Long-term mortality after endovascular thrombectomy for stroke

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Objectives: Endovascular thrombectomy (EVT) has become the standard treatment for large vessel occlusion (LVO) in acute ischemic stroke. Stroke trials typically report clinical outcome at the three-month time point but there is a lack of studies focusing on the long-term outcome after EVT.

The aim of this study is to assess the long-term mortality after EVT for stroke and to determine the factors that are associated with mortality. *Methods:* Retrospective single-center analysis of 323 patients who underwent EVT for stroke between the years 2015-2019 and survived at least 30 days. Patients were followed up until the end of the year 2020. Cox regression analysis was used to identify the factors associated with mortality. *Results:* A total of 53 (16.4%) of the 30-day survivors died during the follow-up. According to the Cox regression analysis, mortality was associated with functional dependence (modified Rankin Scale (mRS) >2, HR 2.7 (95% CI 1.2-5.9), p=0.013), comorbidity (Charlson Comorbidity Index (CCI) ≥3, HR 2.7 (95% CI 1.4-5.5), p=0.004), stroke severity at baseline (National Institutes of Health Stroke Scale (NIHSS) >8, HR 1.9 (95% CI 1.1-3.3), p=0.026), and medical complications (HR 2.4 (95% CI 1.2-4.8), p=0.011). Procedural variables did not have an impact on mortality. *Conclusions:* Functional dependence, stroke severity, comorbidity, and medical complications during the hospital stay were associated with the long-term mortality after EVT for stroke.

Introduction

Hyperacute treatments for acute ischemic stroke (AIS) have evolved in the recent years as endovascular thrombectomy (EVT) has become well established standard treatment in large vessel occlusion (LVO)[1−7] and the treatment of distal medium vessel occlusions with EVT is emerging.[8] Despite the advances in the acute stroke treatments, stroke is still the second leading cause of death globally.[9]

Life expectancy is increasing worldwide and the incidence of stroke is greatly influenced by age.[10] Hence, the total number of strokes is evidently expected to increase in coming years. The benefit of EVT is confirmed also in patients older than 80 years[11] thus it is not appropriate to exclude elderly patients from the intervention solely based on age. For cost-effective utilization of healthcare resources, the recognition of patients who will benefit from acute stroke interventions becomes essential. There is a need to identify factors which are associated with poor outcome and mortality after EVT to improve patient selection and to prevent futile treatment.

Outcomes after EVT are typically reported at standard 90-day time point. However, stroke patients often have comorbidities[12] and suffer from disability.[13] Patients undergoing EVT are also prone to medical complications which are strongly associated with comorbidity and

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mortality in short-term follow-up.[14] The data regarding long-term survival after EVT is limited, although a few studies suggest that the benefits on functional outcome are sustained and similar to 90-day outcome.[15−17] We aimed to investigate the long-term mortality after EVT for stroke and to determine the factors which are associated with mortality.

Material and methods

This retrospective study was conducted at Oulu University Hospital, Finland, the Comprehensive Stroke Center for the four Primary Stroke Centers in Northern Finland. The study protocol was approved by the hospital administration (reference number 268/2019) and due to the retrospective study design no statement from the local ethics committee was needed.

Patients and inclusion criteria

During the time period between January 2015 and December 2019, 380 consecutive patients received EVT for acute stroke at Oulu University Hospital. In our hospital patients are eligible for EVT when they present with acute ischemic stroke due to an occlusion in the intracranial internal carotid artery, the first or second segment of the middle cerebral artery or in the basilar artery established on computed tomographic angiography (CTA) and a score of 6 or higher on the National Institutes of Health Stroke Scale (NIHSS) and no large ischemic lesion on baseline non-contrast head computed tomography (CT). In extended time-window patient selection is based on perfusion imaging. These patients were retrospectively identified and screened from the Thrombectomy Registry of Oulu University Hospital. A total of 323 patients who survived at least 30 days after intervention were included into the present study.

We collected patients` baseline demographics and characteristics including age, sex, National Institutes of Health Stroke Scale (NIHSS) score on admission, pre-stroke modified Rankin scale (mRS) score, and Charlson Comorbidity Index (CCI). CCI is a method which categorizes patient`s comorbidities based on the diagnoses in medical records.[18] Procedural data included treatment with intravenous thrombolysis and the type of stroke onset. We used the determination of occlusion site as either anterior or posterior circulation. The grade of recanalization was defined as modified Thrombolysis in Cerebral Infarction Scale (mTICI).[19] Post-procedural variables included NIHSS score on the first post-procedural day, infarction size in 24 h control head computed tomography (CT), and medical complications during the hospital stay. Laboratory results during the first three days of the hospital stay were collected and the hospital LOS was determined. The data was collected on structured forms and digitalized.

Complications were classified as reported in our previous study which focused on medical complications in this patient group[14] including medical complications (pneumonia, acute myocardial infarction, acute kidney injury, cardiac insufficiency, pulmonary embolism, deep venous thrombosis, delirium, gastrointestinal bleeding and atrial fibrillation) and neurological complications (any hemorrhagic findings in control head CT and acute seizures).

Statistics Finland provided the data concerning the dates of death. Patients were followed until the end of the year 2020.

Statistical analysis

The data was analyzed using IBM SPSS Statistics for Windows (Version 27 IBM Corp). Categorical variables, presented as numbers and percentages, were compared using Pearson`s Chi square test. Continuous variables, presented as medians and 25th and 75th percentiles [25th−75th PCT], were analyzed using the non-parametric Mann-Whitney test. P-value less than 0.05 was considered statistically significant. Variables with univariate significance less than 0.1 were entered into a multivariate proportional hazards Cox model to assess hazard ratios (HR) and 95% confidence intervals (95% CI) for mortality. Variables with multivariate significance less than 0.05, and those with significant impact on the log likelihood function were kept in the model. According to the Cox regression model, Kaplan-Meier survival curves were drawn for the clinically most significant variables.

Results

During the study period 379 patients underwent EVT. One patient experienced two separate interventions due to a recurrent stroke during two hospital admissions. During the hospital stay 18 (4.8%) patients died. At 30 days, there were 323 (85.2%) patients alive. The median age of these 30-day survivors was 70 [60-79] years and 177 (54.8%) of them were male. (Table 1).

The median follow-up time was 2.9 [1.9-4.1] years and 53 (16.4%) of the 30-day survivors died during the follow-up. The mortality of the 30-day survivors was 3.1% at 90 days and 9.0% at one year. Patient baseline characteristics are shown in Table 1. The non-survivors were older (78 [69-84] vs 69 [58-77] years, $p<0.001$), had higher CCI-score (6 [4-7] vs 3 [2-5], $p<0.001$), lower pre-stroke functional status (1 [0-2] vs [0-1] mRS, $p<0.001$), and higher CRP (9 [0-20] vs 0 [0-7], $p<0.001$) compared with the survivors.

There were no differences in procedural variables between the non-survivors and the survivors. The rate of complete recanalization was comparable in both groups (54.3% vs 61.3%, p=0.376) as was also the rate of posterior circulation stroke (15.1% vs 18.7%). (Table 2).

The non-survivors had higher NIHSS-score (12 [4-16] vs 6 [4-13] p=0.009) on the first post-procedural day. They also had lower albumin levels (30 [26-33] vs 32 [29-34], p=0.008) and suffered more often medical complications

Table 1. *Baseline characteristics of 30-day survivors after endovascular thrombectomy for stroke.*

	Alive N=270	Deceased N=53	Missing	P-Value
Gender, male	154 (57.0)	23 (43.4)	0	0.068
Age, yr	69 [58-77]	78 [69-84]	0	<0.001
Weight, kg	80 [67-86]	75 [67-84]	32	0.220
Smoking	54(20.0)	3 (5.7)	0	0.012
CCI-score >3 †	129 (48.0)	41 (77.4)	1	<0.001
mRS baseline ‡	0 [0-1]	1 [0-2]	3	<0.001
NIHSS baseline §	13 [7-16]	15 [11-18]	0	0.008
Laboratory Results				
Hemoglobin g/L	136 [126-148]	130 [118-142]	4	0.019
Thrombocytes			2	0.514
E^9/L	216 [178-252]	225 [170-270]		
Creatinine			4	0.202
μmol/L	72 [59-85]	77 [59-90]		
CRP mg/L¶	0 [0-7]	9 [0-20]	0	<0.001

Categorical variables are presented as absolute numbers (N) and percentages (%). Continuous variables are presented as medians with 25th and 75th percentiles [25-75th PCT].

†Charlson Comorbidity Index

‡modified Rankin Scale of functional dependence ranges from 0 (no symptoms) to 6 (death)

§National Institutes of Health Stroke Scale range from 0 to 42, with higher scores indicating a greater clinical deficit

¶C-reactive protein

(77.4% vs 53.7%), p=0.001) compared with the survivors. Hemorrhagic transformation in control neuroimaging was more common among the non-survivors, but the difference was not statistically significant (26.4% vs 18.7%, p= 0.196). The size of the infarction was larger in the non-survivors (p=0.036) (Table 3). The rate of the symptomatic intracranial hemorrhage among the 30-day survivors was 5.4%.

According to the Cox regression analysis pre-stroke functional dependence (mRS >2, HR 2.7 (95% CI 1.2-5.9),

Table 2. *Procedural data of 30-day survivors after endovascular thrombectomy for stroke.*

	Alive N=270	Deceased N=53	Missing	P-value
Treatment with intravenous thrombolysis				
IVT †+EVT ‡	138 (51.5)	25 (47.2)	2	0.565
EVT alone ‡	130 (48.5)	28 (52.8)		
Type of stroke onset				
Witnessed	209 (78.6)	44 (83.0)	4	0.694
Unwitnessed	57 (21.4)	9 (17.0)		
Occlusion site				
Anterior circulation	217 (81.3)	45 (84.9)	3	0.531
Posterior circulation	50 (18.7)	8 (15.1)		
Recanalization result §				
TICI 3	149 (61.3)	25 (54.3)		
TICI 2B-2C	83 (34.2)	17 (36.9)	34	0.429
TICI 0-2A	11 (4.5)	4 (8.6)		
Process measures				
Median time from stroke onset to groin puncture (min)	309 [210-516]	314 [235-488]	0	0.556
Median time from hospital admission to groin puncture (min)	74 [44-114]	81 [55-128]	0	0.165
Median time from groin puncture to recanalization (min)	45 [29-70]	50 [28-84]	0	0.369
Contrast media amount (ml)	170 [140-205]	170 [135-200]	0	0.881

Categorical variables are presented as absolute numbers (N) and percentages (%). Continuous variables are presented as medians with 25th and 75th percentiles [25−75th PCT].

†Intravenous thrombolysis

‡Endovascular thrombectomy

§The modified Thrombolysis in Cerebral Infarction scale, ranges from 0 to 3, with a grade of 2b, 2c and 3 indicating successful reperfusion

Table 3. *Post-procedural outcome of 30-day survivors after endovascular thrombectomy for stroke.*

	Alive N=270	Deceased N=53	Missing	P-Value
Clinical				
Median NIHSS score on 1st post-procedural day[†]	6 [4-13]	12 [4-16]	0	0.009
Control Imaging				
Infarction size				
No infarction	35 (13.0)	11 (20.7)		
Small-medium infarction	142 (53.0)	18 (34.0)		
Large infarction	91 (34.0)	24 (45.3)	2	0.036
Hemorrhage				
No hemorrhage	218 (81.3)	39 (73.6)		
Any hemorrhage	50 (18.7)	14 (26.4)		0.196
Medical complications				
No	125 (46.3)	12 (22.6)		
Yes	145 (53.7)	41 (77.4)	0	0.001
Neurological complications				
No	224 (83.0)	39 (73.6)		
Yes	46 (17.0)	14 (26.4)	0	0.108
Laboratory results				
Creatinine μmol/L	65 [55-78]	72 [58-85]	47	0.059
Albumin g/L	32 [29-34]	30 [26-33]	113	0.008
Hosp LOS (d) [‡]	6 [4-8]	6 [4-8]	0	0.916

Categorical variables are presented as numbers (N) and percentages (%). Continuous variables are presented as medians with 25th and 75th percentiles [25−75th PCT].
[†]National Institutes of Health Stroke Scale range from 0 to 42, with higher scores indicating a greater clinical deficit
[‡]Hospital length of stay

p=0.013), medical complications (HR 2.4 (95% CI 1.2-4.8), p=0.011), stroke severity at baseline (NIHSS >8, HR 1.9 (95% CI 1.1-3.3), p=0.026), and comorbidity (CCI≥3, HR 2.7 (95% CI 1.4-5.5), p=0.004) were associated with death during the follow-up (Table 4).

The cumulative survival of the patients with medical complications compared with the patients with no medical complications is presented in Fig. 1. The cumulative survival in comparison between the patients with high and low comorbidity burden is presented in Fig. 2.

Table 4. *HR and 95% confidence intervals for death among 30-day survivors after endovascular thrombectomy for stroke.*

	HR (95% CI)	P-value
mRS >2 [†] At least moderate dependence	2.7 (1.2-5.9)	0.013
At least one medical complication	2.4 (1.2-4.8)	0.011
NIHSS baseline >8 [‡]	1.9 (1.1-3.3)	0.026
CCI ≥3 [§]	2.7 (1.4-5.5)	0.004

[†]modified Rankin Scale of functional dependence ranges from 0 (no symptoms) to 6 (death)
[‡]National Institutes of Health Stroke Scale range from 0 to 42, with higher scores indicating a greater clinical deficit
[§]Charlson Comorbidity Index

Discussion

Our study shows that after surviving the acute phase, a total of 16% of patients who underwent EVT for stroke died during the long-term follow-up. Pre-stroke functional dependence, comorbidity, stroke severity, and medical complications during the hospital stay were independently associated with mortality. There was no difference in recanalization result, hemorrhagic transformation, or posterior circulation stroke between the survivors and the non-survivors.

In the present study, the mortality among 30-day survivors was lower compared with previous anterior circulation EVT studies; REVASCAT and MR CLEAN reported 23% mortality at one year and 26.0% cumulative mortality in two-year follow-up, respectively.[16,17] Accordingly, Chinese study reported a mortality rate of 28% in a median follow-up period of 20 months.[20] Comparably Wu et al reported a rate of 38% for one-year mortality in basilar artery occlusion patients treated with EVT.[21] Our study population represents real-world clinical environment since we are the only operating Comprehensive Stroke Center in Northern Finland. We included all consecutive EVT-patients in this study and our study population contains both anterior and posterior circulation occlusions. Interestingly, our data suggests that posterior circulation occlusion does not have an impact on long-term mortality,

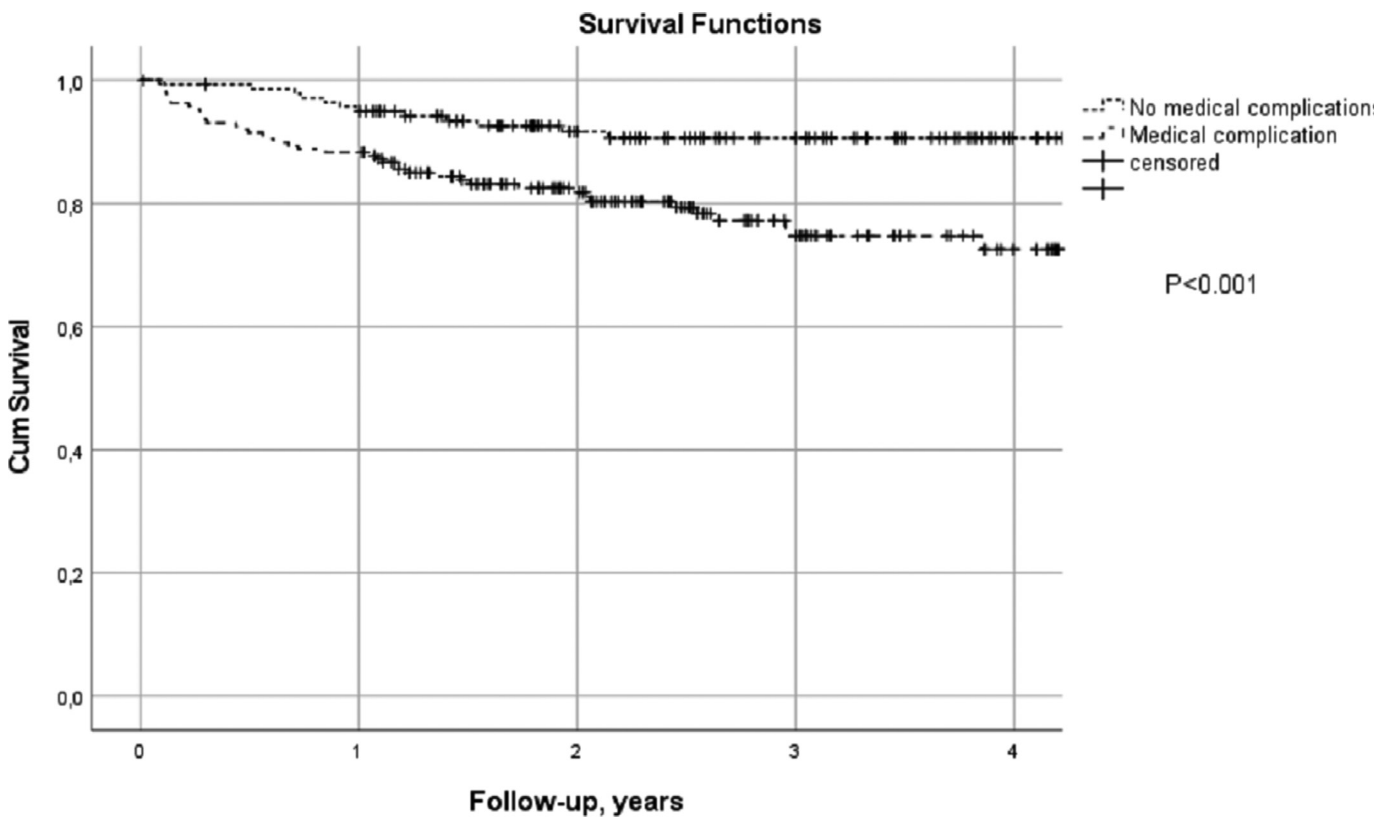

Fig. 1. *Kaplan-Meier curve for long-term cumulative survival in the 30-day survivors with and without medical complications in 3-year follow-up.*

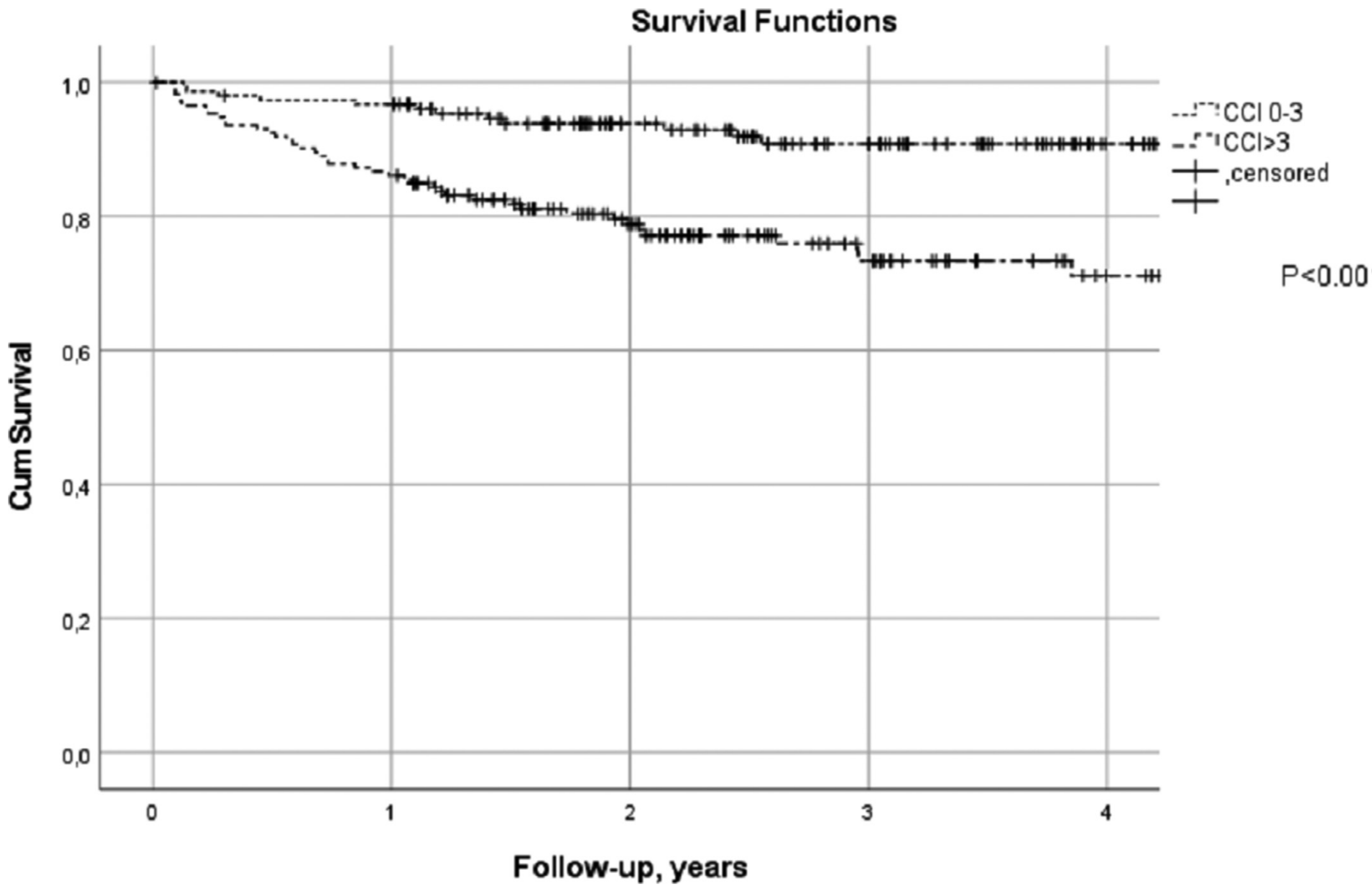

Fig. 2. *Kaplan-Meier curve for long-term cumulative survival in the 30-day survivors with either high or low comorbidity burden in 3-year follow-up.*

even though short-term mortality in posterior circulation stroke is rather high.[22]

Although data regarding prognostic factors for long-term survival after EVT are limited, other studies have previously identified that stroke severity,[20,23–25] comorbidity,[26] and pre-stroke functional dependence[27,28] are associated with poor outcome. Our study presents a novel finding of these variables being independently associated with the long-term mortality in EVT-patients. According to the present results, after the primary survival from the stroke, the patient-related factors instead of the stroke-related factors play a major role in the survival. According to our knowledge, medical complications have not previously been reported to be related to the long-term mortality in this patient group. We have recently shown that the medical complications are common after EVT and have a negative impact on the short-term functional outcome.[14] Patients with comorbidities are prone to medical complications.[29] According to these findings, medical complications are not directly related to unfavorable outcomes; they are rather a surrogate of poor health leading to death during the recovery phase of acute disease. Among surgical patients, postoperative complications which occurred during the first 30 postoperative days are more significantly related to survival than operative risk or perioperative risk factors.[30] Our finding that medical complications are associated with long-term mortality suggests the same and indicates that medical complications have a sustained negative impact on the survival after invasive treatments.

Functionally dependent patients have been excluded from randomized trials of acute stroke treatments[1–5] and there is uncertainty if they could benefit from the intervention. Despite conflicting results concerning possible benefits of acute treatments in this patient group,[31,32] our study shows that pre-stroke dependency has an independent association with mortality. Similarly, Swedish group reported a clear association between pre-stroke functional dependency and high mortality rate in a long-term follow-up after acute ischemic stroke.[33] The current knowledge suggests withholding EVT or at least making treatment decisions upon individual basis in this patient group. However, in the every-day clinical practice time-sensitive assessments of patient's functional capacity may be complex and not always precise.

According to previous studies, successful recanalization has been associated with favorable outcome[28,34] and decreased likelihood of death.[34,35] In contrast to previous results, we did not find an association between recanalization result and mortality. This difference may be explained by the fact that previous studies have focused on the short-term outcome and survival. It may be hypothesized that there are different factors impacting the short- and long-term mortalities. Moreover, we serve as Comprehensive Stroke Center and approximately 40% of our patients are transferred from other hospitals. Transfer delay contributes to expansion of neuronal injury and reduces the impact of successful recanalization.

Clinical significance

The benefits of EVT are confirmed in wide range of patients[11] and in extended time-window.[6,7] Increasing amount of acute stroke patients are being evaluated to meet eligibility for acute stroke treatments, including thrombectomy. Despite promising results there are still patients who remain severely disabled or die after acute interventions.[36,37] Appropriate patient selection is essential for optimal and cost-effective utilization of limited health care resources. Identifying factors which are associated with mortality provide tools for stroke clinicians for the every-day decision making.

Comorbidity and functional dependence have a close relationship.[38] According to our results, these factors should be assessed when acute stroke patients are being evaluated to meet eligibility for EVT to prevent futile recanalization. Furthermore, every attempt should be made to prevent medical complications in this patient group.

We defined stroke severity as high baseline NIHSS similarly to many previous studies.[20,21,35,37] Although we found baseline NIHSS to have an independent association with long-term mortality, it alone possesses an incomplete ability to predict outcome. Beyond admission, there are several additive factors having an impact on outcome. Baseline NIHSS is a good clinical tool but should not be used alone in the decision making when selecting patients for the intervention.

Limitations

The present study has some limitations. First, low number of patients can be considered as a limitation but increasing the number of patients would have expanded the time period remarkably. On the other hand, we are the only operating Comprehensive Stroke Center in Northern Finland and therefore this is a population-based study. Although we used CCI to measure comorbidities precisely, we did not estimate the prognostic effects of individual comorbid conditions. Different comorbid conditions have unequal effects on mortality and survival, which should be kept in mind when making treatment decisions on the basis of comorbidity. Additionally, we were not able to provide ASPECTS on imaging at baseline because it is not commonly used score in our hospital. Furthermore, we did not explore the causes of death and are not able to determine if there were preventable or avoidable factors affecting mortality. The retrospective study setting is also a limitation since there might be factors which cannot have been observed and reported and might still have an impact on the survival. However, due to retrospective design the study protocol itself has not interfered in the treatment decisions or evaluation of treatment results. Thus, the study depicts reliably the real-life course of EVT for acute ischemic stroke.

Conclusion

According to the present results, the 30-day survivors of acute ischemic stroke treated with EVT have relatively good prognosis in the long-term follow-up. Comorbidity, functional dependency, stroke severity, and medical complications during the hospital stay were independently associated with the long-term mortality after EVT for stroke. These factors should be considered when evaluating stroke patients to meet eligibility for acute stroke interventions.

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