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Progression of cerebral infarction before and after thrombectomy is modified by prehospital pathways

Alexander M Kollikowski ,[1] Franziska Cattus,[1] Julia Haag,[1] Jörn Feick,[1] Alexander G März,[1] Franziska Weidner,[1] Michael K Schuhmann,[2] Wolfgang Müllges,[2] Guido Stoll,[2] Mirko Pham,[1] Marc Strinitz[1]

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[1]Institut für Diagnostische und Interventionelle Neuroradiologie, Universitätsklinikum Würzburg, Würzburg, Bayern, Germany
[2]Neurologische Klinik und Poliklinik, Universitätsklinikum Würzburg, Würzburg, Bayern, Germany

Correspondence to
Dr Alexander M Kollikowski, Institut für Diagnostische und Interventionelle Neuroradiologie, Universitatsklinikum Würzburg, Würzburg, Bayern, Germany; kollikowsk_a@ukw.de

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ABSTRACT

Background Evidence of the consequences of different prehospital pathways before mechanical thrombectomy (MT) in large vessel occlusion stroke is inconclusive. The aim of this study was to investigate the infarct extent and progression before and after MT in directly admitted (mothership) versus transferred (drip and ship) patients using the Alberta Stroke Program Early CT Score (ASPECTS).

Methods ASPECTS of 535 consecutive large vessel occlusion stroke patients eligible for MT between 2015 to 2019 were retrospectively analyzed for differences in the extent of baseline, post-referral, and post-recanalization infarction between the mothership and drip and ship pathways. Time intervals and transport distances of both pathways were analyzed. Multiple linear regression was used to examine the association between infarct progression (baseline to post-recanalization ASPECTS decline), patient characteristics, and logistic key figures.

Results ASPECTS declined during transfer (9 (8–10) vs 7 (6-9), p<0.0001), resulting in lower ASPECTS at stroke center presentation (mothership 9 (7–10) vs drip and ship 7 (6–9), p<0.0001) and on follow-up imaging (mothership 7 (4–8) vs drip and ship 6 (3–7), p=0.001) compared with mothership patients. Infarct progression was significantly higher in transferred patients (points lost, mothership 2 (0–3) vs drip and ship 3 (2–6), p<0.0001). After multivariable adjustment, only interfacility transfer, preinterventional clinical stroke severity, the degree of angiographic recanalization, and the duration of the thrombectomy procedure remained predictors of infarct progression (R^2=0.209, p<0.0001).

Conclusions Infarct progression and postinterventional infarct extent, as assessed by ASPECTS, varied between the drip and ship and mothership pathway, leading to more pronounced infarction in transferred patients. ASPECTS may serve as a radiological measure to monitor the benefit or harm of different prehospital pathways for MT.

INTRODUCTION

In many regions of the world, the two most frequent treatment pathways in the management of acute large vessel occlusion strokes are intravenous thrombolysis in the nearest thrombolysis facility (drip and ship concept) prior to mechanical thrombectomy in endovascular capable comprehensive stroke centers or, as the main alternative, direct transfer to a comprehensive stroke center for mechanical thrombectomy (mothership concept).[1] The population based benefit or harm of either scenario is region specific and not externally generalizable.[2] Although certain stroke networks have evaluated prehospital triage systems based on stroke severity scales, it will likely remain elusive, from a methodological perspective, to study optimal prehospital routing strategies by performing trials where the treatment pathway is randomized in the field and which at the same time will account for region specific factors or by performing such trials separately by region.[2 3]

Functional clinical measures are the standard of reference as primary endpoints in randomized stroke trials. However, observational investigation using standardized and widely used radiological measures, such as the Alberta Stroke Program Early CT Score (ASPECTS), may be valuable to indicate benefit or harm in a setting where randomization of different treatment pathways for acute large vessel occlusion stroke remains a serious obstacle or is not feasible across multiple centers, each with distinct region specific features.[1 2 4] Recently, ASPECTS has been proposed as an imaging tool to assess the dynamics of infarction during interfacility transfer.[5 6] We add to previous studies on ASPECTS by investigating whether the infarct extent before and after mechanical thrombectomy differs between the mothership and drip and ship pathways, and aim to quantify the imaging defined effect size of pre- to postinterventional worsening of stroke over time for both pathways.

METHODS

This retrospective observational study was approved by the local ethics committee. The period of observation was from May 2015 to July 2019. A total of 535 consecutive anterior circulation ischemic stroke patients intended to be treated by mechanical thrombectomy at an academic comprehensive stroke center in our regiopolitan area were analyzed to investigate whether preinterventional and early postinterventional follow-up ASPECTS at 24–48 hour after symptom onset differed between the mothership and drip and ship treatment pathways for mechanical thrombectomy (online supplemental figure 1). In addition, we compared the course of decline in ASPECTS over time (difference in follow-up ASPECTS to baseline) between the two treatment pathways, and assessed the association of

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key patient, interventional, and logistic variables with ASPECTS-defined infarct progression.

The stroke network of the regiopolitan area surveyed covers a population of ~1.4 million inhabitants and is composed of one academic comprehensive stroke center and 11 associated hospitals within a maximum ground transfer distance of 149 km.[7] To ensure guideline compliant neurointerventional and pharmacological stroke treatment in a 24/7 setting,[1] the academic comprehensive stroke center provides teleradiological and teleneurological support on request (ie, the assessment of thrombectomy eligibility), coordination of patient transfer from associated hospitals (individual decision making), and, following transfer, subsequent mechanical thrombectomy if indicated.[7]

All symptomatic acute ischemic stroke patients with proven occlusion of the distal internal carotid artery, middle cerebral artery M1 segment, and proximal M2 segment were eligible for study entry. Of those, we included patients either directly admitted or transferred from associated referring hospitals for which initial non-invasive imaging by means of non-contrast CT and CT angiography were available for both the comparison with non-contrast CT (Somatom Definition AS, Siemens Healthcare, Erlangen, Germany) at stroke center presentation and at 24–48 hours (postinterventional imaging, cut-off for contrast agent resorption).[8] Thrombectomy eligibility was guided using consensus recommendations or current guidelines if available.[1]

The following demographic, clinical, radiological, interventional, and logistical data were collected according to the available medical records: age, sex, baseline medication and medical history, time of symptom onset, heart rate and blood pressure at presentation, National Institutes of Health Stroke Scale (NIHSS) score at presentation and at 24 hours, time of non-invasive and angiographic image acquisition, occlusion location, baseline ASPECTS (referring hospital/comprehensive stroke center), ASPECTS after patient transfer and at 24–48 hour, and alteplase administration. Imaging data were stored in the respective picture archiving and communication system and were available via teleradiological access. ASPECTS values were independently evaluated by two of the authors (FC/JH) trained in ASPECTS scoring (http://www.aspectsinstroke.com), both blinded to clinical information. Interobserver agreement was assessed by the intraclass correlation coefficient (ICC). Recanalization success was assessed by the modified Treatment in Cerebral Ischemia Scale (mTICI) and determined by finding a consensus between two examiners with longstanding expertise in vascular neurointervention (AMK/MP). A mTICI score of ≥2b was defined as successful recanalization.

Logistic key figures were obtained as described previously.[7] Briefly, the overall treatment chain ranging from symptom onset to stroke center admission and initiation of mechanical thrombectomy was divided into chronological intervals. For each patient, we reconstructed and geocoded the actual transport routes by time and distance between symptom onset, initial hospital, and the comprehensive stroke center, applying Google's Distance Matrix Application Programming Interface (Mountain View, California, USA). All calculations were carried out under the assumption that the documented time of image acquisition (referring hospital/comprehensive stroke center) approximates the time of clinical presentation. The time interval between non-invasive imaging (non-contrast CT) at the referring facility and the subsequent CT at the comprehensive stroke center was defined as time surrogate for the duration of the overall transfer process.

The manuscript was prepared according to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement for observational studies.[9]

Statistical analysis

All data were stored and processed in Microsoft Office 365 ProPlus Excel (V.2102, Microsoft Corporation, Redmond, Washington, USA). Statistical analyses were performed using GraphPad Prism (GraphPad Prism 9.1, GraphPad Software, San Diego, California, USA) and MedCalc 19.7.2 (MedCalc Software, Ostend, Belgium). Gaussian distribution was tested by the D'Agostino and Pearson omnibus normality test. Standard descriptive statistical measures were used, including median (IQR) for numerical data or absolute and relative frequency distribution for categorial variables. ICC was used as a statistical measure of interobserver agreement for radiological scoring of ASPECTS and is given with 95% CI. Single comparison between two groups was done by χ^2 test for categorial variables and by unpaired t test or Mann–Whitney U test for parametric and non-parametric data. The Kruskal–Wallis test was used for non-parametric repeated measures and followed by Dunn's multiple comparison test. Variables of univariate association ($p<0.1$) were chosen for entry into multiple linear regression to evaluate the association between ASPECTS decline over time, patient characteristics, and logistic key figures. Stepwise backwards selection procedures were used to fit a model to these variables. A two sided p value <0.05 was predetermined as the threshold for statistical significance.

RESULTS

Between May 2015 and July 2019, 535 consecutive patients with large vessel occlusion of the anterior circulation were primarily admitted (mothership) or secondarily referred (drip and ship) to our comprehensive stroke center with the intention to be treated by mechanical thrombectomy. The demographic, clinical, and radiological characteristics according to the prehospital pathway (mothership vs drip and ship) are given in table 1.

There were no differences in patient age (mothership 77 (66-83) vs drip and ship 77 (66-82) years, p=0.912) or gender distribution (mothership 47% men vs 42% for drip and ship, p=0.433). Hypertension was the most prevalent comorbid disease and similarly distributed across both groups (mothership 81% vs drip and ship 82%, p=0.659). The rate of atrial fibrillation was significantly higher in transferred patients (mothership 31% vs drip and ship 42%, p=0.014). No differences were observed for the use of antithrombotic (mothership 50% vs drip and ship 50%, p=0.733) or antihypertensive drugs (mothership 71% vs drip and ship 72%, p=0.667). We found significantly more patients with unknown time of symptom onset (mothership 17% vs drip and ship 11%, p=0.025) and higher degrees of stroke severity in the mothership group (NIHSS, mothership 16 (11-20) vs drip and ship 14 (10-14), p=0.016). Both groups showed elevated systolic blood pressure levels at the time of stroke center presentation (mothership 158 (137-179) vs drip and ship 160 (144-225) mm Hg, p=0.125). The rate of intravenous alteplase administration was almost 50% in both groups (mothership 49% vs drip and ship 52%, p=0.508). In 34 patients (11%) after interfacility transfer, eventual mechanical thrombectomy was not performed because of significant infarct progression on arrival.

Transport distances and quantitative time metrics are given in table 2. In the drip and ship group, interfacility transfer delayed the initiation of mechanical thrombectomy by 319% (picture to

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Table 1 Patient characteristics

Characteristics	MS (n=221)	DS (n=314)	P value
Age (years) (median (IQR))	77 (66–83)	77 (66–82)	0.912
Males (n (%))	104 (47)	137 (42)	0.433
Medical history (n (%))			
Hypertension	179 (81)	259 (82)	0.659
Diabetes mellitus	53 (24)	61 (19)	0.205
Hyperlipidemia	72 (33)	91 (29)	0.373
Atrial fibrillation	69 (31)	131 (42)	0.014
Smoking history	79 (36)	96 (31)	0.209
Baseline medication (n (%))			
Antithrombotic medication	110 (50)	161 (51)	0.733
Antihypertensive drugs	156 (71)	227 (72)	0.667
Clinical presentation			
Unknown time of symptom onset (n (%))	38 (17)	33 (11)	0.025
NIHSS at CSC presentation (median (IQR))	16 (11–20)	14 (10–14)	0.016
Systolic blood pressure mm Hg) (median (IQR))	158 (137–179)	160 (144–225)	0.125
Diastolic blood pressure (mm Hg) (median (IQR))	80 (70–95)	85 (72–99)	0.35
Heart rate (beats/min) (median (IQR))	78 (67–90)	79 (67–90)	0.982
Treatment			
IV alteplase (n (%))	109 (49)	164 (52)	0.508
Intervention (n (%))			
No MT after interfacility transfer		60 (19)	
Recanalization after remote IV alteplase		10 (3)	
No large vessel occlusion after transfer		5 (2)	
Far distal occlusion not suitable for MT		6 (2)	
Far advanced infarct progression not suitable for MT		34 (11)	
No consent for treatment		2 (1)	
No endovascular access route to the occlusion location		3 (1)	
Onset to puncture (min) (median (IQR))	136 (110–164)	266 (230–326)	<0.0001
Occlusion location (n (%))*			
M1	131 (59)	195 (62)	0.509
M2	33 (15)	60 (19)	0.209
ICA	90 (41)	121 (39)	0.61
Stent retrieval maneuvers (median (IQR))	2 (1–3)	2 (1–3)	0.779
Successful recanalization (mTICI ≥2 b) (n (%))	181 (82)	219 (87)	0.001
Duration of MT procedure (min) (median (IQR))	70 (45–111)	75 (49–99)	0.947
Onset to recanalization (min) (median (IQR))	210 (168–271)	346 (296–416)	<0.0001
Cervical ICA stenting (n (%))	36 (16)	52 (17)	0.934
Clinical outcome			
NIHSS score 24 hours postintervention (median (IQR))	6 (1–15)	5 (2–13)	0.854
Intracranial hemorrhage (n (%))	35 (16)	42 (13)	0.425
Inhouse mortality (n (%))	41 (19)	51 (16)	0.486

Values are number (%) for categorial variables and median (IQR) for continuous variables.
*Including combined vessel occlusions.
CSC, comprehensive stroke center; DS, drip and ship; ICA, internal carotid artery; IV, intravenous; M1/M2, middle cerebral artery segment; MS, mothership; MT, mechanical thrombectomy; mTICI, modified Treatment in Cerebral Ischemia Scale; NIHSS, National Institutes of Health Stroke Scale.

puncture time mothership 57 (47-75) vs drip and ship 182 (144-217) min, p<0.0001).

The middle cerebral artery M1 segment (mothership 59% vs drip and ship 62%, p=0.509) and the distal internal carotid artery (mothership 41% vs drip and ship 39%, p=0.61) were the most common sites of vascular occlusion in both groups (table 1). In both groups, a median of two retrieval maneuvers (mothership 2 (1–3) vs drip and ship 2 (1–3), p=0.779) were necessary to achieve successful recanalization (mTICI ≥2 b). Although statistically significant, the rate of successful

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Table 2 Logistic key figures

	MS (n=221)	DS (n=314)	P value
Ground bound transport distances (km) (median (IQR))			
Onset to RH		12 (4–21)	
RH to CSC		48 (23–50)	
Onset to CSC*	9 (3–23)	60 (36–82)	<0.0001
Time metrics (min) (median (IQR))			
Onset to RH imaging		83 (63–118)	
RH to CSC imaging		141 (112–181)	
Onset to CSC imaging	72 (56–102)	232 (191–291)	<0.0001
Picture to puncture time†	57 (47–75)	182 (144–217)	<0.0001

*Including all transfer routes.
†Picture to puncture time=time interval between initial CT scan and groin puncture at the CSC.
CSC, comprehensive stroke center; DS, drip and ship; MS, mothership; RH, referring hospital.

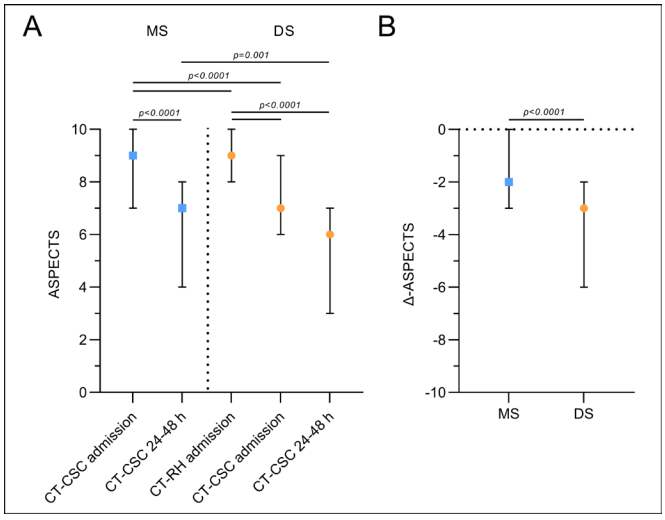

Figure 1 (A) Serial Alberta Stroke Program Early CT Score (ASPECTS) of directly admitted (mothership (MS)) and referred patients (drip and ship (DS)) at the time of initial imaging, at admission to the comprehensive stroke center (CSC), and at 24–48 hours after symptom onset. (B) Decline in ASPECTS between baseline and follow-up imaging according to treatment pathway. Data are median (IQR). RH, referring hospital.

recanalization of the infarct related artery was only slightly higher in transferred patients (mothership 82% vs drip and ship 87%, p=0.001). Interfacility transfer extended the time interval from symptom onset to recanalization by 136 min (onset to recanalization time mothership 210 (168-271) vs drip and ship 346 (296-416) min, p<0.0001), while the overall duration of thrombectomy procedures (puncture to final recanalization result) did not differ between the two groups (mothership 70 (45-111) vs drip and ship 75 (49-99), p=0.947). No differences were observed regarding the occurrence of tandem lesions represented by cervical internal carotid artery stenosis of ≥50% requiring angioplasty with or without stenting (mothership 16% vs drip and ship 17%, p=0.934). Short term clinical improvement in the mothership group did not significantly differ from the drip and ship group (NIHSS 24 hours post intervention mothership 6 (1–15) vs drip and ship 5 (2-13), p=0.854). There were no intergroup differences with regard to intracranial hemorrhage (mothership 16% vs drip and ship 13%, p=0.425) or death during hospital stay (mothership 19% vs drip and ship 16%, p=0.486).

Serial ASPECTS are given in figure 1A and online supplemental table 1. The ICC for interobserver agreement of ASPECTS was good to excellent in both groups (mothership 0.876 (95% CI 0.788 to 0.924); drip and ship 0.958 (0.9381 to 0.971)).[10] Interfacility transfer in the drip and ship pathway was associated with a significant drop in median ASPECTS on stroke center admission by 2 points (preinterventional ASPECTS, comprehensive stroke center 7 (6–9) vs external ASPECTS 9 (8–10), p<0.0001). Preinterventional ASPECTS on stroke center admission was significantly lower in drip and ship (7 (6–9)) versus mothership (9 (7–10)) patients (p<0.0001). Infarct extension on follow-up imaging was significantly more favorable in the mothership pathway (mothership 7 (4–8) vs drip and ship 6 (3–7), p=0.001). Consistently, the decline in ASPECTS between baseline (CT at remote hospitals for drip and ship patients and at stroke center presentation for mothership patients) and postinterventional follow-up imaging (figure 1B) was significantly steeper in transferred patients (points lost, mothership 2 (0–3) vs drip and ship 3 (2–6), p<0.0001).

Multiple linear regression was performed to identify relevant recorded patient characteristics (ie, age, sex, unknown time of symptom onset, baseline ASPECTS, NIHSS at presentation (comprehensive stroke center), blood pressure, heart rate, hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, smoking, antithrombotic medication and use of antihypertensive drugs, intravenous thrombolysis, time interval from symptom onset to groin puncture, site of occlusion, stent retrieval maneuvers, angiographic degree of recanalization, duration of thrombectomy, time interval from symptom onset to recanalization, and stenting) and logistic key figures (ie, interfacility transfer, air transport, transfer time, and ground bound transport distance) associated with ASPECTS decline (online supplemental table 2). A model covering all variables of univariate association (p<0.1) is given in table 3, revealing that only interfacility transfer (drip and ship), NIHSS at presentation, degree of angiographic recanalization (mTICI), and duration of the thrombectomy procedure were significant predictors of infarct progression (adjusted R^2=0.209, p<0.0001).

DISCUSSION

Prehospital triage and interfacility transfer are critical factors that potentially worsen clinical outcome in acute large vessel occlusion stroke.[11 12] So far, there are no data on the extent to which different prehospital pathways affect radiological measures of structural damage and the dynamic progression of cerebral infarction before and after mechanical thrombectomy, which can be semiquantitatively assessed through radiological scoring of ASPECTS.[4–6 13–15] Our study addressed this issue with the following main results. Preinterventional ASPECTS declined significantly during interfacility transfer, resulting in significantly lower ASPECTS at stroke center presentation and on follow-up imaging in the drip and ship group compared with the mothership group. Infarct progression from baseline to postinterventional imaging was significantly higher in transferred patients. In the multivariable model, only interfacility transfer, NIHSS at presentation, degree of angiographic recanalization, and duration of the thrombectomy procedure proved to be independent predictors of structural infarct progression.

ASPECTS is a 10 point non-contrast CT scoring system of early ischemic changes within the middle cerebral artery territory.[4] For large vessel occlusion stroke, ASPECTS has been increasingly exposed to internal validation with good estimates

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Table 3 Multiple regression model of ASPECTS decline between baseline and postinterventional follow-up imaging

Variable	B	SE	T	P value
Interfacility transfer (drip and ship)	3.898	1.031	3.782	0.0002
NIHSS at CSC presentation	0.13	0.029	4.517	<0.0001
mTICI	−0.543	0.236	−2.303	0.023
Duration of MT procedure	0.015	0.004	3.535	0.0006

R^2=0.231, adjusted R^2=0.209, F=10.501, p<0.0001
ASPECTS, Alberta Stroke Program Early CT Score; CSC, comprehensive stroke center; MT, mechanical thrombectomy; mTICI, modified Treatment in Cerebral Ischemia Scale; NIHSS, National Institutes of Health Stroke Scale.

of internal consistency (Crohnbach's alpha=0.859) and varying interobserver reliability (ICC=0.672–0.834).[1 16 17] In our study, good to excellent levels of inter-rater agreement could be achieved, further supporting that ASPECTS is a reliable tool to assess the extent of cerebral infarction across different CT scanners, scan acquisition protocols, and time points.[5 10]

Recently, ASPECTS has been used to investigate the dynamics of infarct progression during interfacility transfer, revealing that one of three patients becomes ineligible for mechanical thrombectomy based on ASPECTS imaging criteria,[6 13] and that every 1 point increase in ASPECTS decline per hour correlates with a 23 fold lower probability of good functional outcome (modified Rankin Scale score of 0–2) at 90 days.[5] In our study, the ASPECTS decline of 2 points that occurred during interfacility transfer was more severe than observed previously by others (1 point), although transfer times were nearly identical.[5 14] This discrepancy in early ASPECTS decline may be best explained by the rate of distal internal carotid artery occlusions which was three times higher in our observation. This highlights that not rigid absolute time windows but rather local cerebral pathophysiology and individual collateral recruitment, which critically depend on precise occlusion location, likely affects the dynamics of how the penumbra is transformed into infarction.[15 18–20] Prospective registry data revealed that significant treatment delays in the drip and ship treatment pathway (onset to recanalization time, mothership 202 (160-265) vs drip and ship 312 (255-286) min, p<0.0001) lead to worse clinical outcome (modified Rankin Scale score of 0–1 at 90 days, mothership 47,4% vs drip and ship 38%, p=0.005).[21] This is in line with the fact that a significant proportion of large vessel occlusion stroke patients (≥70%) can be assigned to the categories of rapid and intermediate infarct progressors,[18 22] in whom the frequency of good outcome (modified Rankin Scale score of 0–2) is highly time dependent and declines from 64.1% for those recanalized within 180 min to 46.1% for those recanalized within 480 min.[23] In our study, multimodal imaging selection was applied to identify recanalization responders in the extended or unknown time window,[24 25] which consequently dissolved the association of time and imaging defined pre- to postinterventional worsening of stroke. Importantly, interfacility transfer remained the most powerful predictor of structural infarct progression.

Although ASPECTS values following interfacility transfer were significantly lower in our cohort, short term functional outcomes at 24 hours were not different between the two prehospital pathways. Each ASPECTS value, by definition, is associated with a spectrum of different infarct volumes for which a strong correlation with NIHSS has been reported (r=0.79, p<0.0001).[4 26] However, for small infarct volumes, this correlation does not hold.[27] There are various explanations as to why a greater infarct extent may remain neutral with regard to functional outcome, as was observed in our cohort. The clinical endpoint of NIHSS may be biased towards good functional outcome as it does not reflect more subtle neuropsychological deficits.[28] Alternatively, or in addition, NIHSS may have underestimated the degree of favorable outcome due to the short follow-up period. Also, the beta error of statistical decision making may have occurred for which this retrospective study may have been at risk because statistical power was not adjustable a priori.

There are certain limitations to this study. First, all referring hospitals were heterogeneously located in peri-urban, urban, and rural areas. This reflects specific geographical and organizational characteristics of our region but limits external generalizability. Second, ASPECTS is an established marker of baseline infarct extent but is not established for the quantification of infarct extent on postinterventional follow-up imaging. Third, ASPECTS is unable to detect volumetric infarct progression due to edema in already affected ASPECTS regions, which may have reached substantial levels at the time of follow-up imaging.[29]

CONCLUSION

Infarct progression and postinterventional infarct extent, as assessed by ASPECTS, varied between the drip and ship and mothership pathways for mechanical thrombectomy, leading to more pronounced infarction in transferred patients. ASPECTS may serve as a radiological measure to monitor benefit or harm of different prehospital pathways and to advocate for the direct transfer to a comprehensive stroke center in regions with similar landscapes and infrastructure.

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ORCID iD
Alexander M Kollikowski http://orcid.org/0000-0002-0288-5928

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SUPPLEMENTAL MATERIAL

Progression of cerebral infarction before and after thrombectomy is modified by pre-hospital pathways

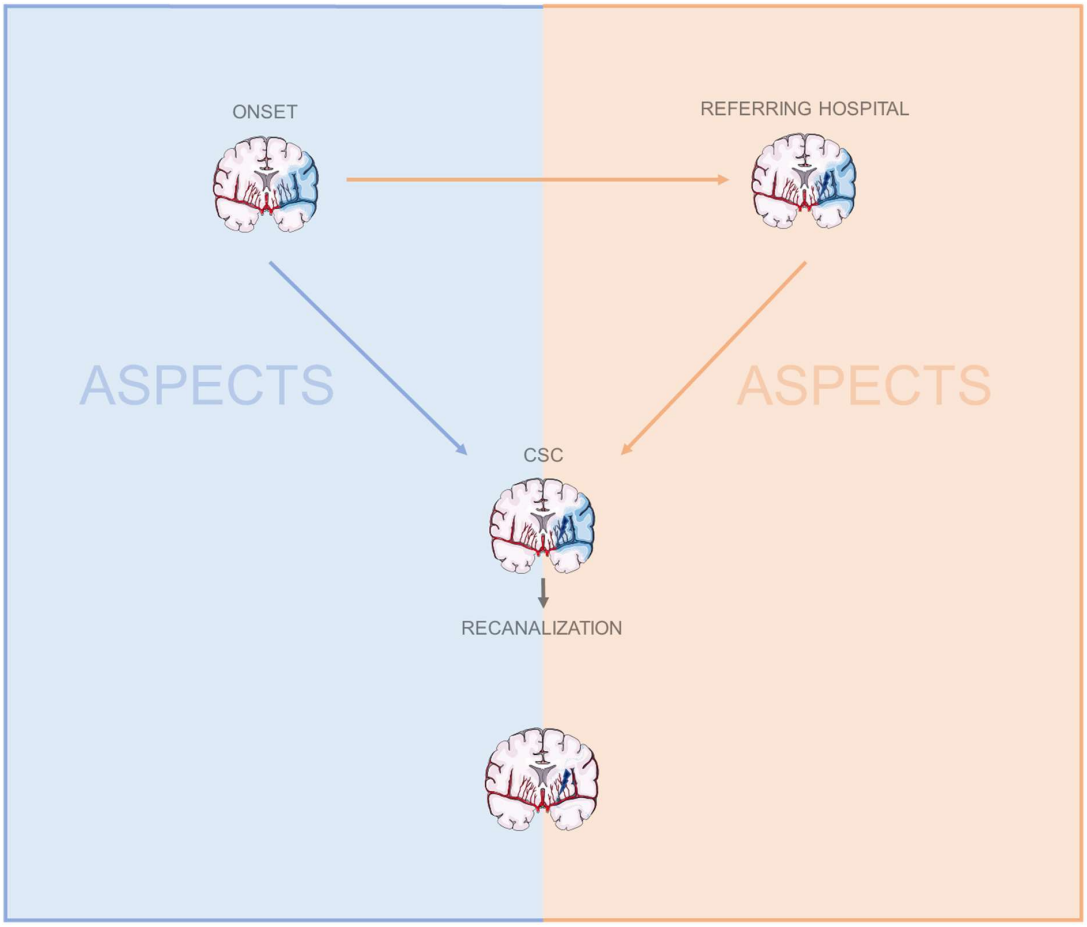
Alexander M Kollikowski,[1] Franziska Cattus,[1] Julia Haag,[1] Jörn Feick,[1] Alexander G März,[1] Franziska Weidner,[1] Michael K Schuhmann,[2] Wolfgang Müllges,[2] Guido Stoll,[2] Mirko Pham,[1] Marc Strinitz[1]

[1]Institut für Diagnostische und Interventionelle Neuroradiologie, Universitätsklinikum Würzburg, Würzburg, Bayern, Germany

[2]Neurologische Klinik und Polklinik, Universitätsklinikum Würzburg, Würzburg, Bayern, Germany

Correspondence to: Dr Alexander M Kollikowski, Institut für Diagnostische und Interventionelle Neuroradiologie, Universitätsklinikum Würzburg, Würzburg, Bayern, Germany; kollikowsk_a@ukw.de

Supplemental Figure 1: Treatment pathways for mechanical thrombectomy and the putative effect on infarct extent as assessed by ASPECTS.



Left panel, mothership pathway; Right panel, drip-and-ship pathway. ASPECTS, Alberta Stroke Program Early CT Score; CSC, comprehensive stroke center.

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Supplemental Table 1: ASPECTS according to the mothership and drip-and-ship treatment pathway for mechanical thrombectomy.

	MS n=221	**DS** n=314	***p***
ASPECTS-RH admission	-	9 (8-10)	
ASPECTS-CSC admission	9 (7-10)	7 (6-9)	<0.0001
ASPECTS-CSC FU	7 (4-8)	6 (3-7)	0.001
Δ-ASPECTS‖	2 (0-3)	3 (2-6)	<0.0001

ASPECTS, Alberta Stroke Program Early CT Score; MS, mothership; DS, drip-and-ship; RH, referring hospital; CSC, comprehensive stroke center; FU, follow-up. ‖Decline between baseline and postinterventional follow-up imaging.

Supplemental Table 2: Exploratory univariate regression analysis between recorded patient characteristics, interventional-, and logistic variables, and ASPECTS decline.

Variable	**B**	**SE**	**t**	***R*²**	***p***
Male sex	0.392	0.249	1.573	0.005	0.117
Age	-0.011	0.01	-1.113	0.003	0.266
Inter-facility transfer (drip-and-ship)	1.514	0.242	6.249	0.077	<0.0001
Transport distance (ground bound)	0.009	0.004	2.015	0.014	0.045
Transfer time	0.000096	0.002	0.005	0.0000001	0.996
Air transport	1.491	0.317	4.702	0.047	<0.0001
Baseline ASPECTS (initial imaging)	0.168	0.085	1.983	0.008	0.048

Unknown time of symptom onset	-0.665	0.357	-1.862	0.007	0.063
NIHSS at CSC-presentation	0.091	0.018	5.053	0.059	<0.0001
Systolic blood pressure	0.005	0.005	1.001	0.003	0.3174
Diastolic blood pressure	0.014	0.009	1.654	0.008	0.099
Heart rate	0.005	0.007	0.731	0.002	0.465
Hypertension	0.289	0.334	0.866	0.002	0.387
Diabetes mellitus	0.387	0.301	1.286	0.004	0.199
Hyperlipidemia	-0.187	0.272	-0.686	0.001	0.493
Atrial fibrillation	0.409	0.255	1.602	0.006	0.11
Smoking history	-0.349	0.263	-1.332	0.004	0.184
Antithrombotic medication	-0.169	0.254	-0.666	0.00099	0.506
Antihypertensive drugs	-0.038	0.297	-0.129	0.000037	0.898
IV alteplase	-0.118	0.252	-0.47	0.00048	0.638
Onset-to-puncture time	-0.00016	0.00091	-0.171	0.000084	0.865
M1 occlusion	-0.404	0.254	-1.587	0.005	0.113
M2 occlusion	-0.363	0.328	-1.107	0.0026	0.269
ICA occlusion	0.746	0.252	2.963	0.018	0.003
Stent-retrieval maneuvers	0.357	0.069	5.151	0.063	<0.0001
mTICI	-0.861	0.163	-5.297	0.064	<0.0001
Duration of MT procedure	0.004	0.002	2.502	0.015	0.013
Onset-to-recanalization time	0.00137	0.00086	1.579	0.007	0.115
Cervical ICA stenting	0.322	0.3118	1.033	0.003	0.302

ASPECTS, Alberta Stroke Program Early CT Score; NIHSS, National Institutes of Health Stroke Scale; CSC, comprehensive stroke center; IV, intravenous; M1/M2,

middle cerebral artery segment; ICA, internal carotid artery; mTICI, modified treatment in cerebral ischemia scale.