline	10 (9–10)	9 (8–10)	0.19	0.21
Final TICI = 3	31/60 (52%)	11/39 (28%)	0.02	0.49
Onset to TICI, min	197 (146–290)	279 (162–372)	0.03	−0.57
Onset to groin, min	157 (122–248)	218 (129–315)	0.07	−0.48
Core volume (rCBF), ml	10 (5–20)	14.0 (5–35)	0.20	−0.47
Mismatch volume, ml	98 (52–131)	104 (53–121)	0.95	−0.26
EVT method: Aspiration	50/60 (84%)	33/40 (82%)	0.61	0.10
EVT method: Stent-retriever thrombectomy	33/60 (55%)	26/40 (66%)	0.36	−0.19
General anesthesia during EVT	12/60 (20%)	19/40 (48%)	0.04	−0.40
Number of passes median	1 (1–2)	3.0 (1–5)	<0.01	−1.16
Stroke characteristics				
Left hemisphere stroke	30/60 (50%)	17/40 (42%)	0.46	0.15
NIHSS pre-MT	12 (7–15)	15 (10–17)	0.02	−0.45
NIHSS post-MT 0 h	6 (5–9)	12 (9–15)	<0.001	−1.00
Pre-stroke mRS = 0	54/60 (90%)	34/40 (85%)	0.45	0.15
mRS 7 Day	2 (1–2.2.2)	5 (4–5)	<0.01	3.6
mRS 30 Day	1 (1–2)	5 (4–5)	<0.01	5.4
mRS 3 M	1 (0–2)	5 (3–5.2.2)	<0.01	2.5
Onset to Cerebrolysin, min	209 (128–289)	270 (163–377)	0.8	−0.4
Secondary intracranial hemorrhage	8/60 (13%)	18 (45%)	<0.01	−0.7
Symptomatic intracranial hemorrhage	3/60 (5%)	10 (25%)	<0.01	−0.9

Data are presented as median (Q1–Q3) for continuous variables and n (%) for categorical variables. Q1 and Q3 denote the 25th and 75th percentiles, respectively. Std diff: standardized difference (absolute values≥0.1 considered potentially meaningful, ≥0.8 large)

Results

Between June 2021 and December 2023, 291 mothership patients with anterior-circulation LVO treated with MT within 6 h were screened, and 50 (17%) were enrolled in the Cerebrolysin cohort after meeting stringent clinical and imaging eligibility criteria, including successful reperfusion (mTICI 2b–3), good collaterals (CTA-CS 2–3), and persistent post-MT deficit (NIHSS≥5 with cortical signs) with treatment initiation within 8 h of onset. The most common reasons for screening failure were insufficient collateral flow and severe aphasia/neglect precluding informed consent (Fig. 1S). Enrollment by year was 15 patients in 2021, 13 in 2022, and 22 in 2023. These patients were propensity-score matched 1:1 to 50 historical controls drawn from EVT registry (2019: $n=6$; 2020: $n=15$; 2021: $n=29$). There were no significant differences in demographics, comorbidities, stroke etiology, baseline severity, median mismatch ratio, core volume, or procedure-related parameters (onset-to-reperfusion time, number of passes) (Table 1). All endovascular thrombectomy procedures achieved successful recanalization, and no major periprocedural complications were observed. There was no loss to follow-up or missing data at 12 months follow-up for the clinical outcome measures, except for those related to deceased patients. Of the 50 patients assigned to Cerebrolysin, all survivors ($n=46$; 92%) initiated the second 21-day course.

Outcome

60% of the whole cohort achieved independence at 12 months, 62% of them received Cerebrolysin (Table 2).

Primary Outcome

The study showed higher functional independence at 12 months (mRS 0–2) in the Cerebrolysin group vs. control (74% vs. 46%; χ^2 $p=0.01$; unadjusted OR 3.34, 95% CI 1.44–7.75; NNT 3.6). In the multivariable logistic regression adjusting for age, post-EVT NIHSS, baseline ASPECTS, CTA collateral score, final TICI 3 reperfusions [2b,2c,3], sICH, bridging IV thrombolysis, and CT perfusion core and mismatch volumes, Cerebrolysin use was associated with higher odds of 12-month functional independence (aOR 6.10, 95% CI 1.64–22.66; $p<0.01$).

Secondary Outcomes

Figure 1 shows the unadjusted 12-month mRS distribution, suggesting lower disability in the Cerebrolysin group (Wilcoxon–Mann–Whitney $p=0.01$), while mortality was similar between groups (18% in each). In an adjusted proportional-odds ordinal model including prespecified confounders (age, post-EVT NIHSS, baseline ASPECTS, CTA collateral score, final TICI 3 reperfusion, sICH, bridging IV thrombolysis, and CT perfusion core and mismatch volumes), Cerebrolysin use was associated with a shift toward lower disability across the entire 12-month mRS distribution (common OR for better outcome 3.57, 95% CI 1.42–8.93; $p<0.01$).

Significantly more patients from Cerebrolysin group compared to controls achieved functional independence at 7-Days, 1 month and 3 months (mRS_{7D}, mRS_{1M}, mRS_{3M} 0–2, respectively 60% vs. 36%, $p=0.02$ and 60% vs. 40%, $p=0.046$ and 68% vs. 44%, $p=0.02$) (Fig. 2) [6]. The

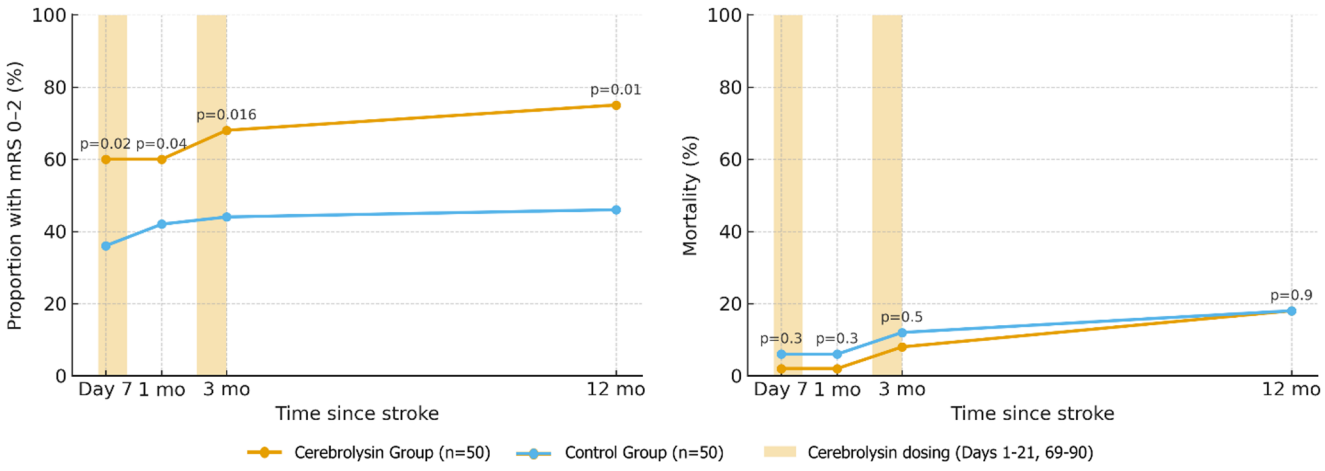


Fig. 2 Functional independence (**A**) and mortality (**B**) trends over 12 months

Table 3 Trajectory classes in 12 months functional status by study arm

Outcome/Metric	Cerebrolysin (*n*/*N*,%)	Control (*n*/*N*, %)	Effect size	95% CI	*p* (χ^2-Yates)
Sustained independence (90 d & 12 m≤2)	33/50, 66%	22/50, 44%	OR 2.47	1.10–5.55	0.04
Net ΔmRS (7 d→12 m)	median −1.0	median 0.0	-	-	0.33*
Monotonic improvement	25/50, 50%	17/50, 34%	OR 1.94	0.87–4.35	0.15
Monotonic worsening	7/50, 14%	7/50, 14%	OR 1.00	0.32–3.09	1
Fluctuating course	18/50, 36%	26/50, 52%	OR 0.53	0.24–1.16	0.15
Any improvement (any interval)	29/50, 58%	23/50, 46%	OR 1.62	0.74–3.55	0.31
Any worsening (any interval)	11/50, 22%	13/50, 26%	OR 0.79	0.33–1.91	0.81
Deterioration after improvement	4/50, 8%	1/50, 2%	OR 4.27	0.46–39.55	0.35
Early improvement (7 d→30 d)	8/50, 16%	8/50, 16%	OR 1.00	0.36–2.80	1
Late improvement (≥30 d)†	21/50, 42%	15/50, 30%	OR 1.70	0.75–3.86	0.29
Convert to independence (90 d→12 m)	4/50, 8%	1/50, 2%	OR 4.27	0.46–39.55	0.35
Convert to dependence (90 d→12 m)	1/50, 2%	0/50, 0%	—	—	1
Death 90 d→12 m	5/50, 10%	3/50, 6%	OR 1.74	0.39–7.71	0.71
Death 0–12 m (any time)	9/50, 18%	9/50, 18%	OR 1.00	0.37–2.71	1

†Late improvement: no improvement 7 d→30 d, but ≥1-point improvement between 30 d→90 d or 90 d→12 m. Effect sizes are odds ratios (OR) with Wald CIs when all cells>0; Fisher's exact CIs omitted where zero cells occur. * Mann–Whitney U

cumulative 7-day, 1-month and 3-month mortality rates were similar in these groups (2% vs. 6%, $p=0.3$; 2% vs. 6%, $p=0.3$, and 8% vs. 12%, $p=0.5$, respectively).

Patients receiving Cerebrolysin more often achieved excellent outcome (mRS 0–1) at 12 months compared to controls (54% vs. 34%, unadjusted OR 2.3,95%CI 1.01–5.1; NNT 5). Among survivors 6% vs. 19% of controls required institutional care (OR 0.26; 95%CI 0.07–0.99; NNT 8). There was a significant difference in Barthel Index scores between the Cerebrolysin and control groups at 30 days (median [Q1–Q3]: 77 [61–93] vs. 63 [38–88], $p=0.03$), at 3 months (86 [75–97] vs. 75 [61–90], $p=0.01$), and at 12 months (92 [82–100] vs. 83 [73–93], $p=0.01$), driven primarily by higher mobility and transfer component scores at each time point.

Sustained independence (mRS≤2 at both 3 M and 12 M) was more frequent with Cerebrolysin group vs. controls (66% vs. 44%, unadjusted OR 2.47, 95%CI 1.1–5.5) (Table 3). Several trajectory tendencies (more monotonic improvement, late improvement, and last-quarter conversion

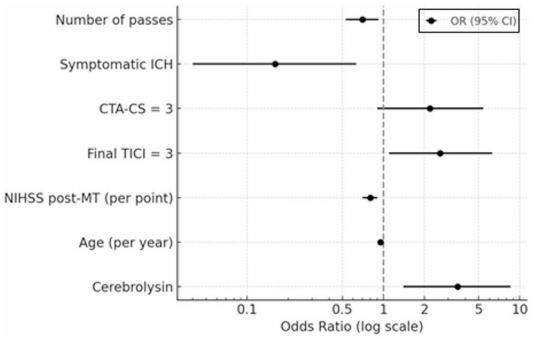


Fig. 3 Independent predictors of functional independence at 12 months

to independence) numerically favored Cerebrolysin group but did not cross the 0.05 threshold given sample size. Net change in mRS from 7D to 12 M (ΔmRS) trended better with Cerebrolysin treated patients (median −1.0 vs. 0.0) but was not statistically significant ($p=0.33$).

In the multivariate logistic regression model, Cerebrolysin treatment (OR 3.5, 95%CI 1.4–8.6), younger age (OR 0.95; 95%CI 0.91–0.99), lower NIHSS immediately post-thrombectomy (OR 0.80; 95%CI 0.7–0.9), complete reperfusion [TICI 3] (OR 2.6; 95%CI 1.1–6.3), absence of symptomatic ICH (OR 0.16; 95%CI 0.04–0.63), and fewer device passes (OR 0.70; 95%CI 0.53–0.92) were independently associated with functional independence at 12 months (Fig. 3). This model showed excellent discrimination (AUC=0.90, Nagelkerke R^2=0.72) and good calibration (Hosmer–Lemeshow $p=0.47$).

Sensitivity Analysis

Prespecified sensitivity analyses incorporating calendar time and additional EVT-related covariates (anesthesia type, number of passes, atrial fibrillation, and diabetes) yielded directionally consistent results for both 12-month functional independence (mRS 0–2) and the ordinal mRS shift (Table 4). Replacing post-EVT NIHSS with pre-EVT NIHSS produced similar estimates; the association with mRS 0–2 remained statistically significant, whereas the ordinal shift analysis was of borderline significance ($p=0.053$).

Analysis within Cerebrolysin group demonstrated key predictors of favorable and unfavorable outcome at 12 months (Table 5). Younger patients (OR per year: 0.91; 95%CI 0.85–0.98) with less severe stroke symptoms after EVT at 7 days (NIHSS per 1 point: OR 0.83; 0.74–0.93; mRS per 1 point: OR 0.69; 0.52–0.91), 30 days (OR 0.006; 95%CI 0.0005–0.07) and 3 months mRS (OR 0.32; 95%CI 0.15–0.68) demonstrated significantly higher rates of favorable outcomes at 12 months while those with any ICH performed worse (OR 0.09; 0.01–0.60). Due to small sample and strong multicollinearity of mRS with NIHSS, the multivariable analysis was not performed.

Table 4 Sensitivity analysis results

Model	aOR (mRS0–2)	*p*-value	Common OR (favorable shift)	*p*-value
Primary adjusted	6.10 (1.64–22.66)	0.007	3.57 (1.42–8.93)	0.007
1) Pre-EVT NIHSS instead of post-EVT NIHSS	3.75 (1.18–11.95)	0.025	2.44 (0.99–6.02)	0.053
2) + Calendar time	5.48 (1.23–24.47)	0.026	3.58 (1.28–10.02)	0.015
3) + Anesthesia (GA vs. non-GA)	6.10 (1.64–22.78)	0.007	3.63 (1.44–9.15)	0.006
4) + Number of passes	5.64 (1.52–20.99)	0.010	3.60 (1.42–9.08)	0.007
5) + Atrial fibrillation	6.06 (1.61–22.89)	0.008	3.47 (1.37–8.79)	0.009
6) + Diabetes	5.95 (1.59–22.24)	0.008	3.40 (1.35–8.59)	0.010
Fully adjusted (+ time + anesthesia + passes + AF + Diabetes)	5.30 (1.15–24.39)	0.032	3.51 (1.24–9.93)	0.018

Abbreviations: *aOR* adjusted odds ratio for 12-month functional independence (mRS 0–2) from multivariable logistic regression, *Common OR* common odds ratio for better outcome (shift toward lower mRS) from a proportional-odds ordinal logistic model (mRS 0–6), *GA* general anesthesia, *PASSES* number of thrombectomy passes, *AF* atrial fibrillation

Table 5 Univariate analysis of predictors of 12 months outcomes in cerebrolysin group

Characteristics	mRS 0–2	mRS 3–6	*p*-value	Std diff
N	37	13		
Demographics and clinical factors				
Age, years, median (Q1-Q3)	71 (60–75)	79 (67–80)	0.04	−0.77
Sex: male n (%)	21 (57%)	7 (54%)	0.8	0.06
AF	12 (32%)	7 (54%)	0.17	−0.46
Diabetes	11 (30%)	2 (15%)	0.3	0.37
Anticoagulation	7 (19%)	6 (46%)	0.05	−0.6
Antiplatelets	6 (16%)	1 (8%)	0.4	0.25
Periprocedural and radiological factors				
Bridge tPA	17 (46%)	3 (23%)	0.14	0.5
Time to Groin	170 (126–265)	229 (114–294)	0.7	−0.5
Onset to TICI	209 (149–310)	271 (146–359)	0.8	−0.44
Mismatch vol, ml	104 (52–151)	101 (81–144)	0.65	0.03
Core volume, ml	10 (7–22)	10 (9–34)	0.67	0
Aspects baseline	9 (8–10)	8 (8–9)	0.24	0.85
Aspects 24 h	9 (8–10)	8 (7–9)	0.21	0.68
Anesthesia	5 (19%)	4 (50%)	0.08	−0.69
Aspiration	26 (74%)	13 (100%)	0.05	−0.84
Thrombectomy	23 (65%)	8 (62%)	0.78	0.06
Stroke characteristics				
Side of stroke: L	18 (49%)	4 (31%)	0.26	0.37
NIHSS post EVT	6 (5–9)	12 (7–15)	0.02	−1.28
mRS post EVT	2 (1–2)	5 (3–5)	< 0.01	−1.81
mRS 30 Day	2 (1–2)	5 (4–5)	< 0.01	−4.05
mRS 3 M	1 (0–2)	5 (3–6)	< 0.01	−2.12
Any ICH	2 (5%)	5 (38%)	< 0.01	−0.88
sICH	0 (0%)	1 (8%)	0.08	−0.42

Data are presented as median (Q1–Q3) for continuous variables and n (%) for categorical variables. Q1 and Q3 denote the 25th and 75th percentiles, respectively. Std diff: standardized difference (absolute values ≥ 0.1 considered potentially meaningful, ≥ 0.8 large)

sICH symptomatic intracranial hemorrhage, *AF* atrial fibrillation

Safety Outcomes

The cumulative 12-month mortality rates were similar in both groups (18% vs. 18%, $p = 0.5$). In the Cerebrolysin group, deaths occurring between the 3- and 12-month follow-ups were due to multiorgan and respiratory failure secondary to COVID-19 ($n = 3$), sepsis ($n = 1$), and cardiac causes ($n = 1$); in the control group, deaths were due to COVID-19 ($n = 2$), cardiac causes ($n = 2$), and traumatic brain injury ($n = 1$). No recurrent strokes were observed in any group. Forty six patients (92% of the initial cohort) began second cycle of Cerebrolysin treatment, 35/46 (76%) completed all 21 infusions of second Cerebrolysin cycle; the remainder discontinued after a median of 13 days (8–19) due to: patients preference ($n = 10$) or superficial venous thrombosis at an IV site ($n = 1$) which was classified as adverse event related to the Cerebrolysin infusion. No adverse events considered related to Cerebrolysin infusion were reported during follow-up between 3 and 12 months.

Discussion

This hypothesis-generating 12-month extension of a previously reported pilot study suggests that Cerebrolysin, administered shortly after successful recanalization following EVT and again between days 69 and 90, may help convert early neurological gains into sustained functional independence in a carefully selected patient cohort [6]. Patients receiving Cerebrolysin demonstrated higher odds of independence at one-year, greater global disability shift, improved activities of daily living, and a lower need for institutional care. To our knowledge, this is the first study to evaluate the long-term effectiveness of combining EVT with Cerebrolysin treatment guided by selection criteria favorable for cerebroprotection - small ischemic core, good collaterals, effective recanalization, and two 21-day treatment cycles.

The magnitude of the association in our primary model (aOR 6.10 for 12-month functional independence) is substantial. This may partly reflect the highly selected population (small core, good collaterals, successful reperfusion) but could also be inflated by residual confounding and the small sample size. The direction of effect is consistent with prior randomized trials and meta-analyses of Cerebrolysin, which predominantly reported short-term (typically 90-day) outcomes; therefore, effect-size comparisons at 12 months should be interpreted cautiously [7].

The mechanistic rationale aligns with contemporary understanding of acute ischemia–reperfusion injury and the evolving concept of secondary ischemic injury mechanisms [2]. In AIS dysfunction of the BBB and NVU perpetuates oxidative stress, inflammation, and cytotoxicity - processes that define the acute ischemic core and drive the progression of secondary, delayed injury. However, in that phase, the persistence and specific roles of innate and adaptive immune responses within the post-ischemic brain and the peripheral system remain poorly defined and incompletely understood. Thus, multimodal, multicellular cerebroprotective agents - tailored to pathway- and time-specific responses—may offer greater therapeutic efficacy [15, 16]. Post-recanalization outcomes are now recognized to depend not only on the restoration of large-vessel flow but also on the adequacy of microvascular reperfusion, endothelial function, and chronic NVU integrity. Persistent dysfunction within this multicellular interface can sustain inflammation, oxidative stress, and metabolic uncoupling, delayed cell death ultimately limiting tissue recovery even after technically successful reperfusion and limit translation from reperfusion to network recovery. Therapies that stabilize or restore NVU function, therefore, represent a logical next step in extending the benefits of EVT from macrovascular to microvascular and cellular levels.

Cerebrolysin has pleiotropic actions consistent with these mechanisms; the two-course regimen in this study was designed to address both acute neuroprotection and the subsequent window of neural plasticity [7]. In this pilot, hypothesis-generating study, Cerebrolysin use was associated with greater long-term functional independence after adjustment, but the observational design precludes causal inference. Consistent with our findings, ElBassiouny et al. reported favorable 90-day outcomes in a cohort restricted to acute cardioembolic stroke patients who received a single 14-day course of Cerebrolysin after EVT [17]. In the recently published ESCAS randomized pilot study, adding 3 courses of Cerebrolysin (on days 1–14, 29–42, and 57–70 post-stroke) to intensive speech-language therapy in patients with non-fluent post-stroke aphasia produced greater improvements in language and other neurological deficits [18]. Functional neuroimaging evidence from the ECOMPASS study supports Cerebrolysin's role in promoting neuroplasticity. Resting-state fMRI revealed enhanced reorganization of the sensorimotor network, with restoration of symmetric connectivity between bilateral primary motor cortices in patients after stroke - suggesting improved interhemispheric balance and motor cortical recovery [19]. In a recently published multinational comparative effectiveness registry (C-REGS2) of patients with moderate AIS, Cerebrolysin plus standard care was associated with better functional outcome at 90 days on the ordinal mRS (primary endpoint; Mann–Whitney effect size 0.6157, corresponding to an OR of approximately 2.03) [20]. Favorable outcomes were also observed for early mRS/NIHSS recovery and for the proportions achieving mRS 0–1 and mRS 0–2 at 90 days. Safety outcomes were reassuring, with no significant differences in death or serious adverse events compared with standard therapy alone.

As reported in our study, a benefit persisting beyond 90 days - which extends our prior report-is consistent with sustained neuroprotection and neurorestoration after the acute ischemic phase and with established post-ischemic mechanisms [8, 21]. Importantly, the treatment association persisted after adjustment for established predictors of long-term outcome following EVT—reperfusion quality (mTICI 3 vs. 2b), number of device passes, early post-EVT NIHSS, and the occurrence of sICH [22]. While residual confounding cannot be excluded in a matched cohort, the results of multivariable analysis, alongside favorable safety, strengthens the case for definitive testing. Similar findings were reported in the only other published pilot study on the combined use of reperfusion therapy (r-tPA and/or EVT) with Cerebrolysin vs. controls by Poljakovic et al. [25]. The study showed better functional outcomes at 12 months (mRS 0–2: 70% vs. 48%, $p=0.1$) and significant reduction in the 12-month mortality (13% vs. 43%, $p=0.03$). While we could not confirm a significant impact of Cerebrolysin on 12 months mortality, this may be attributed to the small sample size limiting the statistical power or patient selection favoring those with a more favorable prognosis (e.g., good collaterals, effective recanalization). Numerous adjunctive cerebroprotective drugs are currently in development, and they tackle different ischemic tissue damage mechanisms. Beyond Cerebrolysin, candidates such as imatinib or ApTOLL (a Toll-like receptor 4 antagonist) have shown promise in phase-II studies [23, 24]. In the ESCAPE-NA1 trial, nerinetide did not improve 90-day functional independence compared with placebo (mRS 0–2: 61.4% vs. 59.2%), with a potential benefit limited to patients not receiving alteplase (59.3% vs. 49.8%) [25]. The subsequent ESCAPE-NEXT trial, enrolling patients undergoing thrombectomy without prior thrombolysis, likewise demonstrated no treatment effect (mRS 0–2: 45% vs. 46%) [26].

Although single-endpoint analyses at 3 and 12 months in our study showed positive results, they do not capture the timing and dynamics of recovery. We therefore assessed the trajectory of mRS at the patient level over 12 months to provide a more nuanced view of improvement, stabilization, and relapse over time. By distinguishing early and late recovery phases, this approach revealed patterns of delayed improvement and sustained independence - features relevant to neurorestorative interventions with prolonged biological effects. This evaluation showed that participants receiving Cerebrolysin had a higher likelihood of sustained independence, demonstrated greater gains particularly after day 30, were more likely to convert to independence beyond 3 months, and exhibited less fluctuation in functional status over 12 months. However, several other trajectory advantages were directionally consistent but underpowered to reach statistical significance in this sample. Thus, examining the shape and stability of functional change across the first post-stroke year in future studies on neuroprotection could offer a richer account of treatment effects on long-term neurological recovery.

The optimal timing and duration of Cerebrolysin remain uncertain. The durability of any neuroprotective benefit remains unknown, and no other agent has been tested systematically out to one year in conjunction with EVT. Although clinical and preclinical data suggest benefits beyond 72 h - plausibly via enhancement of neuroplasticity and recovery pathways - a meta-analysis indicates that initiating Cerebrolysin within 24–72 h is associated with superior functional outcomes [7, 27]. On this basis, the EFNR (European Federation of Neurorehabilitation), Polish Society of Neurology and other scientific societies have recently recommend starting Cerebrolysin as early as feasible after moderate–severe AIS within this window and continuing for 10–21 days, while acknowledging that further trials are needed to define precise temporal dynamics [28, 29]. Biologically, early initiation is justified: it coincides with secondary injury cascades—excitotoxicity, oxidative stress, inflammation—and the initial window for experience-dependent plasticity, whereas a 10–21-day course spans the subacute phase of synaptic remodeling and network reorganization. The optimal thresholds for initiation, duration, and taper—and whether extended or cyclic courses benefit selected patients (e.g., large core, LVO with delayed recovery)—remain unresolved and require adequately powered, timing-stratified randomized controlled trials. Notably, findings from CARS and ESCAS suggest that Cerebrolysin is most effective when paired with structured, task-specific rehabilitation; isolated pharmacotherapy without high-quality rehabilitation may confer limited benefit. Positive results of our pilot study suggest that the favorable effect of Cerebrolysin as an add-on to EVT and rehabilitation may reflect mitigation of reperfusion-related injury, stabilization of peri-infarct networks, and promotion of neuroplasticity. These observations are consistent with the STAIR XI recommendations to shift emphasis from purely neuroprotective strategies toward cerebroprotection/neurovascular protection [30].

Cerebrolysin's multimodal actions align with contemporary frameworks for neuroprotective therapies targeting the complex cascade of ischemia–reperfusion injury [31–33]. By attenuating reperfusion-related oxidative and inflammatory damage and supporting neuroplastic repair, Cerebrolysin may complement successful recanalization in patients with preserved collateral flow and predominantly cortical infarcts. These mechanistic considerations guided the design of the current study and may explain the sustained functional benefits observed at 12 months, although confirmation in larger, multicenter trials remains warranted [34]. Recent large-core trials, such as SELECT2 and TESLA, reported functional independence in only 22–24% of patients at one year, underscoring the limited durability of reperfusion benefit in extended time windows and the urgent need for effective neuroprotective adjuvants (Table 3S). Absolute independence rates remain modest – even in contemporary trials, only about 1 in 4 patients with large cores and 1 in 3–4 unselected patients in MR CLEAN are independent at a year or beyond. Benefit is durable – every randomized dataset that has reported ≥ 12-month results show the 90-day treatment effect is maintained or widens, with consistent ordinal-shift benefit.

The residual burden of post-stroke sequelae is high: across cohorts, cognitive decline, depression, and incontinence are frequent, reported in up to 30–40% of survivors in registry-based substudies, including those with mRS ≤ 2 [35]. Post-stroke apathy or depression affects approximately one in three survivors, with significant implications for quality of life and rehabilitation engagement [36]. Additionally, many experience persistent urinary incontinence, often under-recognized despite its strong association with institutionalization and reduced long-term independence. However, short- and long-term rates of these complications as well as the impact of neuroprotective agents have also not been systematically studied after EVT, and these require urgent studies. Debate over long-term outcomes after EVT highlights the need for holistic assessment strategies that integrate cognitive and emotional measures alongside physical rehabilitation. The interplay of pre-stroke cognitive status, stroke severity, and sociodemographic factors shape post-stroke mental health, underscoring the complexity of recovery. Future studies should adopt multidimensional outcome frameworks and tailor interventions that address both physical rehabilitation and psychological needs after stroke and EVT. Such a balanced approach may enhance overall

recovery, reduce post-stroke depression, and mitigate long-term cognitive impairment, ultimately improving quality of life. It remains unknown whether neuroprotective agents are effective in this domain; thus, tailored rehabilitation strategies and comprehensive care pathways- including add-on therapies that target the full spectrum of post-stroke recovery are warranted.

The safety profile of Cerebrolysin, particularly when used for longer duration or in repeated cycles, remains an important consideration. Previous controlled clinical trials have demonstrated that the overall frequency of adverse events in patients receiving Cerebrolysin in different dosages and time of duration is comparable to placebo, with most reactions being mild and transient [37, 38]. In the present study, no treatment-related serious adverse events were observed during the 12-month follow-up, further supporting the established safety profile of Cerebrolysin in the context of AIS.

Strenghts

The present study has several strengths. First, the extended 12-month follow-up with detailed assessment of neurological and functional outcomes provides a comprehensive view of recovery trajectories after mechanical thrombectomy. This multidimensional approach enhances clinical applicability and reflects real-world practice. Second, the identification of lower post-EVT NIHSS, younger age, and absence of intracranial hemorrhage as independent predictors of long-term independence extends prior 3-month observations and underscores the potential durability of benefit with Cerebrolysin. Although meta-analyses suggest early neurological benefit after EVT, effects on long-term disability have remained inconclusive so far. Our findings therefore provide preliminary evidence that adjunctive neurorestorative therapy may help sustain early recovery into long-term functional gains. These results are consistent with preclinical data supporting Cerebrolysin's multimodal neuroprotective and neurorestorative actions, strengthening the biological plausibility of its use as an adjunctive therapy in acute ischemic stroke [18]. Collectively, the data provides a rationale for larger, multicenter, randomized studies to confirm long-term efficacy and safety in the contemporary reperfusion era.

Limitations

While the 12-month results are encouraging, several limitations warrant consideration. First, the single-center, non-randomized design with historical controls carries a substantial risk of residual confounding and selection bias despite propensity-score matching. Although outcome assessment was blinded, open-label Cerebrolysin administration could have influenced patient and provider behavior (e.g., rehabilitation engagement or care intensity). In addition, unmeasured factors, including baseline cognitive status and post-acute rehabilitation adherence and intensity—may have affected comparability between groups and long-term outcomes. Secular improvements in stroke care over time could also have biased results, potentially in favor of the more recent Cerebrolysin cohort. To mitigate this, the control source population was restricted to patients treated after implementation of a uniform EVT workflow with mandatory CT perfusion and standardized post-stroke care; moreover, the 90-day and 12-months independence rates in controls (44% and 46%) fall within the range reported in some EVT trials and stroke registries (Table 3S). Nevertheless, residual confounding and temporal trends cannot be excluded.

Second, CT perfusion mismatch parameters and baseline ASPECTS were not included in the propensity score model. Baseline ASPECTS was slightly lower in the Cerebrolysin group (median 9 vs. 10), which would be expected to bias against observing better outcomes in the treated group. To avoid overfitting in this small sample, we prespecified matching on post-EVT NIHSS and nine additional covariates (age, sex, stroke laterality, occlusion location, CTA-CS, pre-stroke mRS, bridging IV thrombolysis, final reperfusion grade, and onset-to-reperfusion time). We acknowledge that omission of baseline ASPECTS and perfusion mismatch may have left residual confounding; therefore, we included these variables in fully adjusted sensitivity models, and the associations remained directionally consistent. Because post-EVT NIHSS is a post-treatment measure that may be influenced by procedural factors and early complications, we also performed a sensitivity analysis replacing post-EVT NIHSS with pre-EVT NIHSS to minimize potential post-treatment adjustment bias and to adjust for baseline stroke severity.

Third, our cohort was highly selected (good collaterals, small core, successful reperfusion), which likely limits generalizability to broader EVT populations, including patients with large cores, poorer collaterals, or incomplete reperfusion. The sample size (n = 50 per group) limits statistical power, particularly for safety and subgroup analyses, and contributes to wide confidence intervals in multivariable models; effect size estimates should therefore be interpreted cautiously and require confirmation in adequately powered randomized trials. Overall, these limitations mean the results should be interpreted as hypothesis-generating rather than definitive evidence of efficacy.

Future Directions

Our findings should be interpreted as exploratory, informing the design of adequately powered randomized trials. Future studies should confirm the effectiveness of adjunctive Cerebrolysin after EVT in large, multicenter randomized controlled trials. Several such studies are currently underway across different settings and research centers under the CERECAP initiative [39]. Long-term follow-up that integrates clinical, cognitive, and quality-of-life outcomes is required to capture the full spectrum of recovery beyond motor function. From a translational perspective, defining the optimal therapeutic window for neuroprotection remains a key frontier; very early administration—ideally in the prehospital phase or immediately before endovascular reperfusion—may enhance neuronal survival and synaptic recovery by attenuating ischemia–reperfusion injury and cell death. Trials should also extend inclusion to wake-up strokes, patients with large-core or those selected by advanced tissue-viability imaging to align with contemporary precision-medicine paradigms. Ultimately, integrating multimodal neuroprotective agents such as Cerebrolysin into reperfusion workflows could help bridge the gap between acute recanalization success and long-term neurological restoration. Given the historical challenges of neuroprotective agents in clinical trials, ongoing work should test both timing and delivery methods. Strategies that enable prehospital neuroprotection with prehospital triage protocols, in mobile stroke units, or within streamlined emergency pathways—may mitigate ischemic damage before stroke unit-based treatments are initiated [40, 41].

Conclusions

Adjunctive Cerebrolysin use was associated with higher odds of long-term functional independence after EVT in this highly selected, propensity-matched cohort, after adjustment for age, stroke severity, and reperfusion quality; however, residual confounding and indication bias cannot be excluded. Across models, early neurological status, successful reperfusion, good collaterals, and absence of hemorrhagic complications remained strong correlates of 12-month outcome. These findings should be considered hypothesis-generating, and adequately powered randomized trials are needed to determine whether Cerebrolysin provides incremental benefit after EVT and to define optimal timing, duration, and patient selection.

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Data Availability De-identified participant-level data underlying the analyses are available from the corresponding author upon reasonable request and with appropriate institutional approvals/data-use agreement, in accordance with local regulations and ethical requirements. Statistical analysis code is available from the corresponding author upon reasonable request.

Declarations

Competing Interests The authors declare no competing interests.

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