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Thrombectomy in large vessel occlusion stroke—Does age matter?

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Objectives: Endovascular treatment (EVT) is the gold standard treatment for emergent large vessel occlusion (LVO). The benefit of EVT for emergent LVO in elderly patients (>80 years old) is still debated as they have been under-represented in randomized controlled trials. Elderly patients with an emergent LVO are a growing population warranting further study.

Materials & Methods: We included 225 consecutive patients treated with EVT for LVO either in the anterior or posterior circulation. The clinical outcome was assessed using the National Institute of Health Stroke Scale (NIHSS). Long-term functional outcome was assessed using 90-day modified ranking scale (mRS).

Results: Neurological improvement: A five-year higher age predicted a 0.43 higher mean NIHSS score after EVT ($p = .027$). After adjusting for confounders (influencing variables), the association between age and post-interventional NIHSS was reduced and non-significant ($p = .17$). At discharge, a five-year higher age predicted a 0.74 higher mean NIHSS ($p = .003$). After adjusting for confounders this association was reduced and non-significant ($p = .06$).

Long-term functional outcome: A five-year higher age predicted a 0.20 higher mRS at three months ($p < .001$). When adjusting for confounders this number was reduced to 0.16, yet still highly significant ($p < .001$).

Conclusions: Age seems to have a minor role in predicting neurological improvement after EVT but has an impact on long-term functional outcome. The decision to perform or withhold EVT should therefore not solely be based on age.

KEYWORDS
acute treatment, elderly, endovascular treatment, general interventional radiologists, large vessel occlusion, stroke, thrombectomy

1 | INTRODUCTION

15 million people worldwide suffer a stroke each year and it is estimated that the total number of ischemic strokes will rise by approximately 68% until 2050.[1] The natural course of ischemic stroke, especially an emergent large vessel occlusion (LVO) is devastating, with high rates of morbidity and mortality.[2] Endovascular treatment (EVT) has become the standard of care for acute stroke

patients presenting with an emergent LVO stroke in the anterior circulation.[3] Elderly patients with an emergent LVO stroke are an ever-growing and fragile population, where outcomes are usually worse.[4] Although elderly patients account for a substantial part of stroke admissions,[5] they have been under-represented in randomized controlled (RCTs) trials for EVT. In the HERMES meta-analysis of the five pivotal EVT trials, only 15% of those included were aged ≥80 years.[3] Despite this, the meta-analysis concluded that EVT is of benefit across a wide range of age including octogenarians. We have previously shown that elderly stroke patients presenting with LVO stroke have a similar early neurological improvement; however, their functional outcomes are worse as compared to those aged <80.[6] A recent meta-analysis confirmed this finding, where successful recanalization rates and symptomatic intracerebral bleeding (sICH) rates were similar, a significantly lower proportion of the elderly achieved a good clinical outcome at 3 months.[7] There is evidence to undermine a strict upper age limit for emergent LVO treatment, the effect of age on patient outcome has yet to be determined. Our primary aim was to assess the role of age, not dichotomized in age groups, with regard to clinical neurological improvement and functional long-term outcome adjunct to EVT.

2 | MATERIAL AND METHOD

2.1 | Patients

Prospective inclusion of all patients with a verified LVO in both the anterior and posterior circulation from September 2009 up to and including December 2020.

Prior to treatment, a non-enhanced computed tomography (NECT), perfusion CT (CTP) and CT angiography were performed. In patients where penumbra was difficult to assess, a supplementary magnetic resonance imaging (MRI) scan was performed. In patients with unknown onset time or wake-up strokes, MRI was performed as the first choice imaging tool.

Upon detection of an emergent LVO, a multidisciplinary team considered EVT eligibility. The multidisciplinary team comprised a stroke neurologist, a general interventional radiologist, and a diagnostic neuroradiologist. All patients were older than 18 years of age without any strict upper age limit. Patients eligible for IVT were pretreated with rt-PA prior to/during EVT.

2.2 | Revascularization procedures

EVT was performed by six experienced general interventional radiologists. All procedures were performed in a monoplane angiography suite equipped with a Siemens Artis zee (December 2009–June 2014) or a Philips Allura FD20 Clarity (Philips, Best; Netherlands) (June 2014–to date). Interventional details are described earlier.[6] Most of the procedures in the first years of the study were performed under general anesthesia, in later years conscious sedation was preferred.[8]

2.3 | Clinical evaluation

Neurological impairment was assessed using the National Institutes of Health Stroke Scale (NIHSS). NIHSS was performed at admission, at 24 h, and on the day of hospital discharge. Functional outcome was assessed using the Modified Rankin Scale (mRS). The mRS assessment was performed at admission and after 3 months either during an outpatient consultation or by telephone interview conducted by a certified stroke nurse. Good functional outcome was defined as a mRS score 0–2, poor functional outcome as a mRS score 3–6.

Patients where more than one EVT procedure was performed during the same hospital admission, patients transferred to other hospitals, patients with a pre-stroke mRS of ≥2 and those unable to perform the follow-up telephone interview were excluded from analysis ($n = 40$).

2.4 | Efficacy and safety evaluation

Technical revascularization outcomes were graded using the modified thrombolysis in cerebral infarction (mTICI) scoring system.[9] Successful recanalization was defined as mTICI grade 2b or 3. To determine the infarct volume or any complications, a follow-up MRI was performed 24 h after symptom onset/post-EVT in majority of patients, with the remaining minority undergoing a CT scan. A supplementary CT or MRI scan was performed in patients where clinical deterioration was observed. Safety of treatment was determined by the incidence of procedural complications (within 24 h). This was based on angiographic findings during the procedure, MRI and/or CT scans performed after the procedure, and clinical neurological examination. Intracranial hemorrhage (ICH) was classified according to the European Cooperative Acute Stroke Study II (ECASS II)[10]; sICH was defined as ICH associated with a four-point or greater deterioration in NIHSS.

2.5 | Statistics

Descriptive statistics are presented at count and percentages for categorical variables and as medians and interquartile ranges (IQR) for continuous variables. Associations between age and clinical/functional outcomes were assessed using linear regression. Unadjusted and adjusted effect estimates for age (per five years) were presented with 95% confidence interval (CI), *p*-value from test of no effect, and the change in R^2 after including age in the model. The linearity of the age effect was checked using fractional polynomial regression.

Gender, NIHSS prior to EVT, pre-stroke mRS (0 or 1), occlusion in the anterior circulation, history of stroke or myocardial infarction, hypertension, atrial fibrillation, diabetes, logarithmic scale of glucose at admission and ongoing statin treatment were included as potential confounders. Furthermore, IVT administration, successful recanalization, and peri-interventional complications were included as potential mediators of the age effect.

The association between age and the odds of successful recanalization was assessed using binary logistic regression.

SPSS Statistics version 24 (IBM Cooperation) was used for descriptive statistics, Stata version 17 for regression analyses. *p*-values $<.05$ were considered statistically significant.

2.6 | Ethics statement

The study was approved by the Regional Committee for Medical and Health Research Ethics, the Norwegian Centre for Research Data and the local hospital authorities.

3 | RESULTS

A total of 298 patients were included in the study. Median age at baseline was 72 years (IQR 61–80), 43% of patients included were female, and 37% had atrial fibrillation (55% newly diagnosed, 30% of patients with known atrial fibrillation were insufficiently anticoagulated). Median NIHSS at admission was 17 (IQR 12–21). A summary of baseline characteristics is shown in Table 1. The site of occlusion is shown in Table 2. 89.6% had an occlusion in the anterior circulation, 10.4% in the posterior circulation. A good technical reperfusion result was achieved (TICI 2b–3, Table 3) in 79.9% of the patients. Median post-interventional NIHSS was 12 (IQR 5–19) and upon discharge 6 (IQR 1–12). At 3-months follow-up 44.6% achieved good functional outcome (mRS 0–2) and 57.7% a mRS of 0–3. A mortality rate of 18.5% was seen (Table 3).

3.1 | Neurological improvement

In the unadjusted analysis, we found that a five-year higher age predicted a 0.43 higher mean NIHSS score after EVT ($p = .027$) (Table 4).

TABLE 1 Patient baseline characteristics and cerebrovascular risk factors ($N = 298$)

Age in years, median (IQR)	72 (61–80)
Female	129 (43.3%)
Hypertonia	170 (57.0%)
Atrial fibrillation	111 (37.2%)
Diabetes	34 (11.4%)
Prior stroke	38 (12.8%)
Prior cardial infarction	48 (16.1%)
IVT pre-treatment	199 (66.8%)

Abbreviations: IQR, interquartile range; IVT, intravenous thrombolysis.
Note: Data presented as count (%) unless otherwise specified.

Adjusted for the confounders, in particular pre-intervention NIHSS scores and whether the patient had a previous stroke or not (data not shown), the effect of age on post-intervention NIHSS was reduced to 0.29 per five years and statistically non-significant ($p = .17$). The estimate of the age effect was further reduced when adjusting for successful reperfusion ($\beta = 0.19$, $p = .33$); although age was not found to be statistically significantly associated with the odds of successful reperfusion (odds ratio per five years 0.94, 95% CI 0.85 to 1.04, $p = .25$). Age explained 1.7% of the variance in post-interventional NIHSS scores. After adjusting for confounders, age explained a mere 0.6% of the variance.

3.2 | NIHSS at discharge

In the unadjusted analysis, we found that a five-year higher age predicted a 0.74 higher mean NIHSS score after EVT ($p = .003$) (Table 5). Adjusted for confounders, the effect of age on NIHSS at discharge was reduced to 0.52 per five years and statistically non-significant ($p = .06$). As for post-procedure NIHSS, the estimate of the age effect was further reduced when adjusting for successful reperfusion ($\beta = 0.37$, $p = .13$).

3.3 | Functional outcome

A five-year higher age predicted in the unadjusted analysis a 0.20 higher 3 months mRS ($p < .001$) (Table 6). When adjusting for all potential confounders, the most important being NIHSS score prior to EVT (data not shown), this number was reduced to 0.16 ($p < .001$). Age accounted for 8.6% of the variation in mRS scores. When adjusting for the confounders, age accounted for 4.2% of the residual variance. There was a remaining effect of age on the long-term functional outcome ($\beta = 0.15$, $p < .001$) also after adjusting for potential mediators.

3.4 | Sub-group analyses

Analyzing anterior circulation separately (excluding posterior LVO) did not change the results substantially; when solely analyzing posterior circulation LVO ($n = 31$; only unadjusted analyses) we did not see any significant age associations.

For those with IVT pre-treatment, we found for neurological improvement that a five-year higher age predicted a 0.54 higher mean NIHSS post-interventionally ($p = .023$) and 0.84 higher NIHSS at dismissal ($p = .005$). When adjusting for confounders, this effect was reduced to, respectively, 0.24 and 0.45 and lost significance ($p = .35$ and .18).

For functional outcome, we saw that a five-year higher age predicted a 0.21 higher 3 months mRS ($p < .001$) in the unadjusted analysis. When adjusting for confounders, this number was reduced to 0.15 ($p = .005$).

For patients not receiving IVT pre-treatment, we found for neurological improvement that a five-year higher age predicted a 0.11 higher age post-interventionally ($p = .73$) and 0.33 higher age at dismissal ($p = .33$). When adjusting for confounders, this effect was, respectively, 0.14 and 0.46 ($p = .73$ and .36). For functional outcome, a five-year higher age predicted a 0.14 higher 3 months mRS ($p = .026$) in the unadjusted analysis. When adjusting for confounders, this number was 0.18 ($p = .0028$).

TABLE 2 Site of artery occlusion ($N = 298$)

ICA	15 (5.0%)
Carotid T-occlusion	31 (10.4%)
ICA and M1 (tandem)	48 (16.1%)
ICA and M2 (tandem)	2 (0.7%)
M1	156 (52.3%)
M2	14 (4.7%)
M1 + A2	1 (0.3%)
BA	31 (10.4%)

Abbreviations: A, anterior cerebral artery; BA, basilar artery; ICA, internal carotid artery; M, middle cerebral artery.

Note: Data presented as count (%).

TABLE 3 Technical and clinical outcomes ($N = 298$)

TICI 2b/3	238 (79.9%)
mRS 0–2	133 (44.6%)
mRS 0–3	172 (57.7%)
mRS 6	55 (18.5%)
sICH	19 (6.4%)
NIHSS at admission, median (IQR)	17 (12–21)
NIHSS at 24 h, median (IQR)	12 (5–19)$^{N = 297}$
NIHSS at dismissal, median (IQR)	6 (1–12)$^{N = 291}$

Abbreviations: IQR, interquartile range; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; sICH, symptomatic Intracerebral Hemorrhage; TICI, Thrombolysis in cerebral infarction scale.

Note: Data presented as count (%) unless otherwise specified.

4 | DISCUSSION

Successful EVT leads to significantly improved clinical outcomes for emergent LVO stroke and several studies have demonstrated its efficacy beyond the strict RCT inclusion criteria.[11,12] However, in the context of limited resources, substantial procedural costs, globally increasing stroke cases, and the socioeconomic costs of healthcare selecting those patients likely to benefit from EVT is of increasing importance. In the setting of patient selection and prognostication for good EVT outcome, age is an important variable.[13] Our study did not show that patient age had an independent influence on neurological improvement post-intervention or at discharge after accounting for other influencing variables (confounders). Yet, we did find that age had an effect on long-term outcome. After adjusting for confounders, the effects on neurological improvement and long-term outcome were similar in patients pre-treated with IVT and in those were no prior IVT treatment was performed.

EVT requires considerable resources and several works have aimed to stratify patient selection and outcome prognostication.[14–16] Stroke severity and age are identified as strong determinants of outcomes, and in real-world observational studies, EVT in the elderly is associated with a lower likelihood of a good clinical outcome as well as higher mortality rates.[3,6,17] Subsequently, age has clearly influenced the decision to perform EVT and there are concerns regarding the benefit of EVT in the elderly in the real-world setting.[13] However, age alone does not seem to influence initial neurological improvement post-EVT.[3] We have previously shown that successful EVT leads to equally pronounced neurological improvement when dichotomizing by the age of 80.[6] In the analyses put forward here, we can demonstrate that the mere number of years the patient has

TABLE 4 Association between age and NIHSS at 24 h post-EVT

	n	β (95% CI)	*p*-value	R^2 (%)	ΔR^2
Unadjusted[a]	297	0.43 (0.05, 0.80)	.027	1.7	
Unadjusted[b]	285	0.40 (0.02, 0.78)	.041	1.5	
Adjusted for confounders	285	0.29 (−0.12, 0.71)	.17	21.1	0.6
Adjusted for confounders + IVT	285	0.28 (−0.13, 0.69)	.18	22.5	0.5
Adjusted for confounders + successful reperf	285	0.19 (−0.19, 0.56)	.33	37.0	0.3
Adjusted for confounders + complications	285	0.32 (−0.09, 0.74)	.12	22.4	0.7
Adjusted for confounders and mediators	285	0.19 (−0.18, 0.56)	.32	37.9	0.3

Abbreviations: CI, confidence interval; EVT, endovascular thrombectomy; IVT, intravenous thrombolysis; NIHSS, National Institutes of Health Stroke Scale.

Note: Effect estimate β gives expected difference in mean post-EVT NIHSS for a five-year increase in age. *p*-values from tests of $\beta = 0$. R^2 (given in percent) measures the proportion of variation in post-EVT NIHSS explained by the total model, and ΔR^2 measures the proportion of residual variation explained by age (after adjustment).

[a]Including all available cases.

[b]including only complete cases. Patients who died in hospital ($n = 35$) had their dismissal NIHSS score imputed to 38.

TABLE 5 Association between age and NIHSS at dismissal

	n	β (95% CI)	*p*	R^2 (%)	ΔR^2
Unadjusted[a]	291	0.74 (0.26, 1.22)	.003	3.0	
Unadjusted[b]	279	0.69 (0.20, 1.17)	.006	2.7	
Adjusted for confounders	279	0.52 (−0.02, 1.07)	.060	16.6	1.1
Adjusted for confounders + IVT	279	0.51 (−0.04, 1.05)	.069	17.4	1.1
Adjusted for confounders + successful reperf.	279	0.37 (−0.12, 0.86)	.13	34.6	0.6
Adjusted for confounders + complications	279	0.55 (0.01, 1.09)	.047	17.7	1.3
Adjusted for confounders and mediators	279	0.37 (−0.12, 0.86)	.14	34.8	0.5

Abbreviations: CI, confidence interval; IVT, intravenous thrombolysis; NIHSS, National Institutes of Health Stroke Scale.

Note: Effect estimate β gives expected difference in mean NIHSS at dismissal for a five-year increase in age. *p*-values from tests of $\beta = 0$. R^2 (given in percent) measures the proportion of variation in dismissal NIHSS explained by the total model, and ΔR^2 measures the proportion of residual variation explained by age (after adjustment).

[a]Including all available cases.

[b]including only complete cases. Patients who died in hospital (*n* = 35) had their dismissal NIHSS score imputed to 38.

TABLE 6 Association between age and mRS at 3 months

	n	β (95% CI)	*p*	R^2 (%)	ΔR^2
Unadjusted[a]	298	0.20 (0.12, 0.27)	<.001	8.6	
Unadjusted[b]	286	0.19 (0.12, 0.27)	<.001	8.2	
Adjusted for confounders	286	0.16 (0.08, 0.25)	<.001	20.8	4.2
Adjusted for confounders + IVT	286	0.16 (0.08, 0.24)	<.001	22.1	4.1
Adjusted for confounders + successful reperf.	286	0.14 (0.07, 0.22)	<.001	36.5	3.2
Adjusted for confounders + complications	286	0.17 (0.09, 0.26)	<.001	23.2	4.7
Adjusted for confounders and mediators	286	0.15 (0.07, 0.22)	<.001	37.8	3.3

Abbreviations: CI, confidence interval; IVT, intravenous thrombolysis; mRS, modified Rankin Scale.

Note: Effect estimate β gives expected difference in mean 3-months mRS for a five-year increase in age. *p*-values from tests of $\beta = 0$. R^2 (given in percent) measures the proportion of variation in 3-months mRS explained by the total model, and ΔR^2 measures the proportion of residual variation explained by age (after adjustment).

[a]Including all available cases.

[b]including only complete cases.

lived only negligibly influences neurological improvement after successful EVT.

Confirming our results, a recent analysis from the HERMES collaboration including more 1750 patients from seven randomized controlled trials showed that EVT was beneficial across all weighted age/NIHSS subgroups.[18] There was a lack of interaction between NIHSS score and age suggesting that each variable has its own independent effect on stroke outcomes. The impact on the chance of good outcome measured by a 1-point increase in NIHSS roughly corresponded to a 3-year increase in patient age.

It is well known that age affects long-term functional outcomes of patients post-EVT.[19] Functional outcome at 3 months had a clear association with higher age in our study (Table 6). The age effect on long-term functional outcome seemed to be mediated by a decreased probability of successful recanalization, although this association was not statistically significant.

After adjusting for confounders, the age effects on neurological improvement and functional outcome were similar in patients pretreated with IVT and in those were no pre-treatment was performed. This confirms a meta-analysis showing that age itself does not seem to influence the IVT effect in acute stroke patients noteworthy.[20]

Initially, the impact of age on long-term functional outcomes post-EVT was unclear. Single center studies did not find that age > 80 predicted poorer functional outcomes.[21,22] Supportive to these findings, the MR CLEAN Registry did not show an interaction between age and ASPECTS on 3 months modified Rankin Scale

($p = 0.925$).[23] In contrast, the HERMES meta-analysis, showed age to be a strong independent predictor of poor functional outcomes after EVT[3] and an analysis from the STRATIS Registry concluded that the combination of low ASPECTS and higher age (>75 years) was associated with poorer rates of functional independence and higher rates of mortality.[24]

The poorer functional outcomes in the elderly also translate into a poorer health-related quality of life.[25] An analysis from the German Stroke Registry revealed that young stroke survivors had fewer complaints in mobility ($p < .001$), self-care ($p < .001$), usual activities ($p < .001$), and pain/discomfort ($p = .008$). No difference was observed in anxiety/depression ($p = .819$).

Despite the limitations of our single, low volume, center study, we did not find that age significantly affects neurological improvement post-EVT. Age, however, has an impact on long-term functional outcomes, which might not seem surprising given the comorbidity and frailty of this patient subgroup. Our data further support current evidence that the decision to perform or withhold EVT should not solely be influenced by age. All factors, such as clinical, radiological, and procedural, should be considered when determining patient eligibility in this emergent setting.

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None.

CONFLICT OF INTEREST

The authors have no conflict of interest to report. The study does not present any potential conflicts.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

PEER REVIEW

RESPONSE TO PEER REVIEW TRANSPARENCY OPTION (reviewer reports, author responses, and decision letter linked from Publons): Yes

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