Stroke: Vascular and Interventional Neurology

ORIGINAL RESEARCH

Long-Term Outcome and Quality of Life in Patients With Stroke Presenting With Extensive Early Infarction

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BACKGROUND: The benefit of mechanical thrombectomy in patients with low Alberta Stroke Program Early Computed Tomography Score (ASPECTS) for short-term outcomes is debatable and long-term outcomes remain unknown. This retrospective, monocentric cohort study aimed to assess the association between reperfusion grade and the long-term functional outcome measured with modified Rankin scale as well as the long-term health-related quality of life recorded at the last follow-up in patients according to baseline ASPECTS (0–5 versus 6–10).

METHODS: Deceased patients were identified from the Swiss population register and follow-up telephone interviews were conducted with all surviving patients with stroke treated with mechanical thrombectomy between January 1, 2010, and December 31, 2018. Favorable outcome was defined as modified Rankin scale 0 to 3; health-related quality of life was assessed using the 3-level version of the EuroQol 5-dimensional questionnaire. The EuroQol 5-dimension utility index was calculated for statistical analyses. The reperfusion grade was core laboratory adjudicated using the expanded treatment in cerebral ischemia score. Adjusted odds ratios for the association between the reperfusion grade assessed by expanded treatment in cerebral ischemia and outcomes were calculated from multivariable logistic regression.

RESULTS: Of the 1114 patients with available long-term follow-up records (median follow-up, 3.67 years), 997 were included in the final analysis. Respectively, patients with low ASPECTS more often had complaints regarding mobility (67.1% versus 42.1%, $P<0.001$), self-care (53.4% versus 31.2%, $P<0.001$), and usual activities (65.8% versus 41.4%, $P<0.001$) than patients with high ASPECTS, whereas reported pain/discomfort (65.7% versus 69.9%, $P=0.49$) and anxiety/depression (71.2% versus 78.9%, $P=0.17$) did not differ. In patients with low ASPECTS, increasing reperfusion grade was associated with a higher likelihood of long-term favorable functional outcome (adjusted odds ratio, 1.43; 95% CI, 1.09–1.88 [$P=0.01$]) and health-related quality of life (adjusted linear correlation coefficient, 0.05; 95% CI, 0.02–0.08) despite early extensive infarction.

CONCLUSION: Despite low baseline ASPECTS, a higher reperfusion grade results in better functional outcomes and may improve health-related quality of life in the long term.

Key Words: ischemic stroke ■ long-term outcome ■ low ASPECTS ■ mechanical thrombectomy ■ modified Rankin scale ■ quality of life

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Patients with low Alberta Stroke Program Early Computed Tomography Score (ASPECTS) treated with mechanical thrombectomy (MT) tend to have less salvageable tissue[1] and a higher rate of symptomatic intracerebral hemorrhage[2,3] than patients with smaller infarcts. Both phenomena may explain the lower rate of functional independence in this patient cohort at 90 days after MT.[1,4] According to current American Stroke Association/American Heart Association guidelines, MT in patients with ASPECTS <6 is not recommended but may be considered on a case-by-case basis.[5] Some retrospective studies have demonstrated a benefit of endovascular therapy compared with standard of care regarding the functional outcome in patients with low ASPECTS, when assessed by the modified Rankin scale (mRS) and mortality at 90 days.[6–9] This benefit was most notable in successfully recanalized patients.[10,11] A recent study, based on computed tomography selection, showed a higher mortality rate at 90 days and increased symptomatic intracerebral hemorrhage in patients with low ASPECTS treated with MT compared with best medical treatment.[12] The authors found a trend toward better functional outcomes only in patients with completed reperfusion and in whom <2 MT attempts were made.

Recently, a real-life prospective observational study demonstrated that a better health-related quality of life (HRQOL), 90 days after MT, was associated with higher ASPECTS at baseline.[13] HRQOL is generally assessed with the EuroQoL 5-dimension (EQ-5D) tool, which has been validated in several stroke studies.[14,15]

This study aimed to investigate the long-term functional outcome and HRQOL in patients with low as compared with high ASPECTS undergoing MT and to estimate the effect of reperfusion on the long-term functional outcome in both patient groups.

Nonstandard Abbreviations and Acronyms

ASPECTS	Alberta Stroke Program Early Computed Tomography Score
BEYOND-SWIFT	Bernese-European Registry for Ischemic Stroke Patients Treated Outside Current Guidelines With Neurothrombectomy Devices Using the SOLITAIRE FR With the Intention for Thrombectomy
DWI	diffusion-weighted magnetic resonance imaging
eTICI	expanded treatment in cerebral ischemia
EQ-5D	EuroQol 5-dimension
EQ-5D-3L	3-level version of the EQ-5D
HERMES	Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke
MT	mechanical thrombectomy
MR CLEAN	Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands
mRS	modified Rankin scale
NIHSS	National Institutes of Health Stroke Scale
RESCUE-Japan Registry 2	Recovery by Endovascular Salvage for Cerebral Ultra-Acute Embolism Japan Registry 2

METHODS

Study Cohort

This retrospective observational study from a single-center prospective stroke registry evaluated all consecutive patients with stroke treated with MT between January 1, 2010, and December 31, 2018, at a comprehensive stroke center for eligibility. The local ethics committee approved the study in accordance with Swiss law (reference ID: 2019-00547, Kantonale Ethikkomission Bern). The present study was reported according to the current STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist for cohort studies. Study data are available from the corresponding author on reasonable request and after clearance by the local ethics committee.

End Points

The primary end point of this study was to assess the association of reperfusion grade with the long-term favorable functional outcome (defined as mRS 0–3) recorded at the last follow-up (study specific) in patients presenting with either low or high ASPECTS (0–5 versus 6–10, respectively). Secondary end points included the evaluation of the long-term good functional outcome (defined as mRS 0–2), long-term HRQOL, and its association with the final reperfusion grade in patients with low and high ASPECTS.

Data Collection

Baseline and 90-day follow-up data from all consecutive patients treated with MT between January

CLINICAL PERSPECTIVE

What Is New?

- We studied the long-term outcomes of patients with low Alberta Stroke Program Early Computed Tomography Score (ASPECTS) (0–5) treated with mechanical thrombectomy. The database used in our study is unique because of the long-term follow-up (1.2–9.5 years) available for 997 patients, of which 200 had low ASPECTS at baseline. We identified higher reperfusion grade after mechanical thrombectomy as a predictor of favorable long-term functional outcomes (modified Rankin scale $\leq$3) and better long-term quality of life in patients with low ASPECTS.

What Are the Clinical Implications?

- These study results suggest long-term benefits for patients with successful reperfusion despite extensive early infarct signs. In the low ASPECTS group, we found a favorable long-term functional outcome in 32.9% of the patients who had undergone successful reperfusion. Furthermore, a gradual increase of favorable long-term outcomes was noted with improved reperfusion grades using the expanded treatment in cerebral ischemia score. These findings should encourage physicians performing mechanical thrombectomy to use rescue or alternative treatments to achieve the best reperfusion possible in patients with low ASPECTS.

2010 and December 2018 were extracted from the local stroke registry according to the ethical approval from the BEYOND-SWIFT (Bernese-European Registry for Ischemic Stroke Patients Treated Outside Current Guidelines With Neurothrombectomy Devices Using the SOLITAIRE FR With the Intention for Thrombectomy) protocol (ClinicalTrials.gov Identifier: NCT03496064). Their vital status at the time of follow-up was obtained from the Swiss population register between September 2019 and May 2020. An information letter was sent before the telephone interview to surviving patients and written consent was returned before final inclusion in the study. Patients who were lost to follow-up or refused to participate were excluded. Patients who were deceased at the time of follow-up were assigned an mRS score of 6 and were included following the ethics committee's decision.

Two neurologists (M.B. and L.W.) conducted a standardized telephone interview with the surviving patients between September 2019 and June 2020. The long-term mRS and responses to the 3-level version of the EQ-5D (EQ-5D-3L) for surviving patients were obtained during the standardized telephone interview from the patients themselves, their next of kin, or health care providers. Both investigators received the list of eligible patients. After extracting the patients' contacts from the local clinical information system, they interviewed the patients or their caretakers. The investigators were blinded to the clinical presentation at admission and discharge, outcome at 90 days, and results of MT. The follow-up time was defined as the interval between the index stroke and the date of extraction of the vital status from the Swiss population register for deceased patients, and the date of the telephone interview for surviving patients. ASPECTS before MT was based on computer tomography (CT-ASPECTS) or diffusion-weighted magnetic resonance imaging (DWI-ASPECTS) assessed by neuroradiologists with 5 years of experience. Patients with posterior circulation stroke missing admission ASPECTS were also excluded. Reperfusion grade was core-lab adjudicated by 3 neuroradiologists (J.K., C.K., and E.P.) using the expanded treatment in cerebral ischemia (eTICI) score proposed by Liebeskind et al.[16] The core-lab interrater reliability was validated using a random sample of 142 patients (Krippendorf α, 0.87; 95% CI, 0.83–0.91). Patients with missing eTICI score were excluded from specific reperfusion analysis.

Assessment of HRQOL

The EQ-5D and EQ-5D-3L are well-established scores for assessing quality of life independently of the underlying disease.[17] The EQ-5D-3L comprises the following dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. One of 3 levels can be chosen for each dimension: no problem, some problems, or extreme problems. A score of 1 (no problem) to 3 (extreme problems) is assigned for each dimension. To evaluate the individual HRQOL, the EQ-5D utility index is usually derived from a country- or region-specific time tradeoff value set.[18]

In the absence of a Switzerland-specific value set, the index values from Sweden were used since the 2 countries report a similar quality of life.[19] Patients who had died before the long-term follow-up were assigned a utility index value of 0 according to the instrument validation.[13] A utility index of 1 represents the best health status possible. Using the EQ-5D-3L, negative values indicate a condition subjectively perceived by the patient as being worse than death.[13]

Statistical Analysis

Baseline differences between patients who were included and those who were excluded were assessed, as well as between patients with low ASPECTS (0–5) and high ASPECTS (6–10). Descriptive statistics using Fisher exact and Wilcoxon rank sum tests were reported as number and percentage for categorical variables, and median and interquartile range (IQR) for continuous variables. Kaplan–Meier estimates with log-rank test were used to define difference in mortality rate in the long-term follow-up. To limit the heterogeneity in the long-term follow-up attributable to the cross-sectional design of the study, subgroups with different follow-up times and equal numbers of patients were identified. All statistical analyses were performed using mixed-effects models with defined follow-up time used as random effect.

Adjusted odds ratios (aORs) for the association between the reperfusion grade assessed by eTICI and long-term functional outcomes were calculated from multivariable logistic regression with adjustments for the following confounders: age on admission, sex, and National Institutes of Health Stroke Scale (NIHSS), imaging modality, independence before stroke (defined as mRS 0–2), intravenous thrombolysis, time from onset of stroke to groin puncture, and ASPECTS on admission. eTICI was implemented as an ordinal variable with the aOR showing an increase of one grade on the eTICI score (eg, from eTICI 2a to eTICI 2b50). To evaluate the influence of ASPECTS group on the association between reperfusion grade and favorable outcomes, interaction terms were used (ie, ASPECTS groups∗eTICI grade improvement with favorable outcome defined as dependent variable). The association between the EQ-5D utility index and reperfusion grade was assessed by multivariable linear regression adjusted for the above-mentioned confounders. Interaction terms were built according to the logistic regression models above. No imputation method was used to compensate for missing data. All statistical analyses were performed with Stata 16 (StataCorp LLC) and R (version 3.6.0, R Core Team).

RESULTS

Study Population

In total, 1313 consecutive patients treated with MT between January 2010 and December 2018 were evaluated. Twenty-eight patients were not found in the Swiss population register, 10 had an unknown date of death, and 161 patients or their next of kin refused to participate in the study (eFigure I—Study flowchart). Because of the heterogeneous follow-up times, the following subgroups were defined: 1.2 to 2 years (n=208), 2 to 3 years (n=248), 3 to 4 years (n=281), 4 to 6 years (n=251), and 6 to 9.5 years (n=287). Follow-up time and follow-up groups are depicted in Figure 1. Of the 1114 patients with long-term follow-up records, 79 had a posterior circulation stroke and 38 had missing admission ASPECTS. In total, 997 patients were included in the final analysis. Of the patients included, 481 (41.2%) had died (mRS 6) and 478 (47.9%) had a favorable outcome (mRS 0 to 3) at the long-term follow-up. The investigators conducted the telephone interview directly with 88% of surviving patients (n=454) and with their caretakers in the remaining 12% of patients (n=67). Median follow-up was 3.67 years (IQR, 2.58–5.80). Seven patients with missing eTICI after final reperfusion were excluded from specific reperfusion analysis.

Baseline Characteristics

Significant differences were found between included and excluded patients (online supplemental eTable 1). Excluded patients were younger, more dependent before index stroke (mRS >2), had longer follow-up, smoked more often, and were more likely to undergo a computed tomography scan than magnetic resonance imaging on admission. There was no difference in ASPECTS on admission (8 versus 8, P=0.14) or in the final reperfusion grade (P=0.91). Overall, 200 patients with baseline ASPECTS 0 to 5 and 790 with ASPECTS 6 to 10 were available for final analysis. Their baseline characteristics are depicted in Table 1 and their long-term outcomes in Table 2. Patients with low ASPECTS were younger (median, 72.9 years [IQR, 59–81.1 years] versus 75.7 years [IQR, 63.3–83.7 years], P=0.014), had higher NIHSS on admission (median, 19 [IQR, 15–22] versus 14 [IQR 8–19], P<0.001), and had more proximal vessel occlusion (internal carotid artery, 40.5% versus 24.2%; first segment of the middle cerebral artery, 51.5% versus 54.3%; second segment of the middle cerebral artery, 8.0% versus 19.9% [P<0.001]). Successful reperfusion (eTICI 2b50–eTICI 3) was achieved in 82.1% of the patients with low ASPECTS (n=161 of 196) and in 86.9% of those with high ASPECTS (n=690 of 794, P=0.11). ASPECTS before MT was available as DWI-ASPECTS for 49.6% (n=493) of the patients and as CT-ASPECTS for the remaining 50.4% (n=501) (P=0.08).

Association Between ASPECTS and Long-Term Functional Outcome

Patients with low ASPECTS had longer follow-up (median 1503 days [IQR, 1028–2668 days], versus 1301 days [IQR, 929–1985 days) and higher mortality rate at 2 years (53.1% versus 35.4%, log-rank test P<0.001) and at 5 years (61.1% versus 46.4%,

Table 1. Comparison of Baseline Characteristics Between Patients With Low ASPECTS (0–5) and High ASPECTS (6–10)

	All (N=997)	ASPECTS 0–5 (n=200)	ASPECTS 6–10 (n=797)	*P* value
Baseline				
Age at admission, median (IQR)	75 (62.4–82.9)	72.9 (59.0–81.1)	75.7 (63.3–83.7)	0.014
Women, No./total No. (%)	501/997 (50.2)	96/200 (48.0)	405/797 (50.8)	0.48
Independence before stroke, No./total No. (%)	870/991 (87.8)	176/199 (88.4)	694/792 (87.6)	0.81
Risk factors, No./total No. (%)				
Diabetes	173/994 (17.4)	38/200 (19.0)	135/794 (17.0)	0.53
Hypertension	699/995 (70.2)	136/200 (68.0)	563/795 (70.8)	0.44
Dyslipidemia	550/991 (55.5)	110/197 (55.8)	440/794 (55.4)	0.94
Smoking	226/989 (22.8)	41/199 (20.6)	185/790 (23.4)	0.45
Previous stroke	129/996 (12.9)	30/200 (15.0)	99/796 (12.4)	0.35
CAD	194/990 (19.6)	43/197 (21.8)	151/793 (19.0)	0.37
Stroke characteristics				
Time from last known well to admission,median (IQR), min	151 (80–275)	136 (77–254)	175 (77–277)	0.23
Transfer, No./total No. (%)	326/996 (32.7)	76/199 (38.2)	250/797 (31.4)	0.076
NIHSS on admission,median (IQR)	15 (9–20)	19 (15–22)	14 (8–19)	<0.001
Admission MRI-/DWI-ASPECTS, No./total No. (%)	493/994 (49.6)	88/200 (44.0)	405/794 (51.0)	0.082
Time from last known well to groin puncture, median (IQR), min	233 (169–355)	240 (179–370)	230 (165–349.5)	0.11
Site of occlusion, No./total No. (%)				
ICA	274/997 (27.5)	81/200 (40.5)	193/797 (24.2)	<0.001
M1	536/997 (53.8)	103/200 (51.5)	433/797 (54.3)	
M2	175/997 (17.5)	16/200 (8.0)	159/797 (19.9)	
Other occlusion	12/997 (1.2)	0/200 (0.0)	12/797 (1.5)	
TOAST classification				
Large-artery atherosclerosis, No./total No. (%)	108/995 (10.8)	25/199 (12.6)	83/796 (10.4)	0.058
Cardioembolism, No./total No. (%)	428/995 (43)	69/199 (34.7)	359/796 (45.1)	
Stroke of other determined cause, No./total No. (%)	71/995 (7.1)	15/199 (7.5)	56/796 (7.0)	
Stroke of undetermined cause, No./total No. (%)	388/995 (39)	90/199 (45.2)	298/796 (37.4)	
NIHSS at 24 h, median (IQR)	8 (3–16)	16 (10–23)	6 (2–13)	<0.001
mRS at 3 mo, median (IQR)	3 (1–6)	5 (3–6)	3 (1–6)	<0.001
Stroke treatment				
IVT-bridging, No./total No. (%)	392/997 (39.3)	76/200 (38.0)	316/797 (39.6)	0.69
No. of maneuvers, median (IQR)	1 (1–2)	2 (1–3)	1 (1–2)	0.006
Successful eTICI, No./total No. (%)	851/990 (86)	161/196 (82.1)	690/794 (86.9)	0.11
eTICI categories, No./total No. (%)				
eTICI 0	46/990 (4.6)	11/196 (5.6)	35/794 (4.4)	0.18
eTICI 1	17/990 (1.7)	4/196 (2.0)	13/794 (1.6)	
eTICI 2a	76/990 (7.7)	20/196 (10.2)	56/794 (7.1)	
eTICI 2b50	114/990 (11.5)	30/196 (15.3)	84/794 (10.6)	
eTICI 2b67	263/990 (26.6)	45/196 (23.0)	218/794 (27.5)	
eTICI 2c	237/990 (23.9)	47/196 (24.0)	190/794 (23.9)	
eTICI 3	237/990 (23.9)	39/196 (19.9)	198/794 (24.9)	

ASPECTS indicates Alberta Stroke Program Early Computed Tomography Score; CAD, coronary artery disease; DWI, diffusion-weighted magnetic resonance imaging; eTICI, expanded treatment in cerebral infarction; ICA, internal carotid artery; IQR, interquartile range; IVT, intravenous thrombolysis; MRI, magnetic resonance imaging; mRS, modified Rankin Scale ; M1, first segment of the middle cerebral artery; M2, second segment of the middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; and TOAST, Trial of Org 10172 in Acute Stroke Treatment.

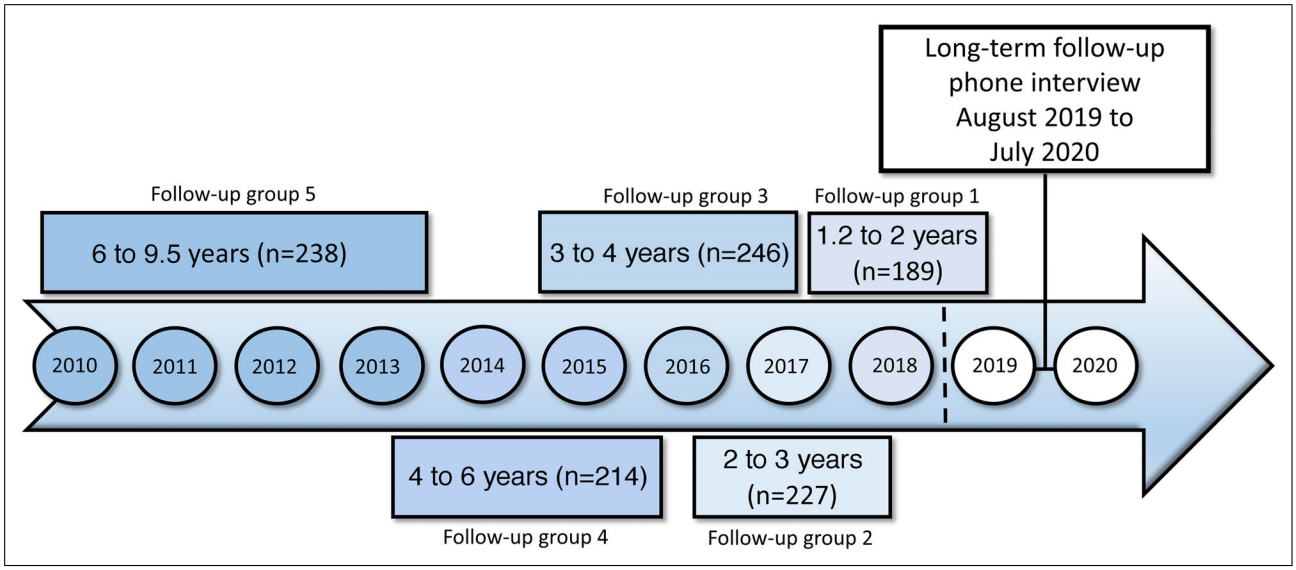

Figure 1. Follow-up time and establishment of follow-up groups.
Patients treated with mechanical thrombectomy between January 2010 and December 2018 were considered for inclusion. The patients who were included were contacted for long-term follow-up by telephone interview between August 2019 and July 2020. Because of the heterogeneous follow-up times, 5 follow-up groups were established (1.2–2 years, 2–3 years, 3–4 years, 4–6 years, and 6–9.5 years) of approximately equal size to guarantee statistical power.

Table 2. Comparison of Long-Term Outcomes Between Patients With Low ASPECTS (0–5) and High ASPECTS (6–10)

	All (N=997)	ASPECTS 0–5 (n=200)	ASPECTS 6–10 (n=797)	*P* value
Long-term follow-up				
Follow-up time in days, median (IQR)	1325 (937–2119)	1503 (1028–2668)	1301 (929–1985)	<0.001
Deaths, No./total No. (%)	481/997 (48.2)	127/200 (63.5)	354/797 (44.4)	<0.001
Long-term mRS, median (IQR)	5 (1–6)	6 (3–6)	3 (1–6)	<0.001
Favorable functional outcome (mRS 0–3), No./total No. (%)	478/997 (47.9)	61/200 (30.5)	417/797 (52.3)	<0.001
Good functional outcome (mRS 0–2), No./total, No. (%)	366/997 (36.7)	39/200 (19.5)	327/797 (41.0)	<0.001
EQ-5D-3L, median (IQR)				
Total	6 (5–9)	8 (6–11)	6 (5–9)	<0.001
Mobility	1 (1–2)	2 (1–3)	1 (1–2)	<0.001
Self-care	1 (1–2)	2 (1–3)	1 (1–2)	<0.001
Usual activities	1 (1–2)	2 (1–3)	1 (1–2)	<0.001
Pain/discomfort	1 (1–2)	1 (1–2)	1 (1–2)	0.43
Anxiety/depression	1 (1–1)	1 (1–2)	1 (1–1)	0.18
EQ-5D utility index, median (IQR)	0.49 (0–0.88)	0 (0–0.65)	0.60 (0–0.91)	<0.001

ASPECTS indicates Alberta Stroke Program Early Computed Tomography Score; EQ-5D, EuroQol 5-Dimension; EQ-5D-3L, 3-level EQ-5D; IQR, interquartile range; and mRS, modified Rankin Scale.

log-rank test $P<0.001$). Kaplan–Meier survival curves are depicted in eFigure II. They also had a lower rate of favorable functional outcome (30.5% versus 52.3%, $P<0.001$) and lower rate of good functional outcome (19.5% versus 41.0%, $P<0.001$) at the time of long-term follow-up (Table 2). In patients with low ASPECT, favorable outcomes decreased from 33.7% (63 of 198) at 90 days to 30.5% (61 of 200) at long-term follow-up. Outcome improvement (from mRS 4–5 to mRS 0–3) between the 90 days and long-term follow-up was present in 7.5% of patients with low ASPECT (n=14 of 187). A deterioration (from mRS 0– 3 to mRS 4–6) was found in 10.2% of patients with low ASPECT (n=19 of 187). The distribution of long-term mRS in all ASPECTS groups and its comparison with the 90-day mRS is depicted in Figure 2.

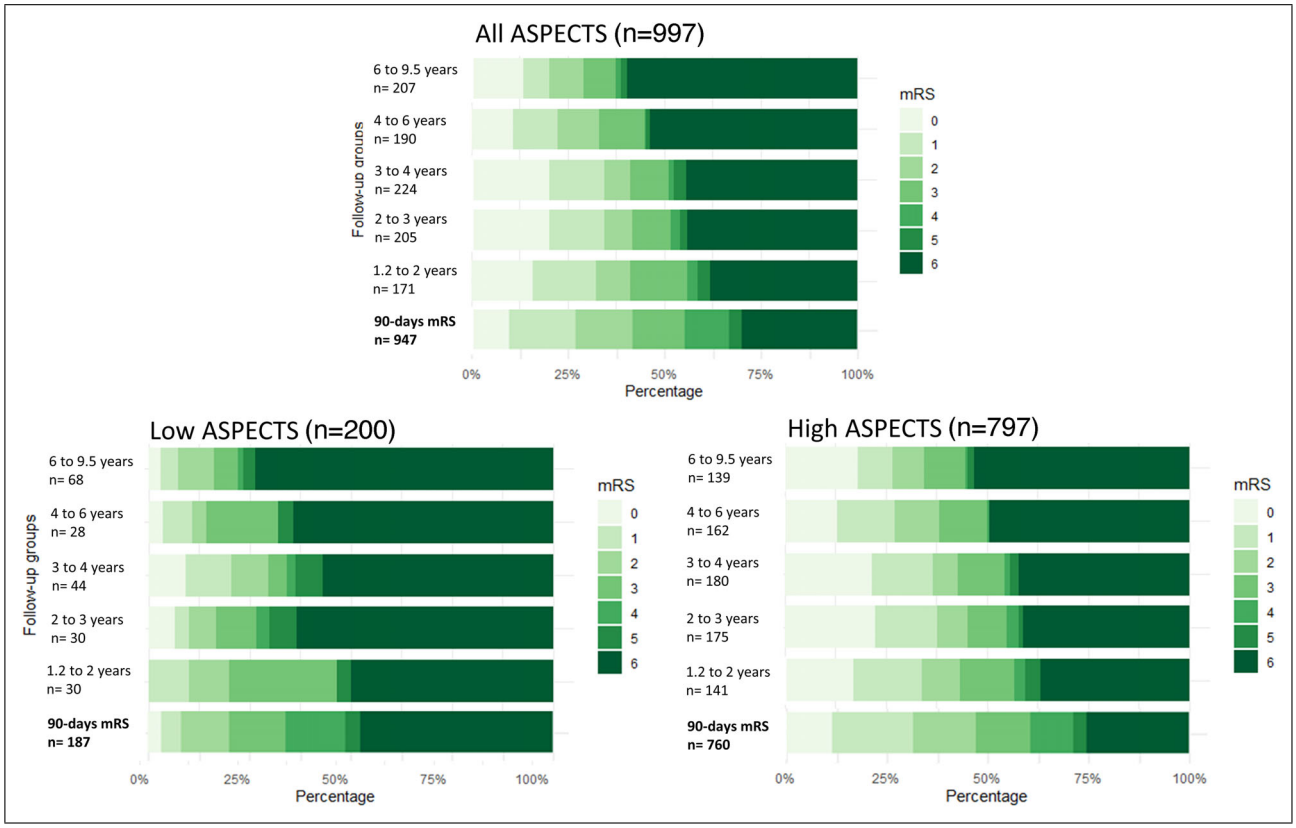

Figure 2. Modified Rankin scale (mRS) recorded from the 90-day control and long-term follow-up stratified according to Alberta Stroke Program Early Computed Tomography Score (ASPECTS) on admission.

According to ASPECTS on admission, patients were dichotomized into low ASPECTS (0 to 5) and high ASPECTS (6 to 10). Because of the heterogeneous follow-up time, 5 groups of patients surviving until the long-term follow-up were defined (see Figure 1). Long-term mRS was higher in patients with high ASPECTS than in those with low ASPECTS (median 3 [interquartile range, 1–6] vs 6 [interquartile range, 3–6], $P<0.001$). The visual trend toward worsening of mRS (0–3) in the long-term follow-up was significant in the low ASPECTS group (adjusted odds ratio [aOR], 0.62 for later follow-up group [$P=0.001$]) and in the high ASPECTS group (aOR, 0.83 for later follow-up group; $P=0.003$). To emphasize the mRS shift in the long-term follow-up, available 90-day mRS was added at the bottom of each group.

Association Between Final Reperfusion Grade and Long-Term Functional Outcome According to ASPECTS

Multivariable logistic regression indicated that increasing reperfusion grade was associated with higher rates of long-term favorable functional outcome (mRS 0–3) after adjusting for predefined variables (aOR, 1.43; 95% CI, 1.09–1.88 [$P=0.01$]) in patients with low ASPECTS. This was comparable to the association found in patients with higher ASPECTS (aOR, 1.32; 95% CI, 1.17–1.48 [$P<0.001$]) (Figure 3). Interaction analyses found no heterogeneity regarding the association of eTICI score and long-term favorable functional outcomes when comparing the low and high ASPECTS groups ($P=0.82$). Higher reperfusion grade was also associated with long-term good functional outcome (mRS 0 to 2) in patients with low ASPECTS (aOR, 1.47; 95% CI, 1.05–2.06 [$P=0.02$]) and high ASPECTS (aOR, 1.36; 95% CI, 1.20–1.53 [$P<0.001$]). Regarding the heterogeneity of follow-up time, all analyses reached a variance of random effects <0.05, which represents a small variability between the different follow-up subgroups. In the sensitivity analyses, low DWI-ASPECTS (0 to 5) was associated with favorable outcomes in terms of higher reperfusion grade (aOR, 1.85; 95% CI, 1.11–3.07 [$P=0.018$]) (eFigure III), although the summary model was not significant for the CT-ASPECTS (0–5) subgroup. Nevertheless, interaction analyses found no heterogeneity regarding long-term favorable functional outcomes in the low ASPECTS group according to imaging modalities at admission (P for interaction=0.47).

Distribution of EQ-5D-3L in Stroke Survivors According to ASPECTS Groups

The distribution of the EQ-5D-3L domains (scored 1–3) assessed in the 575 stroke survivors in the low and high ASPECTS groups is illustrated in eFigure IV.

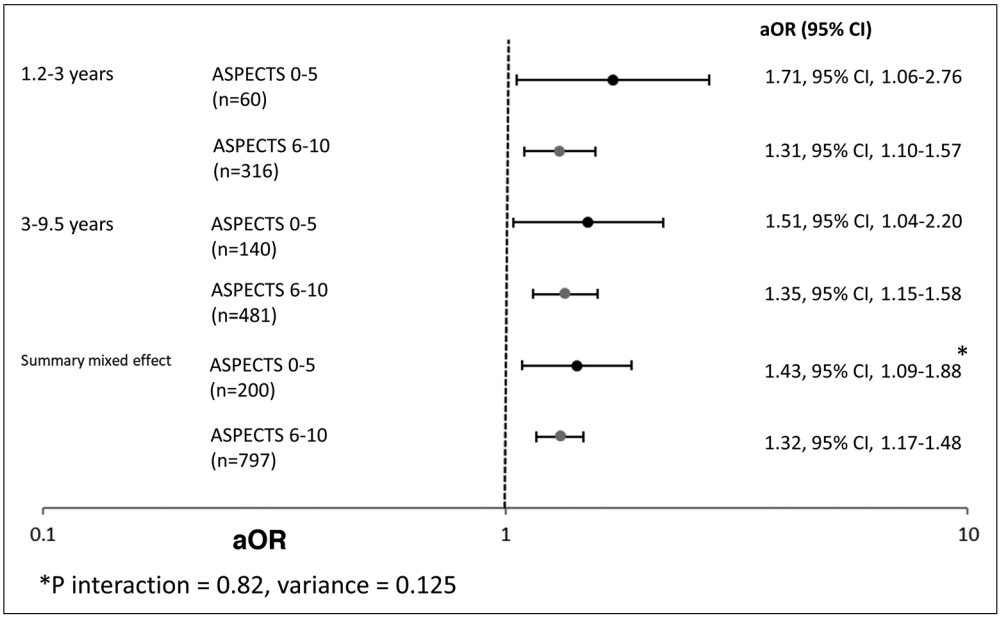

Figure 3. Correlation between expanded Treatment in Cerebral Infarction score (eTICI) grade and favorable functional outcome (modified Rankin Scale [mRS] 0–3) at early and late follow-up.
Adjusted odds ratios (aORs) between final grade of reperfusion (assessed by eTICI) and favorable functional outcome (defined by mRS 0 to 3) for low Alberta Stroke Program Early Computed Tomography Score (ASPECTS) (0–5) and high ASPECTS (6–10) are displayed according to the different follow-up times. To increase the statistical power, early follow-up groups (1.2–3 years) and late follow-up groups (3–9.5 years) were merged. All follow-up groups were assessed together in the mixed-effects model (summary mixed effect). Interaction analyses (∗) did not identify any substantial influence of the ASPECTS group (low vs high) on the relationship between final eTICI and favorable functional outcome. All analyses were adjusted for age, independence before stroke (defined as mRS 0–2), intravenous thrombolysis, time from onset of stroke to groin puncture, sex, National Institutes of Health Stroke Scale on admission, ordinal ASPECTS, and imaging modality on admission. *P* interaction indicates *P* value for interaction from ASPECTS (low vs high ASPECTS).

The percentages of patients without complaints (score 1) for pain/discomfort (65.7% versus 69.9%, P=0.49) and anxiety/depression (71.2% versus 78.9%, P=0.17) were identical in both ASPECTS groups. A significant trend toward higher scores (≥2 points) in the low ASPECTS group was found for mobility (67.1% versus 42.1%, P<0.001), self-care (53.4% versus 31.2%, P<0.001), and usual activities (65.8% versus 41.4%, P<0.001).

Association Between Reperfusion and Long-Term Quality of Life According to ASPECTS

In the multivariable linear regression analysis, higher final reperfusion grade was associated with higher EQ-5D utility index score in both the low and high ASPECTS groups (adjusted linear correlation coefficient, 0.05 [95% CI, 0.02–0.08] and 0.05 [95% CI, 0.03–0.06] per TICI grade increase, respectively). The estimated treatment effect of the final eTICI grade on the EQ-5D utility index at the early and late follow-up times (1.2–3 years versus 3–9.5 years, respectively) was identical in both ASPECTS groups (eFigure V). Moreover, no heterogeneity of the association between eTICI and EQ-5D utility index score was found among the 2 ASPECTS group strata (low and high ASPECTS, respectively; P=0.86).

DISCUSSION

The main findings of this study are: (1) a higher eTICI reperfusion grade after MT was a predictor of better long-term functional outcomes and quality of life in the low ASPECTS group, pointing toward the potential efficacy of reperfusion despite advanced early ischemic changes; (2) one third of patients with ASPECTS 0 to 5 can achieve favorable outcomes at long-term follow-up; and (3) the poor long-term quality of life in patients with low ASPECTS is mainly the result of constraints affecting mobility, self-care, and usual activities.

Sustainable Effect of Higher Final Reperfusion Grade in Patients With Low ASPECTS

Recently, Kakita et al[7] found a trend toward good clinical outcome (mRS 0 to 2) at 90 days in patients treated with MT compared with best medical treatment in a

subanalysis of the RESCUE-Japan Registry 2 (Recovery by Endovascular Salvage for Cerebral Ultra-Acute Embolism Japan Registry 2). In their meta-analysis, Cagnazzo et al[20] demonstrated the same trend in patients with low ASPECTS and successful reperfusion after MT compared with unsuccessful reperfusion. Based on a multicentric register that included the stroke population assessed in this study, Kaesmacher et al[11] described favorable functional outcomes (mRS 0 to 3) at 90 days in 49.7% of the patients with ASPECTS 0 to 5 who had undergone successful reperfusion. A recent study suggested that this trend toward favorable outcomes may be attributable to reduced edema formation and malignant infarction after successful reperfusion.[8] In the present study, a favorable functional outcome was found in 32.9% of the patients who had undergone successful reperfusion at long-term follow-up, and a gradual increase of favorable outcome was noted with improved reperfusion grades (aOR, 1.43; 95% CI, 1.09–1.88 [*P*=0.01]). This study confirmed the sustained effect of better reperfusion at 90-day follow-up.

Estimated Treatment Effect of MT in Patients With Low ASPECTS

Most of the randomized controlled trials (RCTs) that demonstrated the benefit of MT compared with best medical treatment excluded patients with ASPECTS 0 to 5, and the treatment effect of MT in this population has not yet been confirmed in an RCT. The HERMES (Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke) meta-analysis of 5 MT RCTs showed a favorable but not significant effect of MT in patients with ASPECTS 0 to 5 (common odds ratio, 1.24; 95% CI, 0.62–2.49).[1] More recently, Meyer et al[12] showed a trend toward better functional outcomes for thrombectomy in patients with low ASPECTS only when recanalization was complete. The present study revealed no significant difference in patients with low or high ASPECTS regarding the association of higher reperfusion grade and long-term functional outcomes or quality of life, suggesting that the effect of higher reperfusion grade may be preserved in patients with extensive early infarction. This was seen both in patients followed for up to 3 years and in those with long-term follow-up up to 9.5 years. As emphasized by Goyal et al[1] in the HERMES meta-analysis, patients with low ASPECTS treated with MT have generally poor outcomes. This is true even if a treatment effect is present. For this reason, a small treatment effect should not always be considered indisputably useful. Several ongoing RCTs (IN EXTREMIS - LASTE [large stroke therapy evaluation]; TENSION [Efficacy and Safety of Thrombectomy in Stroke With Extended Lesion and Extended Time Window], NCT03094715; SELECT2 [A Randomized Controlled Trial to Optimize Patient's Selection for Endovascular Treatment in Acute Ischemic Stroke], NCT03876457; and TESLA [Thrombectomy for Emergent Salvage of Large Anterior Circulation Ischemic Stroke], NCT03805308) aim to answer this open question.[20] Furthermore, it remains unclear whether ASPECTS is the most appropriate tool in the decision-making for MT. First because ASPECTS weights the brain areas unequally, with disproportional weighting for the striatocapsular region.[21] Second, the interrater variability of the ASPECTS represents a limiting factor in patient selection.[22,23] The use of ASPECTS in assessing eligibility for MT may consequently lead to withholding MT in patients who may benefit from it.

HRQOL in Long-Term Follow-up

Schreuders et al[24] demonstrated a treatment effect of MT versus best medical treatment on HRQOL in the MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) trial population after 90 days. They reported a β-coefficient of 0.06 with an effect principally relevant for "mobility," "self-care," and "usual activities." More recently, Deb-Chatterji et al[13] assessed HRQOL at 90 days in a real-world study population of 504 patients after MT. Among others, higher ASPECTS and successful recanalization were independently associated with better HRQOL. In their study, 22% of stroke survivors treated with MT (n=83) reported no complaints at 90 days. Complaints reported were as follows: usual activities (66%), mobility (57.1%), self-care (50.4%), pain/discomfort (41.7%), and anxiety/depression (40.8%). The authors reported a β-coefficient of 0.26 (95% CI, 0.18–0.34) for successful reperfusion and EQ-5D utility index. The multivariable linear regression analysis from the present study found a β-coefficient of 0.05 (95% CI, 0.02–0.08) for the ordinal eTICI and EQ-5D utility index. This indicates a positive correlation between a higher grade of reperfusion and better quality of life in the long-term follow-up. The distribution of reported complaints between the groups was similar to the aforementioned studies.

Limitations

First, this was a monocentric study with heterogeneous follow-up times resulting in a small number of patients in each subgroup, particularly in the low ASPECTS groups. Second, this study included patients with DWI-ASPECTS and CT-ASPECTS, which are associated with modest intermodality agreement, especially in patients with low ASPECTS.[25] Third, between index stroke and long-term follow-up, new health conditions could potentially have arisen or known conditions could have worsened. Both may have influenced the

long-term outcome. Fourth, reported functional outcomes and EQ-5D-3L by caretakers in 12% of the surviving patients may diverge from patients' reported deficits according to current evidence.[26,27] Fifth, the ethical approval from the BEYOND-SWIFT protocol allowed the inclusion of patients treated with MT only and not of control groups treated conservatively or with intravenous thrombolysis exclusively. Further studies need to investigate the long-term outcome, including patients treated with intravenous thrombolysis and conservatively, to evaluate the recovery according to baseline ASPECTS in all groups of patients with stroke. Finally, 24.6% (n=323) of the initial cohort were not included in the final analysis (15% lost to follow-up and 9.4% with posterior circulation stroke or missing imaging). This might have represented a potential selection bias. All patients who had died by the time of follow-up were included in the study and assigned an mRS score of 6 and an EQ-5D utility index of 0. This resulted in the included patients being older (eTable 1) and an absolute overestimation of a fatal outcome.

CONCLUSIONS

A considerable number of patients treated with MT may achieve favorable long-term functional outcomes and acceptable quality of life despite extensive early ischemic changes. The association between better reperfusion and improved outcomes seemed similar between patients with low and high ASPECTS, pointing toward a beneficial effect of establishing ideally complete reperfusion. Until RCT data become available, the possibility of satisfactory long-term outcomes should be taken into consideration when deciding whether to exclude patients from MT based on admission ASPECTS.

ARTICLE INFORMATION

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Conflict of Interest

None of the other authors report any conflicts of interest.

Author Contributions

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Supplemental Materials

eFigures I-V
eTable I
STROBE Checklist

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