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Posttreatment Ischemic Lesion Evolution Is Associated With Reduced Favorable Functional Outcome in Patients With Stroke

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BACKGROUND AND PURPOSE: Ischemic lesion volume can increase even 24 hours after onset of an acute ischemic stroke. In this study, we investigated the association of lesion evolution with functional outcome and the influence of successful recanalization on this association.

METHODS: We included patients from the MR CLEAN trial (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) who received good quality noncontrast CT images 24 hours and 1 week after stroke onset. The ischemic lesion delineations included infarct, edema, and hemorrhagic transformation. Lesion evolution was defined as the difference between the volumes measured on the 1-week and 24-hour noncontrast CTs. The association of lesion evolution with functional outcome was evaluated using unadjusted and adjusted logistic regression. Adjustments were made for baseline, clinical, and imaging parameters that were associated $P<0.10$) in univariate analysis with favorable functional outcome, defined as modified Rankin Scale score of ≤2. Interaction analysis was performed to evaluate the influence of successful recanalization, defined as modified Arterial Occlusion Lesion score of 3 points, on this association.

RESULTS: Of the 226 patients who were included, 69 (31%) patients achieved the favorable functional outcome. Median lesion evolution was 22 (interquartile range, 10–45) mL. Lesion evolution was significantly inversely correlated with favourable functional outcome: unadjusted odds ratio, 0.76 (95% CI, 0.66–0.86; per 10 mL of lesion evolution; $P<0.01$) and adjusted odds ratio: 0.85 (95% CI, 0.72–0.97; per 10 mL of lesion evolution; $P=0.03$). There was no significant interaction of successful recanalization on the association of lesion evolution and favorable functional outcome (odds ratio, 1.01 [95% CI, 0.77–1.36]; $P=0.94$).

CONCLUSIONS: In our population, subacute ischemic lesion evolution is associated with unfavorable functional outcome. This study suggests that even 24 hours after onset of stroke, deterioration of the brain continues, which has a negative effect on functional outcome. This finding may warrant additional treatment in the subacute phase.

GRAPHIC ABSTRACT: An online graphic abstract is available for this article.

Key Words: edema ■ infarction ■ inflammation ■ ischemia ■ neuroprotection ■ outcome

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Nonstandard Abbreviations and Acronyms

aOR	adjusted odds ratio
ASPECTS	Alberta Stroke Program Early CT Score
CT	computed tomography
IQR	interquartile range
MR CLEAN	Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands
NCCT	noncontrast CT
OR	odds ratio

Recanalization of the occluded artery by intravenous or endovascular treatment aims to quickly restore the blood supply to the ischemic brain tissue and halt the lesion expansion during an acute ischemic stroke due to a large vessel occlusion. Previous studies employing computed tomography (CT) or magnetic resonance imaging have shown that the ischemic lesion does not stabilize but in fact, continues to evolve after treatment.[1–3] There may be ongoing damage after the initial ischemic insult due to the cascade of various pathophysiological processes like excitotoxicity, oxidative stress, breakdown of the blood-brain barrier, microvascular damage, and inflammation.[2,4] However, the relationship between posttreatment ischemic lesion evolution in the subacute period and functional outcome is not known. Elucidating this relationship can help to determine whether exploration of neuroprotective treatments targeted towards reducing reperfusion injury, and true infarct progression is a worthwhile endeavor.

The aim of this study was to characterize the relationship between ischemic lesion evolution in the subacute period between 24 hours and 1 week after stroke onset and functional outcome after 90 days in patients with acute ischemic stroke due to a large vessel occlusion. Furthermore, the influence of successful recanalization on this relationship was assessed.

METHODS

Patient Selection

In this study, we used data of patients included in the MR CLEAN trial (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands).[5] Information regarding inclusion and exclusion criterion is described in the study protocol of the trial. Patients with an acute ischemic stroke due to a large vessel occlusion in the anterior circulation, who were at least 18 years old and in whom endovascular treatment could be started within 6 hours of symptom onset were randomized between best medical management including intravenous treatment with alteplase alone and best medical management including intravenous treatment with alteplase and endovascular treatment. In this study, we analyzed patients who received noncontrast CT (NCCT) imaging 24 hours and 1 week after stroke onset. We excluded patients who underwent a decompressive surgery or have a large diffused hemorrhage. We additionally excluded patients whose images were incomplete or have artifacts due to movement or partial volume effects or technical imaging errors. Details of patient inclusion in current study have been reported previously and is included in the Data Supplement.[1] The MR CLEAN trial was conducted with the approval of a central medical ethics committee and the research board of each participating center. Patients or their legal representatives provided written informed consent. The data that support the findings of this study are available from the corresponding author upon reasonable request. We have followed the STROBE guidelines and a completed STROBE checklist is provided in the Data Supplement.

Imaging Assessment

The protocol for assessment of the follow-up NCCT images has been presented earlier.[1] In summary, relevant ischemic lesions were identified as hypodense regions on NCCT scans obtained after 24 hours and 1 week of stroke onset. Lesions on the 24-hour NCCT scan were manually delineated by trained observers (P. Konduri and A. Bucker) using a fixed center-level setting of 35 Hounsfield units and window width of 30 Hounsfield units to prevent variations in delineations on ITK-Snap software.[6] Lesion delineations included edema/brain swelling that extended into the contralateral hemisphere or resulted in effacement of ventricles or sulci and hyper-densities in or close to the hypodense brain regions that were identified as hemorrhage. Chronic ipsilateral lesions characterized as regions that demonstrated fluid attenuation, with distinct borders and volume loss; were excluded in the lesion assessment.[1] Observers were blinded for clinical data apart from symptomatic side. Lesions on the 1-week NCCT scan were automatically segmented using a validated in-house software.[7] The segmentations were evaluated and corrected where required, by one of 2 experienced neuroradiologists who were also blinded to clinical data (C. Majoie and J. Bot) on ITK-Snap Software.[6] Lesion volumes were the product of the number of voxels in the segmentation and the corresponding voxel size. Lesion evolution was calculated as the difference between the 1-week and 24-hour lesion volume.

The hemorrhagic region was manually delineated by trained observers by identifying hyperdense regions within the 24-hour (P. Konduri) and 1-week (P. Konduri and K. van Kranendonk) NCCT lesions of the patients who suffered from hemorrhagic transformation as assessed on the 1-week NCCT scans by the imaging core lab. Subacute hemorrhagic evolution was defined as the difference between the hemorrhagic volume at 1 week and 24 hours.

Nonhemorrhagic (infarct and edema) volume at each time point were quantified using the volume of the hypodense areas within the lesion, excluding the hemorrhage. Nonhemorrhagic evolution was defined as the difference between the nonhemorrhagic volume at 1 week and 24 hours.

Radiological parameters like ASPECTS (Alberta Stroke Program Early CT Score),[8] Collateral Score,[9] modified Arterial Occlusion Lesion score,[10] were graded by a central blinded

core lab on the baseline NCCT, baseline CT angiography and 24-hour follow-up CT angiography scans, respectively. Due of the difficulty of quantifying lesion volume on the baseline NCCT scan, in this study, we used ASPECTS as an indicator of the extent of lesion of the baseline lesion. Details of these parameters have been provided in the Data Supplement.

Statistical Analysis

In this study, the primary outcome was a favorable functional outcome, defined as modified Rankin Scale score 0 to 2 and the secondary outcome was modified Rankin Scale on the ordinal scale. To evaluate the association of lesion evolution with favorable functional outcome, univariable and multivariable logistic regression after adjusting for confounders was performed. Confounders were identified as baseline, clinical, imaging, and treatment characteristics that were associated with favorable functional outcome at the significance level of $P<0.1$.

To identify the influence of successful recanalization (modified Arterial Occlusion Lesion, 3 points assessed on the 24-hour follow-up CT angiography scan) on the relation between lesion evolution and favourable functional outcome, we performed unadjusted interaction analysis by introducing a multiplicative term. We further divided the population into subgroups of successful and unsuccessful treatment based on recanalization status. We performed logistic regression before and after adjusting for confounders to assess the association between lesion evolution and functional outcome in the 2 subgroups.

We repeated the above-mentioned analysis with modified Rankin Scale on the ordinal scale as the outcome variable using shift analysis (1-step difference towards improved functional outcome) after assuming proportional odds between different outcome levels.

Secondary analysis to distinguish the effect of complete lesion, nonhemorrhagic, and hemorrhagic evolution on favorable functional outcome was performed by assessing the association of each of the lesion characteristics with favorable functional outcome using univariable and multivariable binary logistic regression after adjusting for confounders. The R^2 and Akaike Information Criterion of the 3 models were compared.

Patients with missing values were excluded from the analysis containing those variables. Statistical analyses were performed using SPSS (IBM SPSS Statistics, version 26, 2019) and R (Version 4.0.2 [2020-06-22]) using RStudio (Version 1.2.5033 2009-2019 RStudio, Inc) packages: MASS, dplyr, reshape, ggeffects, foreign, ggplot2, DescTools, ggpubr. A $P\leq0.05$ was considered statistically significant.

RESULTS

Patient Characteristics

Out of the 500 MR CLEAN trial patients, 226 were included in this study. The median age was 67 (interquartile range [IQR], 57–76) years, and 58% of the population was male. Nineteen (8.4%) patients had a previous ischemic stroke, and 63 (28%) patients were using antiplatelet drugs. The median baseline National Institutes of Health Stroke Scale and ASPECTS score were 17 (IQR, 13–21) and 9 (IQR, 8–10), respectively. A 106 (47%) patients underwent endovascular treatment, and the median time between stroke onset to randomization was 196 (IQR, 151–262) minutes. Baseline characteristics of the patients are given in Table 1.

One hundred ten (49%) patients had successful recanalization, and 69 (31%) patients achieved favorable functional outcome after 90 days. Information on recanalization status was missing for 23 (10%) patients. An example of lesion segmentation on NCCT scans obtained at 24-hour and 1-week after randomization is shown in Figure 1. Median lesion volumes measured at 24 hours and 1 week were 43 (IQR, 21–99) mL and 79 (IQR, 33–140) mL, respectively. Median lesion evolution of the entire study population was an increase of 22 (IQR, 10–45) mL. Boxplots to visualize differences in lesion characteristics between patients with successful and unsuccessful treatment and with the favorable and unfavorable functional outcome are given in Figures 2 and 3. Furthermore, boxplots to visualize differences in nonhemorrhagic and hemorrhage volumes between patients with and without favorable functional outcome are provided in the Data Supplement along with a table comparing all lesions characteristics between the subgroups based on successful treatment and favorable functional outcome.

Regression Analysis

Results of the univariable logistic regression analysis of association of the baseline, clinical, imaging treatment, and lesion characteristics with functional outcome are provided in the Data Supplement. Lesion volume increase was negatively associated with favorable functional outcome in univariable logistic regression analysis (odds ratio [OR], 0.76 [95% CI, 0.66–0.86] per 10 mL lesion growth; $P<0.01$). After adjusting for confounders, lesion evolution remained inversely associated with favorable functional outcome (adjusted OR [aOR], 0.85 [95% CI, 0.72–0.97]; $P=0.03$; details are provided in Table 2).

Similarly, shift analysis showed that lesion evolution was inversely associated with functional outcome on the ordinal scale before (common OR, 0.85 [95% CI, 0.80–0.91] per 10 mL lesion growth; $P<0.01$) and after adjusting for confounders (common aOR, 0.88 [95% CI, 0.83–0.94] per 10 mL lesion growth; $P<0.01$; please the Data Supplement).

Influence of Successful Recanalization

The interaction analysis showed no statistically significant effect of successful recanalization (24-hour arterial recanalization) on the association of lesion evolution with favorable functional outcome (OR, 1.01 [95% CI, 0.77–1.36]; $P=0.94$)

Furthermore, in the subgroup with successful recanalization, lesion growth was significantly inversely

Table 1. Baseline Characteristics of Patients Included in the Study Along With a Comparison Between Those With and Without Successful Recanalization

Variable		Study population (n=226)	Unsuccessful recanalization (n=93)	Successful recanalization (n=110)	*P* value
Age, y		67 (57–76)	63 (54–74)	67 (57–76)	0.18
Male sex		132 (58%)	61 (66%)	62 (56%)	0.23
Previous medical history					
Previous ischemic stroke		19 (8.4%)	8 (8.6%)	11 (10%)	0.92
Myocardial infarction		27 (12%)	14 (15%)	11 (10%)	0.38
Diabetes		25 (11%)	12 (13%)	8 (7.3%)	0.27
Hypertension		113 (50%)	44 (47%)	54 (49%)	0.91
Atrial fibrillation		64 (28%)	22 (24%)	32 (29%)	0.48
Hypercholesterolemia		54 (24%)	21 (23%)	26 (24%)	0.99
Current smoking		66 (29%)	30 (32%)	34 (31%)	0.96
Medication					
Antiplatelet drugs		63 (28%)	26 (28%)	30 (27%)	1.00
Coumarins		15 (6.6%)	3 (3.2%)	8 (7.3%)	0.34
Statins		67 (30%)	26 (28%)	33 (30%)	0.87
Antihypertensive drugs		114 (50%)	44 (47%)	56 (51%)	0.71
Clinical parameters					
Systolic blood pressure, mm Hg		141 (130–160)	140 (130–160)	140 (127–156)	0.93
Clinical hemisphere side left		123 (54%)	52 (56%)	57 (52%)	0.66
Prestroke modified Rankin Scale score (0–2)		216 (96%)	90 (97%)	104 (95%)	0.51
Baseline NIHSS		17 (13–21)	17 (13–21)	17 (13–21)	0.91
Radiological parameters					
Proximal occlusion (ICA or ICA-T)		63 (28%)	28 (30%)	28 (25%)	0.56
ASPECTS score		9 (8–10)	9 (8–10)	9 (8–10)	0.43
Missing		2 (0.88%)			
Collateral score	Absent	6 (2.7%)	2 (2.2%)	2 (1.8%)	0.60
	Filling <50% of the occluded area	63 (28%)	22 (24%)	35 (32%)	
	Filling >50% and <100% of the occluded area	84 (38%)	38 (41%)	39 (36%)	
	Filling 100% of the occluded area	71 (32%)	31 (33%)	33 (30%)	
	Missing	2 (0.88%)			
Treatment characteristics					
Received intravenous thrombolysis		204 (90%)	87 (94%)	96 (87%)	0.21
Allocated to EVT		106 (47%)	18 (19%)	78 (71%)	<0.01*
Time to randomization, min		196 (151–262)	210 (153–277)	186 (146–247)	0.06
Missing		3 (1.3%)			

All data are displayed as median (interquartile range) or number (percentage of population). Mann-Whitney *U* test and χ^2/Fischer exact tests were performed to compare continuous and binary/categorical variables between the successful (mAOL=3) and unsuccessful recanalization (mAOL ≤2) subgroups appropriately. ASPECTS indicates Alberta Stroke Program Early CT Score; EVT, endovascular treatment; ICA, intracranial carotid artery; ICA-T, intracranial carotid artery-T junction; and NIHSS, National Institutes of Health Stroke Scale.

*$P \leq 0.01$.

associated with favorable functional outcome without (OR, 0.78 [95% CI, 0.65–0.91] per 10 mL lesion growth; $P=0.01$) and with adjusting for confounders (aOR, 0.80 [95% CI, 0.65–0.95] per 10 mL lesion growth; $P=0.02$). Details of the subgroup analysis are given in Table 2.

In the subgroup of patients with unsuccessful recanalization, the association of lesion evolution and favorable outcome was only statistically significant in the univariable logistic regression (OR, 0.77 [95% CI, 0.60–0.95] per 10 mL; $P=0.03$). Statistical significance was lost after adjustments in the multivariable logistic regression (aOR, 1.05 [0.78–1.38] per 10 mL; $P=0.72$; details are given in Table 2).

Similarly, shift analysis showed no statistically significant interaction between lesion evolution and

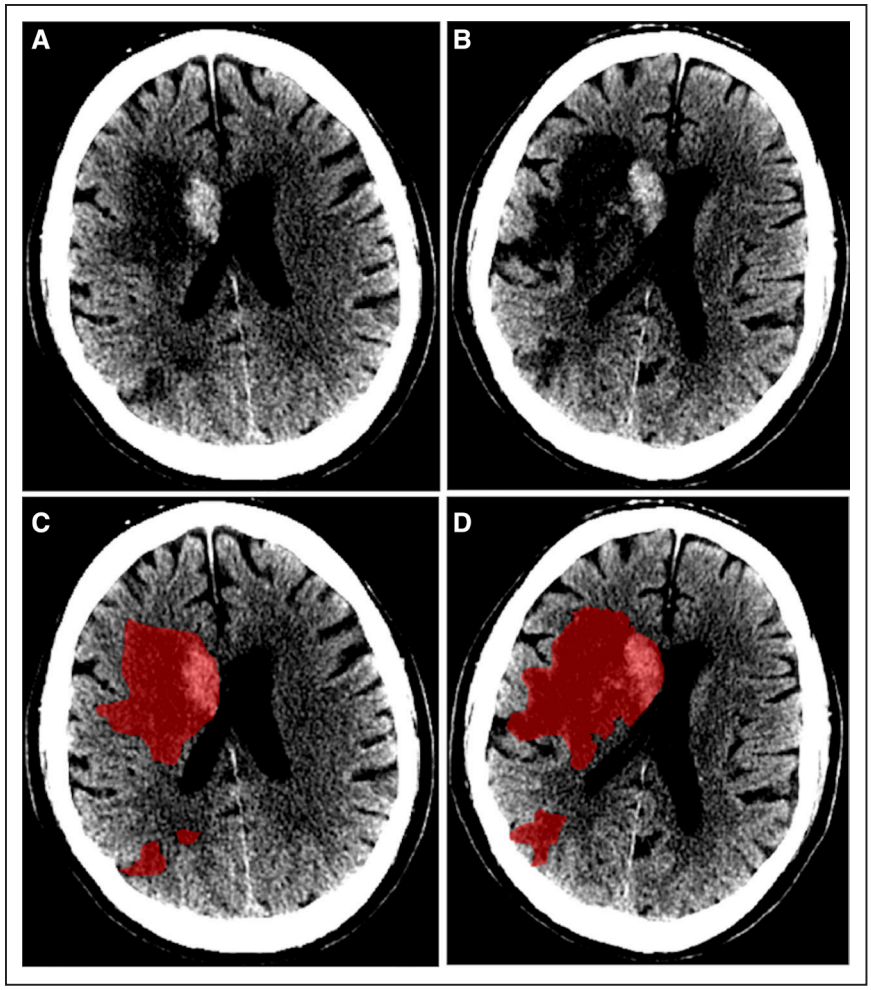

Figure 1. Example of ischemic lesion segmentation (represented in red). Noncontrast CT scans and segmentation of ischemic lesion obtained after 24 h (**A**) and (**B**) and 1 wk (**C**) and (**D**) of stroke onset.

successful recanalization on functional outcome (OR, 1.05 [95% CI, 0.92–1.20]; *P*=0.44). Lesion growth was significantly inversely associated with functional outcome without and with adjustment for confounders in unsuccessful and successful recanalization subgroups with comparable common ORs (details are available in the Data Supplement).

Comparison of the Effect of Total Lesion, Nonhemorrhagic, and Hemorrhagic Evolution on Functional Outcome

Both nonhemorrhagic growth (OR, 0.77 [95% CI, 0.67–0.87] per 10 mL; *P*<0.01) and hemorrhagic growth (OR, 0.80 [95% CI, 0.65–0.94] per mL; *P*=0.02) were associated with reduced functional outcome in univariate logistic regression. After adjusting for confounders, nonhemorrhagic growth (aOR, 0.86 [95% CI, 0.74–0.98] per 10 mL; *P*=0.05) showed a significant trend and hemorrhagic growth (aOR, 0.71 [95% CI, 0.49–1.02] per mL; *P*=0.06) showed a similar trend. The R^2 of the multivariable models with total lesion (0.32), nonhemorrhagic (0.32), and hemorrhagic growth (0.33) were comparable. The Akaike Information Criterion of the multivariable model with hemorrhagic evolution (203) was slightly smaller compared with the multivariable model with lesion (204) and nonhemorrhagic evolution (205; details of the binary logistic regression are available in the Data Supplement).

DISCUSSION

In this study, we showed that posttreatment ischemic lesion evolution in the subacute period (>24 hours to 1 week) after stroke onset is associated with unfavorable outcome. Successful treatment results in smaller lesion growth but, does not appear to influence the association of lesion evolution with unfavorable functional outcome.

The relationship between lesion evolution in the time between before and after treatment with unfavorable functional outcome is well established in literature.[11–14] However, studies have also shown that posttreatment lesion evolution is a common phenomenon.[1,2,15] In line with our results, Federau et al[2] also observed that subacute lesion evolution (between 12 hours and 5 days) evaluated on FLAIR imaging is lower in patients with successful treatment, defined as reperfusion of at least 90% of the baseline lesion assessed on posttreatment magnetic

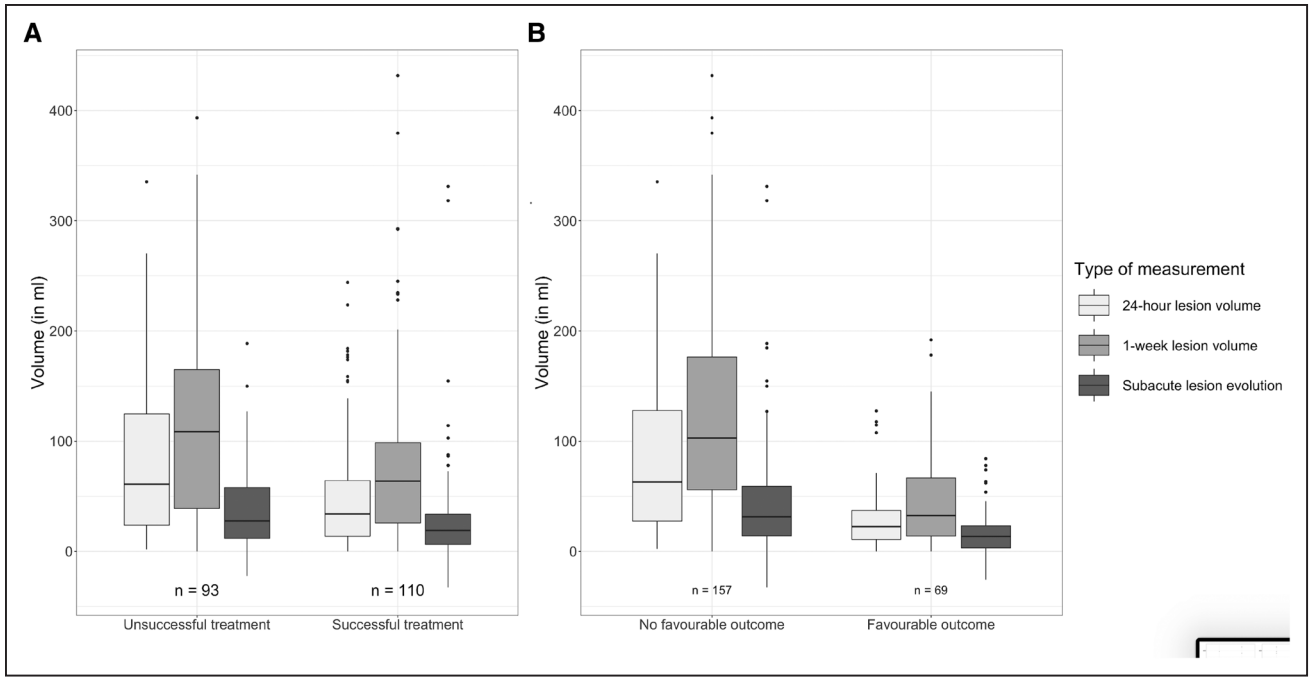

Figure 2. Comparison of subacute lesion characteristics in patient subgroups based on treatment success (modified arterial occlusion lesion [mAOL]: 3) and favorable functional outcome (modified Rankin Scale score: 0–2) after 90 d of stroke onset. **A**, Lesion evolution in patients with successful treatment was significantly lower than those with unsuccessful treatment (P=0.02). **B**, Similarly, lesion evolution in patients with favorable functional outcome was significantly lower than those with the unfavorable functional outcome (P<0.01).

resonance perfusion images. In contrast, Sah et al[15] did not find significant differences in lesion evolution in patients who did and did not achieve successful reperfusion or recanalization. This could be plausible due to their relatively small study population and because they evaluated early lesion evolution between 5 hours and 24 hours after treatment.[15] Furthermore, the baseline, imaging and treatment characteristics that have been identified as confounders in this study namely, age, systolic blood pressure, National Institutes of Health Stroke Scale, proximal occlusion, collateral score, and treatment with IAT are known to be predictors of functional outcome.[5,16]

In the same population as analyzed in this study, Bucker et al[1] showed that the value of the 24-hour lesion

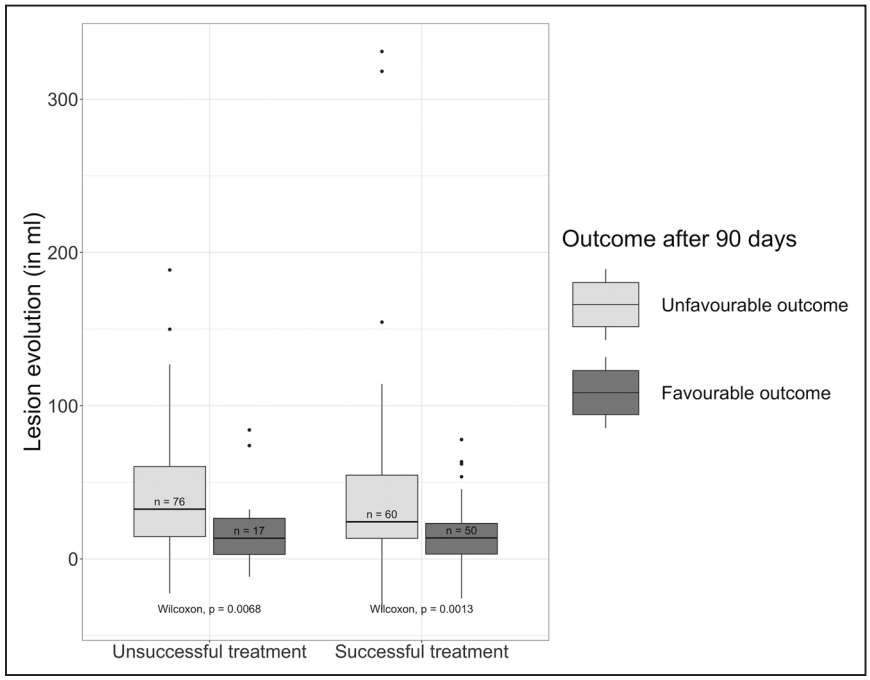

Figure 3. Comparison of lesion evolution in patients with and without favorable outcome for (un-) successful treatment outcome.

Table 2. Multivariable Binary Logistic Regression With Dichotomized Modified Rankin Scale Score (0–2) After 90 Days of Stroke Onset of 226 Patients

Variable	Odds ratio (95% CI)	*P* value	Successful recanalization (mAOL=3)		Unsuccessful recanalization (mAOL ≤2)	
			Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Lesion evolution*	0.85 (0.72–0.97)	0.03†	0.80 (0.65–0.95)	0.02†	1.05 (0.78–1.38)	0.72
24-h lesion volume*	0.79 (0.70–0.88)	<0.01‡	0.82 (0.71–0.93)	<0.01‡	0.67 (0.45–0.87)	0.01‡
Age	0.96 (0.93–0.98)	<0.01‡	0.95 (0.91–0.99)	0.02†	0.95 (0.89–1.00)	0.04†
Systolic blood pressure	0.99 (0.97–1.01)	0.18	0.99 (0.97–1.01)	0.37	0.98 (0.95–1.02)	0.28
Baseline NIHSS	0.94 (0.88–1.01)	0.08	0.97 (0.88–1.06)	0.51	0.86 (0.74–0.98)	0.03†
Proximal occlusion	0.33 (0.13–0.79)	0.02†	0.41 (0.12–1.25)	0.13	0.09 (0–0.64)	0.04†
Collaterals	0.80 (0.47–1.34)	0.40	0.98 (0.51–1.84)	0.95	0.45 (0.12–1.43)	0.20
EVT	2.00 (0.97–4.20)	0.06	1.23 (0.43–3.55)	0.69	1.47 (0.25–8.53)	0.66

EVT indicates endovascular treatment; and NIHSS, National Institutes of Health Stroke Scale.
*Analysis done per 10 mL of lesion volume.
†$P \leq 0.05$, ‡$P \leq 0.01$.

volume is comparable with that of the 1-week lesion volume in predicting functional outcome. That finding may appear to be in contrast to our result. However, since lesion volume only explains a limited part (about 14% as previously presented[17]) of the functional outcome, it is plausible that the difference in the 24-hour versus 1-week volumes in the multivariable models might have had a too small effect to make it significant. Their approach may not have had the power to show any difference owing also to the strong association between the 24-hour and 1-week volumes. Hence, in this study, we directly investigated the association of patient specific subacute lesion evolution with functional outcome.

Our finding that subacute lesion evolution is significantly associated with unfavorable outcome can be attributed to both true infarct progression and development of edema. True infarct progression could result from the expansion of the lesion to new vascular territories and outside the initial hypodense territories. True infarct progression is more plausible in patients that do not achieve successful recanalization.[2] In the absence of reperfusion, tissue may be less likely to swell, instead the cells within the tissue die due to cytotoxic edema that results from osmotic gradients across the intracellular and extra-cellular spaces.[18] Federau et al[2] have shown greater expansion of the lesion in patients who do not achieve successful reperfusion, indicating that in these patients the lesion may be propagating into persistent at-risk regions. Furthermore, ischemia and postischemic reperfusion can both result in the impairment of the capillaries that form the blood-brain barrier, causing edema, and swelling of tissue. Simard et al showed that in patients who achieve successful reperfusion, the addition of new hematologic constituents to ischemic regions can impair the integrity of the capillaries that form the blood-brain barrier, resulting in edema, swelling, and further ischemia. Accumulation of edema increases the tissue volume and pressure, causing it to apply a mechanical force on the surrounding tissue, increasing the tissue pressure and propagating ischemia and edema. Moreover, the capillary integrity in regions of persistent ischemia and edema, especially when reperfused, is further compromised and can lead to hemorrhagic transformation which is known to impair functional outcome.[18] Our finding that hemorrhagic evolution effects favorable outcome supports that finding. We observed that treatment success does not influence the association of subacute lesion evolution with unfavorable outcome. This is, however, not observed in the multivariable binary logistic regression model of the subgroup of unsuccessful treatment, probably due to the limited number of cases with favorable functional outcome or due to presence of outliers. Our finding suggests that lesion evolution continues despite recanalization, probably owing to no-reflow phenomenon, thrombus fragmentation, or formation of microvascular emboli.[19] Since in this study, successful treatment was defined using recanalization status assessed on the 24-hour CT angiography scans and not the reperfusion status assessed on posttreatment digital subtraction angiography scans, these effects have not been accounted for.

The finding that lesion evolution is also associated with unfavorable functional outcome (although, with lower strength compared with the 24-hour lesion volume) suggests that restricting the cascade of events that causes lesion evolution can be beneficial even after 24 hours of stroke onset. Potential treatment targets include protecting against damage to capillaries that form the blood-brain barrier due to reperfusion injury, addressing selective neuronal loss within the lesion, and salvaging late-persisting and at-risk tissue surrounding the lesion. Furthermore, recent magnetic resonance imaging-based studies that found structural changes in white matter regions remote but connected to the core. Due to the lowered collateral supply of the white matter compared with the gray matter, reducing inflammatory responses to ischemia within the white matter could also be a potential treatment target.[4,19–21]

This study has limitations. Including patients who received both 24-hour and 1-week NCCT scans could have introduced a selection bias. However, Bucker et al showed comparable baseline, functional outcome, and adverse events between the entire MR CLEAN population and those included in this study. Furthermore, the 1-week NCCT scan was performed within a time frame of ≈3 to 9 days.[5] As the impact of ionic and vasogenic edema generally peaks between 2 and 5 days,[1,22] further studies evaluating the effects of variability in scan-times are required to mitigate any biases that could have been so incurred. Studies with MR FLAIR and DWI, which are more accurate imaging modalities for distinguishing edema and infarct, are needed to further assess the association of post-treatment subacute lesion evolution and functional outcome. Accounting for expansion of lesion into new cortical regions can aid in identifying true infarct progression. During lesion delineation, all hypodensities in the affected hemisphere were considered, irrespective of the downstream territory of the occluded artery. This could have led to the inclusion of possible secondary infarcts. Comparison with the NCCT scan at baseline may reduce this bias in lesion size. However, all lesions in the contralateral hemisphere and old lesions in the ipsilateral hemisphere were excluded. Owing to the difficulty in delineating lesions on early follow-up scans, future studies assessing the interobserver and intraobserver variability are also required. Lastly, digital subtraction angiography images are mostly used to assess reperfusion status to determine treatment success. But these images are only available for patients randomized to the intervention arm. Hence, in this study modified Arterial Occlusion Lesion assessed on 24-hour follow-up CT angiography scan was used as the score to analyze treatment success. Future studies assessing the impact of early successful reperfusion on the association of lesion evolution and functional outcome can aid in providing more insight into our findings.

CONCLUSIONS

Ischemic lesions continue to evolve and grow in the subacute period after treatment and this evolution is associated with unfavorable functional outcome. Secondary treatments that mitigate the effects of further ischemia and edema formation may thus, be useful even 24 hours after onset of symptoms. Further research directed towards understanding the causes of subacute lesion evolution may aid in developing secondary treatment approaches.

ARTICLE INFORMATION

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Supplemental Materials

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