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Clinical frailty and outcome after mechanical thrombectomy for stroke in patients aged ≥ 80 years

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Objectives: Data concerning the results of endovascular thrombectomy (EVT) in old patients is still limited. We aimed to investigate the outcomes in thrombectomy-treated ischemic stroke patients aged ≥ 80 years, focusing on frailty as a contributing factor. *Patients and methods:* We performed a single-centre retrospective cohort study with 159 consecutive patients aged ≥ 80 years and treated with EVT for acute ischemic stroke between January 1st 2016 and December 31st 2019. Pre-admission frailty was assessed with the Clinical Frailty Scale (CFS). Patients with CFS ≥ 5 were defined as frail. The main outcome was very poor outcome defined as mRS 4-6 at three months after EVT. Secondary outcomes were recanalization status, symptomatic intracerebral haemorrhage (sICH), and one-year survival. Finally, we recorded if the patient returned home within 12 months. *Results:* Very poor outcome was observed in 57.9% of all patients (52.4% in non-frail and 79.4% in frail patients). Rates of recanalization and sICH were comparable in frail and non-frail patients. Of all patients, 46.5% were able to live at home within 1 year after stroke. One-year survival was 59.1% (65.6% in non-frail and 35.3% in frail patients). In logistic regression analysis higher admission NIHSS, not performing thrombolysis, lack of recanalization and higher frailty status were all independently associated with very poor three-month outcome. Factors associated with one-year mortality were male gender, not performing thrombolysis, sICH, and higher frailty status. *Conclusion:* Almost 60% of studied patients had very poor outcome. Frailty significantly increases the likelihood of very poor outcome and death after EVT-treated stroke.

Keywords: Ischemic stroke—Thrombectomy—Frailty—Elderly

Introduction

Endovascular thrombectomy (EVT) is now standard of care for majority of the patients with ischemic stroke due to anterior circulation large vessel occlusion (LVO) within 6 h from the time of symptom onset, and for selected patients with favorable perfusion imaging up to 24 h from symptom onset.[1,2] Data concerning the use and results of EVT in patients older than 80 years is still limited, as many of the randomized controlled EVT trials excluded such patients. Approximately 30% of acute strokes appear in people over 80 years,[3,4] and the number of elderly people is steadily increasing worldwide. A meta-analysis of the randomized controlled EVT studies included 198 patients aged ≥ 80 years and showed a favorable effect of EVT on modified Rankin Scale (mRS) distribution shift at 90 days (OR 3.68, 95% CI 1.95-6.92) also in this subgroup.[5] However, data from the Dutch MR CLEAN Registry with 380 subjects aged ≥80 years found that older adults had a worse functional outcome and higher mortality than younger patients after EVT; good outcome defined as an mRS score 0−2 or maintaining an mRS score 3 for patients with a pre-stroke mRS score 3 was found in 20% vs 45.6%, and the mortality was 51% vs 22%, respectively.[6] Other

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reports confirm significantly lower rates of good outcome defined as mRS 0-2 and higher mortality rate in patients aged ≥ 80 years compared to younger patients, despite similar recanalization and sICH rates.[7–11] Hamann et al found a sharp decrease in likelihood of favorable functional outcome above the age of 78 years in patients with median cerebral artery-M1 occlusion strokes referred to EVT within 6 h of symptom onset.[12]

Frailty is a clinical state characterized by reduced resilience or reserve to physiological stressors, leading to an increased risk of dependency and mortality when exposed to a stressor, e.g., acute stroke. Frailty is attributed to increasing age and/or cumulative multisystem decline. The current estimate of physical frailty prevalence in Europe is around 15% for adults aged 65 years and over.[13] In adults aged over 85 years, prevalence increases to over 25%.[14] Screening for frailty has been advised in all individuals aged 70 years and over.[15] Clinical frailty has been shown to be independently associated with 28-day mortality after ischemic stroke and with less improvement in NIH Stroke Scale (NIHSS) following stroke thrombolysis,[16] and with stroke severity in elderly patients[17]. Frailty is also associated with poor short-term survival in subjects aged ≥ 80 years admitted to the intensive care units (ICU), and in ICU-treated patients frailty is associated with increased risk of developing and dying from persistent critical illness.[18,19] We aimed to investigate the outcomes of ischemic stroke patients aged ≥ 80 years following EVT in our single-center cohort with a special focus on frailty as a contributing factor.

Subjects and methods

All ischemic stroke patients aged ≥ 80 years who underwent EVT in the Department of Neurology, Helsinki University Hospital were analyzed from the Helsinki Stroke Registry from January 1st, 2016, to December 31st, 2019. Patients treated for a basilar artery occlusion were excluded, because they follow a different protocol at our institution. Patients were treated based on our department's written guidelines for acute stroke, which are updated biannually and whenever new scientific evidence becomes available. Thrombolysis and EVT are considered for subjects that are mainly independent in activities of daily living or with adequate reserve for meaningful recovery.

Helsinki Stroke Registry includes records of stroke and treatment details, comorbidities, treatment-related complications, prospectively collected three-month outcome assessed by mRS, and the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification of stroke etiology.[20] NIHSS and mRS scores were assessed by a certified and video−trained stroke neurologist.

Frailty was assessed using Clinical Frailty Scale (CFS) with simple visual description as a categorization tool.[21] The scale ranges from 1 (very fit: people who are robust, active energetic and motivated, exercise regularly and are among the fittest for their age) to 9 (terminally ill, approaching the end of life). Retrospective assessment of premorbid frailty was based on data extracted from hospital charts, notes from general practitioners, therapists, and by patients and proxy. Frailty was considered as both an ordinal scale and a dichotomous variable (CFS 1−4 classed 'non-frail' and CFS 5−9 classed 'frail') in pre-specified analyses. This division was made based on the CFS definitions, where CFS 5 is the first category considered 'mildly frail': people who have evident slowing and need help in high order instrumental activities of daily living like finances, heavy housework, medication, and transportation. The functional outcome was evaluated with mRS three months after thrombectomy. Very poor outcome was defined as mRS 4-6. In this context, good outcome was defined as mRS 0-2 or return to previous level (if pre-stroke mRS was > 2), whereas mRS 3 was considered acceptable. Secondary outcomes were recanalization level (successful recanalization was defined as Thrombolysis in cerebral infarction scale, TICI 2b-3), symptomatic intracerebral hemorrhage (sICH)[22] and one-year survival. We also studied if the patient returned home within 12 months following stroke.

Helsinki Stroke Registry has been approved by institutional authorities. Ethical review for retrospective analysis of data collected prospectively as part of routine clinical care is not required at our institution.

Statistical analyses

Distributions of the continuous variables were studied and tested for normality (data not shown). Univariate analyses were performed with Mann-Whitney U test due to non-normality of the continuous variables. Dichotomous variables were compared with Fisher's exact test. For the very poor outcome at 3 months and 1-year mortality, we have constructed a model of backward conditional binary logistic regression adjusted for the following variables: age, gender, early ischemic signs in more than 1/3 of MCA region, intravenous thrombolysis (IVT) prior EVT, NIHSS prior EVT, TICI after EVT, sICH and CFS. CFS was tested in the regression model separately as (a) an ordinal and (b) a dichotomous parameter. Two-sided values of $P < 0.05$ were considered statistically significant. Continuous variables were reported as median (interquartile range [IQR]). Results from logistic regression analyses were reported as OR (95% CI). We used IBM SPSS Statistics for Windows, Version 25.0 (Armonk, NY: IBM Corp.) for the analyses.

Results

The study cohort consists of 159 consecutive patients, representing 20.4% of all 781 patients treated with EVT for ischemic stroke during the study period. The demographical and clinical data are presented in the Table 1.

Table 1. *Demographics and clinical data.*

	All *N* = 159	non-frail *N* = 125	frail *N* = 34
Age, years	83 (81-86)	83 (81-86)	86 (83-89) *
Gender, male	64 (40.3)	60 (48)	4 (11.8)*
Comorbidities			
hypertension	124 (78)	97 (77.6)	27 (79.4)
history of atrial fibrillation	72 (45.3)	50 (40.0)	22 (64.7) #
coronary heart disease	39 (24.5)	33 (26.4)	6 (17.6)
congestive heart failure	18 (11.3)	7 (5.6)	11 (32.4) *
diabetes mellitus	24 (15.1)	19 (15.2)	5 (14.7)
hyperlipidemia	72 (45.3)	57 (45.6)	15 (44.1)
previous ischemic stroke	23 (14.5)	18 (14.4)	5 (14.7)
previous TIA	8 (5.0)	7 (5.6)	1 (2.9)
previous ischemic stroke in imaging	40 (25.2)	30 (24.0)	10 (29.4)
Medications			
antiplatelet	37 (23.3)	31 (24.8)	6 (17.6)
anticoagulation	60 (37.7)	42 (33.6)	18 (52.9) #
antihypertensives	122 (76.7)	95 (76.0)	27 (79.4)
statins	75 (47.2)	58 (46.4)	17 (50.0)
In-hospital stroke	16 (10.1)	9 (7.2)	7 (20.6) #
NIHSS pre EVT	15 (10-19)	16 (9-19)	16 (12-20)
last known well to arrival, minutes	132 (72-273)	136 (72-291)	151 (76-288)
last known well to puncture, minutes	216 (142-325)	217 (143-328)	221 (150-327)
door-to-groin, minutes	60 (47-81)	59 (47-85)	63 (50-80)
IVT administered	63 (39.6)	52 (41.6)	11 (32.4)
NIHSS at 24 h	12 (6-19)	10 (5-18)	14 (4-22)

Data are given as numbers (%) or median (IQR). # = $p < 0.05$, * = $p < 0.01$. NIHSS: National Institute of Health stroke scale; EVT: endovascular thrombectomy; IVT: intravenous thrombolysis.

Comorbidities were frequent: hypertension in 124 (78%), history of atrial fibrillation in 72 (45.3%) and coronary heart disease in 39 (24.5%) patients. Previous ischemic stroke had been diagnosed in 23 (14.5%) patients, but admission imaging showed findings consistent with previous ischemic stroke in 40 (25.2%) patients. Antihypertensive medication was used by 122 (76.7%), anticoagulation by 60 (37.7%), and antiplatelet medication by 37 (23.3%) patients. Most used anticoagulation was warfarin, used by 34 (24.5%) patients, and most often used antiplatelet medication was acetylsalicylic acid, used by 26 (16.4%) patients. Frail patients were slightly older, were more often females and had more often a history of atrial fibrillation and congestive heart failure compared to non-frail patients, as well as an in-hospital stroke.

The onset of stroke symptoms was witnessed in 62%, unwitnessed in 28%, and 11% of all cases were classified a wake-up stroke. Median time from last-known-well-to-arrival was 132 minutes and median time from last-known-well-to-puncture was 216 minutes. IVT was administered to 63 (39.6%) patients. LVO was detected in 63.5% of cases, 23.3% had M2 occlusion and 13.2% did not have LVO or M2 occlusion (A1, P1). Recanalization was achieved in 110 (69.2%) subjects. The radiological and procedural EVT data are presented in Table 2. sICH was detected in 29 (18.2%) patients.

The etiology of ischemic stroke according to TOAST classification was large artery atherosclerosis in 31 (19.5%), cardioembolism in 107 (67.3%) and other defined (hematological or malignancy related) in 2 (1.3%) subjects. Three subjects had multiple possible causes (1.9%), the cause remained unknown despite full diagnostic work-up in 11 (6.9%) subjects and in five subjects (3.1%) the diagnostic work-up was insufficient.

Outcome

At three months the outcome was good in 35 (22.0%) patients and 51 (32.1%) patients had died. Of all patients 92 (57.9%) had very poor three-month outcome (mRS 4-6). Acceptable outcome (mRS 3) was found in 32 (20.1%). Fig. 1 outlines the three-month mRS outcome for all patients in addition to frail patients vs. non-frails. Table 3 shows the distribution of good three-month outcome according to pre-stroke CFS.

All patients lived at home prior to the index stroke. Of these, 68 (42.8%) lived alone, 83 (52.2%) with spouse and 8 (5%) with offspring. The post-stroke residential situation is presented in the Table 4. Altogether 74 (46.5%) subjects returned to live at home within one year after stroke. One-year survival was 59.1%.

At admission, pre-stroke mRS was evaluated as follows: mRS 0 in 118 (74.2%), mRS 1 in 21 (13.2%), mRS 2 in

Table 2. *Radiological and procedural EVT data.*

	All *N* = 159	non-frail *N* = 125	frail *N* = 34
Site of occlusion			
LVO (ICA, M1, tandem)	101 (63.5)	78 (62.4)	23 (67.6)
M2	37 (23.3)	30 (24.0)	7 (20.6)
no LVO or M2	21 (13.2)	17 (13.6)	4 (11.8)
at least one-third of MCA infarction	13 (8.2)	6 (4.8)	7 (20.6) *
perfusion imaging performed	88 (55.3)	66 (52.8)	22 (64.7)
CTP, core volume (ml)	11 (2-35)	11 (2-43)	9 (2-23)
CTP, flow volume (ml)	113 (63-167)	115 (63-171)	115 (95-165)
CTP, mismatch (ml)	89 (53-130)	82 (51-132)	102 (75-118)
recanalization TICI 0-2A	49 (30.8)	35 (28)	14 (41.2)
recanalization TICI 2B-3 + already recanalized before EVT	110 (69.2)	90 (72)	20 (58.8)
any ICH	62 (39)	49 (39.2)	13 (38.2)
sICH	29 (18.2)	21 (16.8)	8 (23.5)

Data are given as numbers (%) or median (IQR). * = $p < 0.01$. LVO: Large vessel occlusion; CTP: computed tomography perfusion; EVT: endovascular thrombectomy; sICH: symptomatic intracerebral hemorrhage.

12 (7.5%) and mRS 3 in 8 (5.0%) patients. Retrospectively assessed pre-stroke CFS is presented in Table 3. Median CFS was 3 (IQR 3-4), and 18 (11.3%) patients were classified as very fit or fit (CFS 1-2), 72 (45.3%) were managing well (CFS 3), 35 (22.0%) were classified as vulnerable (CFS 4) and 34 (21.4%) were classified as frail (CFS 5-9).

As expected, all subjects with pre-stroke assessment of mRS 3 were evaluated as being frail, however, 11% of patients with evaluated pre-stroke mRS 0 were classified as frail based on CFS. The percentages of frail patients were higher in patients with pre-stroke mRS 1 (33.3%) and mRS 2 (42.9%).

Frailty and outcome

LVO was found in 23 (67.6%) of frail and in 78 (62.4%) of non-frail patients. Recanalization rates did not differ statistically significantly in frail and non-frail subjects. The rates of any ICH were similar in frail and non-frail patients, as were also the rates of sICH (Table 2). The etiology of occlusion was cardioembolic in 26 (76.5%) in frail and 81 (64.8%) in non-frail patients. The three-month outcome was very poor (mRS 4-6) in 27 (79.4%) of frail patients and in 65 (52.4%) of non-frail patients ($p < 0.05$). The mortality rate at three months was 57.8% in frail and 27.4% in non-frail patients (19 and 32 patients, $p < 0.05$). Of frail patients, 8 (23.5%) returned home within one year. The respective number in non-frail patients was 66 (52.8%) ($p < 0.05$). One-year survival was 35.3% (12/34) in frail and 65.6% (82/125) in non-frail patients ($p < 0.05$).

In the multivariable analysis, factors associated with very poor three-month outcome were not performing thrombolysis (OR 2.66, 95% CI 1.23-5.75, $p < 0.01$), NIHSS before EVT (OR 1.10, 95% CI 1.04-1.17, $p < 0.01$), lack of recanalization (OR 4.30, 95% CI 1.79-10.33, $p < 0.01$) and frailty (OR 1.69, 95% CI 1.17-2.44 per each one-point

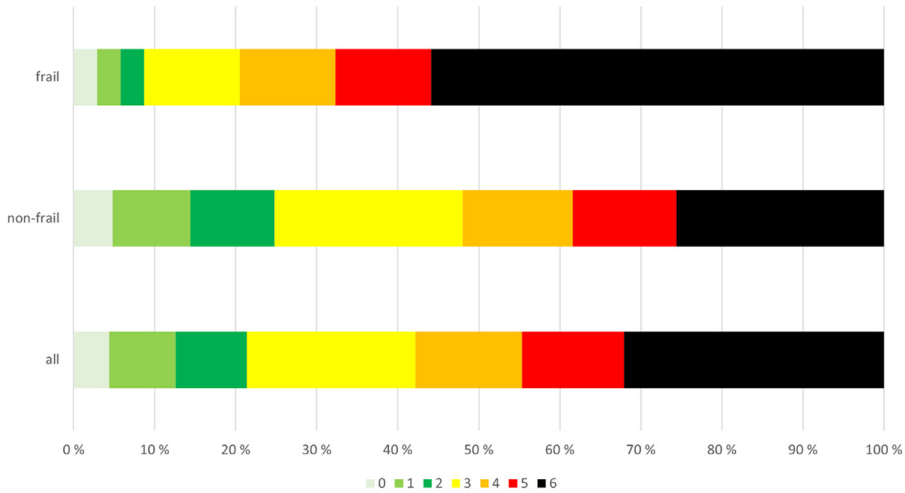

Fig. 1. *Three-month outcome by mRS.*

Table 3. *CFS and good 3-month outcome distribution among patients.*

CFS class	description	N (%)	three-month good outcome, N (%)
CFS 1	very fit	1 (0.6)	1 (100)
CFS 2	fit	17 (10.7)	6 (35.3)
CFS 3	managing well	72 (45.3)	17 (23.6)
CFS 4	vulnerable	35 (22)	7 (20)
CFS 5	mildly frail	24 (15.1)	4 (16.7)
CFS 6	moderately frail	8 (5)	0 (0)
CFS 7	severely frail	2 (1.3)	0 (0)
CFS 8	very severely frail	0	
CFS 9	terminally ill	0	

Data are given as numbers (%).

increase in CFS, $p < 0.01$). When frailty was entered as a dichotomous variable, the corresponding OR was 3.30 (95% CI 1.24-8.81, $p = 0.02$).

Factors predicting one-year mortality were male gender (OR 2.81, 95% CI 1.25-6.23, $p < 0.05$), not performing thrombolysis (OR 2.23, 95% CI 1.01-4.91, $p < 0.05$), sICH (OR 5.45, 95% CI 1.96-15.14, $p < 0.01$) and frailty (OR 1.71, 95% CI 1.19-2.45 per each one-point increase in CFS, $p < 0.01$). For frailty tested as a dichotomous variable, the OR was 3.86 (95% CI 1.48-10.05, $p < 0.01$).

Discussion

In our observational, retrospective study the outcomes of EVT-treated patients aged ≥ 80 years were modest. The rate of good outcome at three months was 22% and the rate of very poor outcome was 57%. Three-month mortality rate was 32% and one-year mortality reached 41%. Of frail patients, 79% had very poor three-month outcome and only 35% were alive at one year. We defined poor three-month outcome as mRS 4-6, because most patients in this age-group as well as professionals would probably consider mRS 3 outcome acceptable, although not necessarily good or desirable. Less than half of all patients returned to live at home after their stroke and in frail patients this number was 24%. Frailty was strongly independently associated with very poor three-month outcome and one-year mortality.

Our results are comparable to previously published real-life cohort studies. In previous reports of thrombectomy-treated patients aged ≥ 80 years good outcome defined as mRS 0-2 (functional independence) has been reached by 20−30%,[6,8,10,11,23] although one study defining good outcome as discharge to home or acute rehabilitation center reported good outcome only in 9% of patients.[9] In previous studies the mortality rate at three months has been 26-40%.[6,8−11,23] Consistently in previous studies the mortality rate has been higher than the rate of good outcome and our findings are also in line with this tendency.

To our knowledge this is the first study to assess the role of frailty in the outcome of EVT-treated ischemic stroke patients. Gensicke et al studied 489 IVT-treated patients with pre-existing disability (mRS 3-5) and found that 38.7% of studied patients had died within three months.[24] They did not assess frailty, but reduced ability to perform activities of daily living could be interpreted as a surrogate of frailty. Another retrospective thrombolysis study reported three-month mortality of 57% in patients aged ≥ 80 years with pre-stroke dependency (mRS ≥ 3),[25] equaling the three-month mortality rate of frail patients in the present study. In the meta-analysis of randomized controlled EVT studies including 198 patients aged ≥ 80 years, the rate of good three-month outcome (mRS 0-2) in this age group was 13.9% in control-arm patients, mortality was 45.2%, and very poor outcome (mRS 4-6) was observed in almost 80%.[5] The present study found almost similar rate for very poor outcome at three months in EVT-treated patients with frailty, but their mortality rate was even higher.

Surprisingly, the percentage of very fit and fit (CFS 1-2) patients in our cohort was only 11.3%. One explanation for this might be the high frequency of cardioembolic

Table 4. *Living arrangements after stroke. All patients lived at home pre-stroke.*

	All *N* = 159	non-frail *N* = 125	frail *N* = 34
at home	74 (46.8)	66 (52.8)	8 (23.5) *
sheltered home	5 (3.2)	4 (3.2)	1 (2.9)
institutional facility with 24/7 care	29 (18.4)	23 (18.4)	6 (17.6)
died in ward before 3 months	51 (32.3)	32 (25.6)	19 (55.9)

Data are given as numbers (%). * = $p < 0.05$

etiology of the stroke, mainly atrial fibrillation. It is likely that elderly subjects with atrial fibrillation have reduced tolerance for straining physical activities and thus are not fit. A substantial number of patients with atrial fibrillation did not use anticoagulation medication. Either atrial fibrillation had not been diagnosed or anticoagulation had been paused without bridging therapy. Considering the modest outcomes of thrombectomy after LVO in this age group, the use of bridging therapy should be emphasized when anticoagulation is paused for medical procedures.

Acute treatment of LVO is characterized by the urge to make rapid decisions. These decisions are often made with incomplete knowledge of the background factors and the treating physician needs to tolerate a certain amount of uncertainty. Our experience shows that the functional limitations and frailty of elderly acute LVO patients are frequently unrecognized during the very acute treatment phase, as a substantial number of frail patients were evaluated as functionally independent during the initial assessment. The elderly patient's ability to perform activities of daily living is often portrayed better than it is. Flaatten et al evaluated frailty in ICU patients and found that 42.9% of ICU-treated patients aged ≥ 80 were frail.[18] This proportion of frail patients seems surprisingly high considering that very old patients are not usually admitted to ICU without careful consideration. It would be helpful if medical records of elderly subjects would systematically include a description of functional measures or frailty.

Stroke neurologists are trained to evaluate functional performance by modified Rankin Scale. It is easier to use for evaluation of change from previous level, but it has limitations in evaluation of pre-stroke situation,[26] especially in elderly subjects with several limitations resulting from impaired vision and hearing, cardiac, musculoskeletal or balance problems and possibly impaired cognition. Clinical Frailty Scale could complement assessment in this population. We encourage integration of out-of-hospital and in-hospital processes if legally possible. Pre-notification of suspected acute stroke patient gives the stroke neurologist the possibility to study patient's medical records in advance or call the family members for information during patient transportation.

Extending the follow-up beyond three months should be considered when evaluating cost-utility of thrombectomy, as some elderly subjects may continue to recover from stroke after three months and on the other hand some may die rather soon after this time point.

There are several limitations to this study. The number of patients and especially the number of frail patients was relatively small. Not all treated patients had LVO as the treatment decision was based on occlusion in M2, P1 or A1 in one third. Also, we do not have the data on outcome of similar patients not treated with EVT. The strengths of the study are the four-year time-period with consecutive patients without missing data, one-year follow-up regarding mortality and return to live at home as well as inclusion of frailty.

Conclusions

The modest results of EVT in patients aged over 80 years should be acknowledged. More research is needed to identify those very old who will or will not benefit from thrombectomy, to optimize patient selection. Frailty significantly increases the likelihood of very poor outcome and death after EVT-treated stroke, and we suggest that assessment of frailty should be included in the clinical evaluation of very old subjects considered for thrombectomy.

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Declaration of Competing Interest

None.

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