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Impact of leukoaraiosis severity on the association of time to successful reperfusion with 90-day functional outcome after large vessel occlusion stroke

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Abstract

Introduction: The chance for a favorable outcome after mechanical thrombectomy (MT) for large vessel occlusion stroke decreases with the symptom onset-to-reperfusion time (OTR). Patients with severe leukoaraiosis are at increased risk for a poor outcome after MT. However, whether leukoaraiosis modulates to the association between OTR and 90-day functional outcome is uncertain.

Methods: We retrospectively analyzed 144 consecutive patients with successful (TICI 2b/3) MT for anterior circulation large vessel occlusion within 24 hours from OTR between January 2012 to November 2016. Leukoaraiosis was dichotomized to absent-to-mild (van Swieten scale score 0–2) versus moderate-to-severe (3–4) as assessed on admission head CT. Multiple linear, logistic, and ordinal regression analyses were used to determine the association between

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Ethical approval: This study was reviewed and approved by our Institutional Review Board and procedures followed were in accordance with institutional guidelines and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Health Insurance Portability and Accountability Act (HIPAA) waiver of authorization was granted. We adhere to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines (www.strobe-statement.org).

leukoaraiosis, OTR and 90-day modified Rankin Scale (mRS) score, after adjustment for pertinent covariates.

Results: Leukoaraiosis was independently associated with OTR on multivariable linear regression ($p=0.003$). The association between OTR and 90-day outcome depended on the degree of preexisting leukoaraiosis burden as shown by a significant leukoaraiosis-by-OTR interaction on multivariable logistic regression (OR 0.76, 95%-CI 0.58–0.98, $p=0.037$) and multivariable ordinal regression (OR 0.87, 95%-CI 0.78–0.97, $p=0.011$).

Conclusions: Pre-existing leukoaraiosis is associated with the 90-day functional outcome after successful reperfusion and impacts the association between the OTR and 90-day mRS among patients undergoing MT. Patients with high leukoaraiosis burden need to present earlier than patients with low leukoaraiosis burden for a similar favorable outcome. Pending confirmation, these results may have important implications for optimizing patient selection for acute stroke therapies.

Keywords

ASPECTS; collaterals; endovascular thrombectomy; leukoaraiosis; large vessel occlusion; small vessel disease; recanalization

Introduction

Several prospective randomized clinical trials have demonstrated overwhelming benefit of mechanical thrombectomy (MT) over best medical therapy alone to improve functional outcome after large vessel occlusion (LVO) ischemic stroke in patients treated within 6 to 12 hours of symptom onset [1–6] and even up to 24 hours from last known well by selecting patients with slow infarct progression [7, 8]. Although treatment efficacy generally declines with longer time from symptom onset to successful reperfusion [9], the time window to achieve a good functional outcome after successful reperfusion differs substantially between patients depending on the extent of the initial ischemic infarct and the progression rate of tissue at risk (i.e., ischemic penumbra) towards infarction. The beneficial effect of MT is related to its very high success rate for achieving substantial reperfusion. Hence, to further improve patient selection for safe and efficacious MT utilization it is critical to understand factors that adversely outcome despite successful reperfusion of the ischemic brain tissue because the lack of improvement in these patients remains only partially understood. Key factor in this respect are the intrinsic capacity of the brain to withstand ischemia and its functional reserve to compensate for the sustained ischemic injury. Frequently, advanced age is used as a surrogate marker for brain reserve.

For example, the recent DAWN (DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo) trial stratified patient eligibility for study inclusion by using more stringent imaging criteria for subjects aged 80 or older as these patients may be less likely to achieve a favorable outcome. However, while this approach is feasible and can be easily implemented in clinical use, the rationale for choosing a specific age cut off is not well established [8, 10–12, 7, 13–15]. Accordingly, it would be important to define factors that define the biological brain age

as a surrogate marker of the brain's ischemic tolerance and reserve to further improve patient selection for MT [9, 16].

The degree of preexisting white matter injury or leukoaraiosis is a particularly promising neuroimaging marker for several reasons: It is (i) readily assessable on routine head CT, (ii) common among ischemic stroke patients and the elderly, (iii) has been repeatedly shown to relate to a greater extent of the acute infarct and its expansion, (iv) predicts a poor outcome in patients with LVO stroke, and (v) has been shown to mediate the age-related association with greater vulnerability to brain ischemia [1, 17–27]. Given the purported adverse impact of leukoaraiosis with the intrinsic capacity of the brain to withstand ischemia it would be expected that patients with leukoaraiosis have a more rapid progression of their ischemic infarct. However, whether leukoaraiosis truly modulates the relationship of the symptom onset-to-reperfusion time (OTR) with the functional outcome is uncertain [20, 18, 17, 28, 27]. Understanding this association is important because the time to reperfusion (both from symptom onset and from the time a patient is selected for treatment) is a key variable determining treatment success of MT [9, 29, 30].

We therefore sought to determine whether the degree of pre-existing leukoaraiosis relates to the 90 day functional outcome in patients with successful MT. Additionally, we sought to determine whether leukoaraiosis affects the association between the OTR and functional outcome. We hypothesized that (1) a greater leukoaraiosis burden is associated with a worse 90-day modified Rankin scale (mRS) score independent of the chronological age and that (2) successful reperfusion needs to occur significantly earlier in patients with severe leukoaraiosis than in individuals with no or minimal leukoaraiosis to achieve a similar outcome. To test this hypothesis, we studied a cohort of patients that had substantial reperfusion within 24 hours from symptom onset after MT for LVO stroke in the anterior circulation. To obtain results that can be extrapolated to contemporaneous clinical trials and practice, we performed our analysis in subjects that were treated with stent-retrievers [1–6, 8, 7] and we assessed the leukoaraiosis burden on non-contrast head CT, which remains the modality of choice for hyperacute LVO stroke imaging [31, 32].

Methods

Study Population

We retrospectively analyzed consecutive patients with acute anterior circulation LVO that were prospectively included in our local stroke registry between January 2012 and November 2016. Data abstraction and analyses were conducted between February 2017 to May 2018. During the study period, patients were generally considered eligible for MT in the anterior circulation if they had an LVO associated with significant neurological deficit (NIHSS ≥ 6), small infarct burden on pre-procedural non-contrast head CT (ASPECTS ≥ 6), good collaterals on admission CTA, and patient presentation within 24 hours from symptom onset. In select patients (n=50), CT perfusion was used to aid decision making at the discretion of the treating physicians. The final decision for endovascular therapy was reached by consensus between the neurointerventional and stroke teams.

Information on patient age, sex, laboratory data (admission glucose, INR, platelet count), admission blood pressure, vascular risk factors, pre-admission medications, and stroke etiology (using the Trial of Org 10172 in Acute Stroke Treatment [TOAST] classification [33]) was collected on all patients after completion of diagnostic evaluation (see Table 1 for details). NIHSS scores were assessed at the time of presentation by members of the stroke team certified in NIHSS. The modified Rankin Scale (mRS) was assessed at admission (pre-stroke mRS) and at 90 days by a stroke-trained physician or stroke study nurse certified in mRS *via* in-person or phone interview using a simplified mRS questionnaire [21, 34]. When the 90-day mRS was unavailable, the same observers reconstructed the score from the case description in the medical records, according to the mRS criteria [21]. In one patient that was lost to follow up we imputed the 90-day mRS by carrying forward the discharge mRS. We defined a good 90-day functional outcome as mRS of 0–2, or return to baseline (the latter was applied to 8 patients with a pre-stroke mRS of 3 and one patient with mRS of 4 who was non-ambulatory due to recent lower extremity fracture). Additionally, to account for pre-existing functional deficits captured by the mRS, we calculated the degree of mRS-worsening as follows: $\text{mRS-worsening} = 90\text{-day mRS} - \text{preadmission mRS}$ (whereby lower numbers indicate better outcomes).

Neuroimaging protocol

All patients had a non-contrast CT of the head as well as CT angiogram (CTA) of the head and neck performed on presentation to the emergency room. All CT sequences were obtained on a 64-row detector scanner (Philips Medical Systems, Best, the Netherlands). CT was performed in a non-helical mode at 120 KvP and 200 mA with data reconstruction at 5 mm axial slices. CTA was performed using 64×0.625 mm detector configuration with a pitch of 0.673 from the arch of aorta to the vertex using 120KvP, 300mA, and 0.5 s rotation time. Patients received 60–80 mL of Isovue 370 (Bracco Diagnostics, Princeton, NJ) in the antecubital vein at a rate of 4 mL/s through a power injector followed by 40 mL saline. 3D orthogonal MIP images were created in 3 planes.

Digital Subtraction Angiography

All endovascular procedures were performed by neurointerventionalists using a biplane angiography unit with 3D rotational angiography capability (Allura Xper FD20/20; Philips Medical Systems, Best, the Netherlands) with patients under conscious sedation or general anesthesia. Endovascular access was obtained by a standard transfemoral approach.

Image review and analysis

CT and CTA were reviewed independently by experienced readers blinded to both clinical data and any follow-up scans. Variable window width and center-level settings were used for optimal ischemic hypoattenuation detection with CT and CTA [21, 22]. Because CT perfusion was not done systematically in all patients we did not include analyses on pre-procedural perfusion status in this study.

Leukoaraiosis was retrospectively defined by two experienced readers as supratentorial white matter hypoattenuation on admission non-contrast head CT according to the Standards for Reporting Vascular changes on nEuroimaging (STRIVE) criteria [35].

Leukoaraiosis severity was graded on the van Swieten scale (VSS) with summing of the score from the anterior and posterior regions to provide a total score ranging from 0–4 as previously described in detail [20, 36, 21]. Leukoaraiosis was separately assessed in each hemisphere but only the score from the non-ischemic hemisphere was considered after unblinding [37]. To avoid classification bias and to minimize inter-rater variability [21], we dichotomized the degree of leukoaraiosis to absent-to-mild (VSS 0–2) versus moderate-to-severe (VSS 3–4) for statistical purposes. Using this approach, we previously demonstrated almost perfect inter-observer and intra-observer agreement for classifying leukoaraiosis to absent-to-mild versus moderate-to-severe (Free marginal kappa $\kappa=0.91$ and $\kappa=0.89$, respectively) [20].

We graded collateral status separately on admission CTA and catheter angiography. However, because no multiphase CTA was obtained during the study period we exclusively report angiography-based collateral flow graded from 0 (no collaterals) to 4 (rapid and complete collateral filling) before MT [38] to minimize potential bias related to differences in contrast bolus timing and collateral changes between the time from presentation to the first image run. We dichotomized the presence of collaterals to good (grade 3–4) versus poor (grade 0–2) for statistical purposes. Final recanalization was assessed according to the TIC1 classification as previously defined [38]. All angiographic analyses were conducted by a board certified neurointerventional radiologist (A.S.P.) masked to clinical data. Weighted kappa statistics were used to determine the degree of agreement in collateral grading and TIC1 scoring in 47 randomly chosen patients. Free marginal kappa values for inter-observer agreement indicated substantial agreement for the (dichotomized) TIC1 score ($\kappa=0.73$) and almost perfect agreement for DSA collaterals ($\kappa=0.82$) [39]. The time to recanalization (OTR) was defined as the time from symptom onset (or last known well time) to the time of TIC1 2b to 3 recanalization.

Assessment of early ischemic changes was based on the initial non-contrast head CT and as defined by Alberta Stroke Program Early CT Score (ASPECTS) system [40, 41]. Scoring was conducted by experienced readers (A.S.P., N.H.) trained in ASPECTS (<http://www.aspectsinstroke.com>). Disagreements in readings were resolved by consensus.

Statistics

Unless otherwise stated, continuous variables are reported as median (25th–75th percentile). Categorical variables are reported as proportions. Normality of data was examined using Shapiro-Wilk test. Between-group comparisons for continuous variables were made with Mann-Whitney U test and one way analysis of variance (ANOVA) on Ranks with post-hoc Dunn's method. Categorical variables were compared using the χ^2 -test or Fisher's Exact test. Correlative analyses were conducted using Spearman rank test.

We used multivariable linear regression with backward elimination to determine factors independently associated with the OTR. The OTR was log-transformed to achieve a more suitable distribution. Factors associated with the OTR in univariate analysis at $p<0.2$ (age [per year], leukoaraiosis severity [per VSS step], admission NIHSS [per point], collateral grade [per point], cardioembolic stroke cause, other determined stroke cause,

hyperlipidemia, atrial fibrillation, history of stroke or TIA, statin therapy, and thrombolysis with rtPA) as well as the ASPECTS (per point) were entered into the model.

We constructed multivariable binary and ordinal logistic regression models to describe the association of leukoaraiosis and the OTR with the 90-day mRS after adjustment for pertinent covariates that related to the outcome in our cohort (including age, ASPECTS, admission NIHSS, pre-admission mRS, collateral status, anti-hypertensives, antiglycemics, as well as history of stroke and TIA, hypertension, atrial fibrillation, and coronary artery disease). To create parsimonious models, we used a backward elimination approach (binary logistic regression) or manually added and removed terms sequentially (ordinal regression). We included the pre-stroke mRS as both ordinal (range 0–4) as well as dichotomized to 0–2 versus >2 in all multivariable regression models to account for the fact that, though an accepted marker of pre-stroke disability in MT trials [5], there is no specific guideline on how to score 1 and 2 in the absence of a prior stroke [42]. Model calibration was assessed by Hosmer-Lemeshow test and model fit determined by examining the -2 log-likelihood statistic and its associated chi-square statistics. To avoid violation of the proportional odds assumption we collapsed mRS 5 ($n=5$) and mRS 4 ($n=10$) into a single category for ordinal logistic regression.

In all regression models, we performed collinearity diagnostics (and rejected its presence). Two-sided significance tests were used throughout and a two-sided $p<0.05$ was considered statistically significant. All statistical analyses were performed using SPSS® Statistics 22 (IBM®-Armonk, NY).

Data Sharing:

The investigators will share anonymized data (with associated coding library) used in developing the results presented in this manuscript upon reasonable request to investigators who have received ethical clearance from their host institution.

Results

Study population

During the study period, 182 patients were treated with MT for anterior circulation LVO. We excluded patients that were not treated with stent retrievers ($n=16$), had incomplete recanalization ($n=14$), or in whom recanalization was not achieved ($n=7$). Lastly, one patient was excluded because the medical records could not be obtained.

There was no difference in the presence of a favorable ASPECTS ($p=0.582$), good collaterals on CTA ($p=0.282$), and a NIHSS deficit of ≥ 6 (4% vs. 1%, $p=0.248$) between patients with an OTR >8 hours ($n=47$) versus ≤ 8 hours ($n=97$). Patients treated beyond 8 hours more frequently had CT-perfusion imaging performed (54% vs 21%, $p<0.001$). There was no difference in the presence of a favorable ASPECTS, good collaterals, NIHSS ≥ 6 , and frequency of CT-perfusion imaging between subjects with absent-to-mild leukoaraiosis versus moderate-to-severe leukoaraiosis ($p>0.05$, each; data not shown).

Baseline characteristics of the included 144 patients as stratified by leukoaraiosis severity are summarized in Table 1. Patients with moderate-to-severe leukoaraiosis were older ($p<0.001$) and had a greater admission NIHSS ($p=0.012$) as well as more frequently had atrial fibrillation ($p<0.001$), a cardioembolic stroke mechanism ($p=0.002$), and history of stroke/TIA ($p=0.001$). In addition, they more frequently had a poor 90-day functional outcome ($p=0.016$) and had a shorter OTR ($p<0.001$, Table 1 and Figure 1). Specifically, no patient with a VSS of ≥ 3 was treated beyond 8 hours from symptom onset (Figure 1).

Leukoaraiosis is independently associated with the OTR

We then conducted additional analyses to better understand the relation between leukoaraiosis severity and OTR. Supplemental Table 1 summarizes the univariate association between the OTR and baseline characteristics. After adjustment for pertinent covariates, greater leukoaraiosis severity (coefficient -0.088 ; 95% CI -0.145 to -0.031 ; $p=0.003$), worse admission NIHSS (coefficient -0.022 ; 95% CI -0.032 to -0.011 ; $p<0.001$), and treatment with rTPA (coefficient -0.395 ; 95% CI -0.526 to -0.264 ; $p<0.001$), but not the chronological patient age, were independently associated with earlier (log-transformed) OTR. Results were similar for the association of leukoaraiosis with the (log-transformed) time from symptom onset (or last known well time) to groin puncture (coefficient -0.114 ; 95%-CI -0.189 to -0.039 ; $p=0.003$).

The effect of the OTR on 90-day outcome depends on the degree of leukoaraiosis

In unadjusted analyses, a greater leukoaraiosis burden ($p=0.005$; Figure 2), older age ($p=0.007$), lower ASPECTS ($p=0.030$), higher admission NIHSS ($p=0.002$), higher pre-admission mRS ($p=0.022$), worse collateral status ($p=0.005$), use of anti-hypertensives ($p=0.007$) and antidiabetics ($p=0.012$), as well as a history of stroke and TIA ($p=0.022$), hypertension ($p=0.004$), atrial fibrillation ($p=0.029$), and coronary artery disease ($p=0.017$) were associated with a poor 90-day mRS.

Conversely, there was no association between the OTR and the 90-day mRS in the entire cohort ($p=0.890$; Figure 3A). However, for subjects with similar 90-day outcomes, the OTR was inversely associated with leukoaraiosis severity (Figure 3B). When stratified in the univariate analyses by leukoaraiosis severity, crossing of the linear regression slopes consistent with a leukoaraiosis-by-OTR interaction was observed (Figure 3C–D). Moreover, comparison of the regression lines indicated that even within the selected population of patients that were deemed eligible for MT, substantial (TICI 2b/3) reperfusion had to occur >2 hours earlier in subjects with moderate-to-severe leukoaraiosis than those with absent-to-mild leukoaraiosis for similar 90-day functional outcomes (Figure 3C–D). Finally, restricting the analyses to patients with an OTR of ≤ 460 minutes confirmed this association (Supplemental Figure I).

In multivariable logistic regression analysis, the leukoaraiosis-by-OTR interaction with a poor 90-day outcome remained significant (OR 0.76, 95%-CI 0.58–0.98, $p=0.037$) in the final parsimonious model. Additional clinical factors associated with a poor 90-day outcome in this model were the OTR (per 10 min; OR 1.33, 95%-CI 1.03–1.73, $p=0.032$), NIHSS (per point; OR 1.104, 95%-CI 1.026–1.187, $p=0.008$), ASPECTS (per point; OR 0.69, 95%-

CI. 0.53–0.90, $p=0.006$), hypertension (OR 3.791, 95%-CI. 1.44–9.96, $p=0.007$), and antidiabetic use (OR 3.63, 95%-CI. 1.07–12.31, $p=0.039$). Restricting the analyses to patients with an OTR of ≤ 460 minutes confirmed a significant leukoaraiosis-by-OTR interaction with a poor 90-day mRS (OR 0.92, 95%-CI 0.87–0.98, $p=0.006$).

Given the ordinal nature of the mRS, we additionally constructed multivariable ordinal regression models. The final parsimonious model was adjusted for pre-stroke mRS, admission NIHSS, collateral status, hypertension, and treatment with iv rtPA. This analysis confirmed the independent association of a leukoaraiosis-by-OTR interaction with the 90-day mRS (Table 2). In none of the multivariable logistic regression models were age, an age-by-OTR interaction, pre-stroke mRS (ordinal or dichotomized), and TICI-status (2b versus 3) significantly associated with the 90-day outcome (not shown).

Discussion

Several factors have been shown to impact outcome in patients presenting with LVO. In addition to the initial infarct size, factors driving the conversion of salvageable ischemic penumbra towards infarction have been the subject of the intense research to best define patients that are likely to benefit from MT and to safely expand the time window for MT [11, 8, 7, 9, 16]. The underlying rationale relates to the observation that the association between time from stroke onset and progression of infarction differs between individuals; i.e., tissue fate and subsequent clinical outcomes do not only depend on the OTR but probably more important on the degree of remaining tissue perfusion and the intrinsic capacity of the brain tissue to withstand ischemia [11].

Consistent with prior observations [18, 17], our analyses demonstrated that the degree of pre-existing leukoaraiosis is related to the 90-day functional outcome among patients deemed candidates for MT. More importantly, we provide novel insight into the complex interaction between leukoaraiosis and time to treatment by showing that the impact of the OTR on a favorable outcome depended on the degree of preexisting leukoaraiosis (but not the chronological age) among patients undergoing MT. These results indicate that leukoaraiosis, as a readily available imaging marker of the biological brain age, may serve as a viable indicator of treatment success.

These results are striking because included patients were deemed to likely benefit from endovascular therapy after assessment of clinical and imaging data by the treating stroke and endovascular radiology teams. Moreover, our restriction of analysis to subjects with substantial recanalization allowed us to study the specific association between leukoaraiosis and OTR on the 90-day functional outcome without possible confounding by incomplete recanalization in a patient cohort treated according to contemporaneous criteria.

Intriguingly, no patient with moderate-to-severe leukoaraiosis was treated beyond 8 hours from symptom onset. Our analyses offer a possible explanation for this selection bias. In light of prior observations [22, 21, 23], and that fact that leukoaraiosis severity was the only imaging variable independently associated with the OTR (and time from symptom onset to groin puncture), supports the notion that patients with severe leukoaraiosis have a faster

progression of their ischemic core than patients with absent or only mild leukoaraiosis and are thus rendered ineligible for MT when presenting late after symptom onset. Probably more important, despite this selection bias (which likely resulted in underestimation of the true impact of leukoaraiosis), substantial reperfusion needed to occur >2 hours earlier in subjects with moderate-to-severe leukoaraiosis to achieve similar 90-day functional outcomes as in patients with absent-to-mild leukoaraiosis. Moreover, because no patient with moderate-to-severe leukoaraiosis was treated beyond 8 hours we conducted additional sensitivity analyses restricted to the cohort of patients with an OTR of ≤ 460 minutes. These analyses confirmed that the association of the OTR with the 90-day functional outcome depended on the degree of pre-existing leukoaraiosis severity. Among patients with moderate-to-severe leukoaraiosis substantial reperfusion had to occur substantially earlier than in patients with absent-to-mild leukoaraiosis to achieve a similar functional outcome 90 days after their stroke. Nevertheless, further research in a larger cohort of patients and without exclusion based on reperfusion success will be required to confirm our results and to determine whether leukoaraiosis assessment can significantly improve patient selection for MT.

The present study has several strengths and limitations. Strengths relate to inclusion of consecutive patients with anterior circulation LVO stroke that were evaluated by clinicians certified in NIHSS and ASPECTS, masked assessment of leukoaraiosis severity and collateral status with respect to clinical variables, rigorous adjustment for clinically relevant confounders that relate to functional outcome after stroke, as well as the use of multiple logistic and ordinal regression analyses for outcome assessment. Therefore, our results provide proof-of-concept that preexisting leukoaraiosis, as a marker of the chronological brain age, relates to worse outcomes after successful reperfusion with MT and may serve as the impetus to for future prospective, multicenter studies to formally test our hypothesis. Given the limitations inherent to a retrospective, single-center study results should not be used for clinical decision making. For example, patient selection for MT was done by consensus of the neurointerventional and stroke teams because of the rapidly evolving nature of the field of stent-retriever based MT during the observation period with proof of efficacy only emerging in the later part of our study [5]. Accordingly, it is possible that patient selection for MT may have been influenced by unmeasured factors. Arguably, however, this does not have a major impact on the interpretation of our results, because the primary goal of our study was to determine whether pre-existing leukoaraiosis modulates the relationship between the OTR and the 90 day functional outcome among patients were deemed good candidates for MT and because our approach to patient selection was both consistent with general clinical practice as well as that of later successful clinical trials [11, 8, 2, 5]. A further potential limitation relates to our semi-quantitative assessment of the leukoaraiosis burden, which may reduce sensitivity to detect subtle differences. However, quantification of leukoaraiosis on non-contrast head CT, the modality of choice for hyperacute stroke assessment in most centers, is not well established. Furthermore, the VSS represents a validated, frequently used image analysis tool in clinical research with high inter-rater reliability and that can be readily assessed on non-contrast head CT rendering it a suitable option for emergent image analysis [43–45]. Lastly, although our approach to estimate the pre-procedural infarct extent by ASPECTS has previously been shown to have similar

prognostic accuracy as CT perfusion based pre-interventional risk-stratification [46], future detailed assessment of the pre-procedural cerebral perfusion status as well as the final infarct extent may provide additional valuable insight into how leukoaraiosis relates to the 90-day outcome.

Conclusion

Our observations provide of proof-of-concept that the severity of pre-existing leukoaraiosis is associated with the 90-day functional outcome after successful reperfusion and, more importantly, impacts the association between the OTR and 90-day mRS among patients undergoing MT. Specifically, to achieve a similar favorable outcome patients with high leukoaraiosis burden need to present earlier than patients with low leukoaraiosis severity. Though the clinical impact of our findings needs further exploration, the results may have implications for future research to improve patient selection for acute stroke therapies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Bracard S, Ducrocq X, Mas JL, Soudant M, Oppenheim C, Moulin T et al. Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial. *Lancet neurology*. 2016;15(11):1138–47. doi:10.1016/S1474-4422(16)30177-6. [PubMed: 27567239]
2. Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *The New England journal of medicine*. 2015;372(24):2296–306. doi:10.1056/NEJMoa1503780. [PubMed: 25882510]
3. Saver JL, Goyal M, Bonafe A, Diener HC, Levy EI, Pereira VM et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. *The New England journal of medicine*. 2015;372(24):2285–95. doi:10.1056/NEJMoa1415061. [PubMed: 25882376]
4. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. *The New England journal of medicine*. 2015;372(11):1019–30. doi:10.1056/NEJMoa1414905. [PubMed: 25671798]
5. Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ et al. A randomized trial of intraarterial treatment for acute ischemic stroke. *The New England journal of medicine*. 2015;372(1):11–20. doi:10.1056/NEJMoa1411587. [PubMed: 25517348]
6. Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *The New England journal of medicine*. 2015;372(11):1009–18. doi:10.1056/NEJMoa1414792. [PubMed: 25671797]
7. Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S et al. Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging. *The New England journal of medicine*. 2018;378(8):708–18. doi:10.1056/NEJMoa1713973. [PubMed: 29364767]
8. Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P et al. Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct. *The New England journal of medicine*. 2018;378(1):11–21. doi:10.1056/NEJMoa1706442. [PubMed: 29129157]

9. Saver JL, Goyal M, van der Lugt A, Menon BK, Majoie CB, Dippel DW et al. Time to Treatment With Endovascular Thrombectomy and Outcomes From Ischemic Stroke: A Meta-analysis. *JAMA : the journal of the American Medical Association*. 2016;316(12):1279–88. doi:10.1001/jama.2016.13647. [PubMed: 27673305]
10. Jovin TG, Saver JL, Ribo M, Pereira V, Furlan A, Bonafe A et al. Diffusion-weighted imaging or computerized tomography perfusion assessment with clinical mismatch in the triage of wake up and late presenting strokes undergoing neurointervention with Trevo (DAWN) trial methods. *International journal of stroke : official journal of the International Stroke Society*. 2017;12(6): 641–52. doi:10.1177/1747493017710341. [PubMed: 28569123]
11. Saposnik G, Strbian D. Enlightenment and Challenges Offered by DAWN Trial (DWI or CTP Assessment With Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With Trevo). *Stroke; a journal of cerebral circulation*. 2018;49(2): 498–500. doi:10.1161/STROKEAHA.117.018560.
12. Liebeskind DS, Jahan R, Nogueira RG, Zaidat OO, Saver JL, Investigators S. Impact of collaterals on successful revascularization in Solitaire FR with the intention for thrombectomy. *Stroke; a journal of cerebral circulation*. 2014;45(7):2036–40. doi:10.1161/STROKEAHA.114.004781.
13. Albers GW, Lansberg MG, Kemp S, Tsai JP, Lavori P, Christensen S et al. A multicenter randomized controlled trial of endovascular therapy following imaging evaluation for ischemic stroke (DEFUSE 3). *International journal of stroke : official journal of the International Stroke Society*. 2017;12(8):896–905. doi:10.1177/1747493017701147. [PubMed: 28946832]
14. Rocha M, Jovin TG. Fast Versus Slow Progressors of Infarct Growth in Large Vessel Occlusion Stroke: Clinical and Research Implications. *Stroke; a journal of cerebral circulation*. 2017;48(9): 2621–7. doi:10.1161/STROKEAHA.117.017673.
15. Meretoja A, Keshkaran M, Tatlisumak T, Donnan GA, Churilov L. Endovascular therapy for ischemic stroke: Save a minute-save a week. *Neurology*. 2017;88(22):2123–7. doi:10.1212/WNL.0000000000003981. [PubMed: 28455382]
16. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet*. 2016;387(10029):1723–31. doi:10.1016/S0140-6736(16)00163-X. [PubMed: 26898852]
17. Gilberti N, Gamba M, Premi E, Costa A, Vergani V, Delrio I et al. Leukoaraiosis is a predictor of futile recanalization in acute ischemic stroke. *Journal of neurology*. 2017;264(3):448–52. doi: 10.1007/s00415-016-8366-y. [PubMed: 28004198]
18. Guo Y, Zi W, Wan Y, Zhang S, Sun B, Shang X et al. Leukoaraiosis severity and outcomes after mechanical thrombectomy with stent-retriever devices in acute ischemic stroke. *Journal of neurointerventional surgery*. 2018. doi:10.1136/neurintsurg-2018-014018.
19. Kongbunkiat K, Wilson D, Kasemsap N, Tiamkao S, Jichi F, Palumbo V et al. Leukoaraiosis, intracerebral hemorrhage, and functional outcome after acute stroke thrombolysis. *Neurology*. 2017;88(7):638–45. doi:10.1212/WNL.0000000000003605. [PubMed: 28130468]
20. Zhang J, Puri AS, Khan MA, Goddeau RP Jr., Henninger N. Leukoaraiosis predicts a poor 90-day outcome after endovascular stroke therapy. *AJNR American journal of neuroradiology*. 2014;35(11):2070–5. doi:10.3174/ajnr.A4029. [PubMed: 24994827]
21. Henninger N, Lin E, Baker SP, Wakhloo AK, Takhtani D, Moonis M. Leukoaraiosis predicts poor 90-day outcome after acute large cerebral artery occlusion. *Cerebrovasc Dis*. 2012;33(6):525–31. doi:10.1159/000337335. [PubMed: 22538962]
22. Henninger N, Lin E, Haussen DC, Lehman LL, Takhtani D, Selim M et al. Leukoaraiosis and sex predict the hyperacute ischemic core volume. *Stroke; a journal of cerebral circulation*. 2013;44(1): 61–7. doi:10.1161/STROKEAHA.112.679084.
23. Ay H, Arsava EM, Rosand J, Furie KL, Singhal AB, Schaefer PW et al. Severity of leukoaraiosis and susceptibility to infarct growth in acute stroke. *Stroke; a journal of cerebral circulation*. 2008;39(5):1409–13. doi:10.1161/STROKEAHA.107.501932.
24. Henninger N, Khan MA, Zhang J, Moonis M, Goddeau RP .Jr, Leukoaraiosis predicts cortical infarct volume after distal middle cerebral artery occlusion. *Stroke; a journal of cerebral circulation*. 2014;45(3):689–95. doi:10.1161/STROKEAHA.113.002855.

25. Patti J, Helenius J, Puri AS, Henninger N. White Matter Hyperintensity-Adjusted Critical Infarct Thresholds to Predict a Favorable 90-Day Outcome. *Stroke; a journal of cerebral circulation*. 2016;47(10):2526–33. doi:10.1161/STROKEAHA.116.013982.
26. Rabinstein AA, Albers GW, Brinjikji W, Koch S. Factors that may contribute to poor outcome despite good reperfusion after acute endovascular stroke therapy. *International journal of stroke : official journal of the International Stroke Society*. 2018;1747493018799979. doi:10.1177/1747493018799979.
27. Shi ZS, Loh Y, Liebeskind DS, Saver JL, Gonzalez NR, Tateshima S et al. Leukoaraiosis predicts parenchymal hematoma after mechanical thrombectomy in acute ischemic stroke. *Stroke; a journal of cerebral circulation*. 2012;43(7):1806–11. doi:10.1161/STROKEAHA.111.649152.
28. Atchaneeyasakul K, Leslie-Mazwi T, Donahue K, Giese AK, Rost NS. White Matter Hyperintensity Volume and Outcome of Mechanical Thrombectomy With Stentriever in Acute Ischemic Stroke. *Stroke; a journal of cerebral circulation*. 2017;48(10):2892–4. doi:10.1161/STROKEAHA.117.018653.
29. Yoo AJ, Andersson T. Thrombectomy in Acute Ischemic Stroke: Challenges to Procedural Success. *Journal of stroke*. 2017;19(2):121–30. doi:10.5853/jos.2017.00752. [PubMed: 28592779]
30. Snelling BM, Sur S, Shah SS, Chen S, Menaker SA, McCarthy DJ et al. Unfavorable Vascular Anatomy Is Associated with Increased Revascularization Time and Worse Outcome in Anterior Circulation Thrombectomy. *World Neurosurg*. 2018;120:e976–e83. doi:10.1016/j.wneu.2018.08.207. [PubMed: 30196176]
31. Powers WJ, Derdeyn CP, Biller J, Coffey CS, Hoh BL, Jauch EC et al. 2015 American Heart Association/American Stroke Association Focused Update of the 2013 Guidelines for the Early Management of Patients With Acute Ischemic Stroke Regarding Endovascular Treatment: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke; a journal of cerebral circulation*. 2015;46(10):3020–35. doi:10.1161/STR.0000000000000074.
32. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K et al. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke; a journal of cerebral circulation*. 2018;49(3):e46–e110. doi:10.1161/STR.0000000000000158.
33. Adams HP Jr., Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke; a journal of cerebral circulation*. 1993;24(1):35–41.
34. Bruno A, Akinwuntan AE, Lin C, Close B, Davis K, Baute V et al. Simplified modified Rankin scale questionnaire: reproducibility over the telephone and validation with quality of life. *Stroke; a journal of cerebral circulation*. 2011;42(8):2276–9. doi:10.1161/STROKEAHA.111.613273.
35. Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet neurology*. 2013;12(8):822–38. doi:10.1016/S1474-4422(13)70124-8. [PubMed: 23867200]
36. van Swieten JC, Hijdra A, Koudstaal PJ, van Gijn J. Grading white matter lesions on CT and MRI: a simple scale. *Journal of neurology, neurosurgery, and psychiatry*. 1990;53(12):1080–3.
37. Gurol ME, Irizarry MC, Smith EE, Raju S, Diaz-Arrastia R, Bottiglieri T et al. Plasma beta-amyloid and white matter lesions in AD, MCI, and cerebral amyloid angiopathy. *Neurology*. 2006;66(1):23–9. doi:10.1212/01.wnl.0000191403.95453.6a. [PubMed: 16401840]
38. Higashida RT, Furlan AJ, Roberts H, Tomsick T, Connors B, Barr J et al. Trial design and reporting standards for intra-arterial cerebral thrombolysis for acute ischemic stroke. *Stroke; a journal of cerebral circulation*. 2003;34(8):e109–37. doi:10.1161/01.STR.0000082721.62796.09.
39. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics*. 1977;33(1):159–74. [PubMed: 843571]
40. Barber PA, Demchuk AM, Zhang J, Buchan AM. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic

- therapy. ASPECTS Study Group. Alberta Stroke Programme Early CT Score. *Lancet*. 2000;355(9216):1670–4. [PubMed: 10905241]
41. Khan M, Baird GL, Goddeau RP Jr., Silver B, Henninger N. Alberta Stroke Program Early CT Score Infarct Location Predicts Outcome Following M2 Occlusion. *Frontiers in neurology*. 2017;8:98. doi:10.3389/fneur.2017.00098. [PubMed: 28352248]
42. Bruno A, Switzer JA. Letter by Bruno and Switzer regarding article, “Prestroke modified Rankin Stroke Scale has moderate interobserver reliability and validity in an acute stroke setting”. *Stroke; a journal of cerebral circulation*. 2013;44(5):e43. doi:10.1161/STROKEAHA.111.000247.
43. van Straaten EC, Fazekas F, Rostrup E, Scheltens P, Schmidt R, Pantoni L et al. Impact of white matter hyperintensities scoring method on correlations with clinical data: the LADIS study. *Stroke; a journal of cerebral circulation*. 2006;37(3):836–40. doi:10.1161/01.STR.0000202585.26325.74.
44. Kim GM, Park KY, Avery R, Helenius J, Rost N, Rosand J et al. Extensive leukoaraiosis is associated with high early risk of recurrence after ischemic stroke. *Stroke; a journal of cerebral circulation*. 2014;45(2):479–85. doi:10.1161/STROKEAHA.113.003004.
45. Valdes Hernandez Mdel C, Morris Z, Dickie DA, Royle NA, Munoz Maniega S, Aribisala BS et al. Close correlation between quantitative and qualitative assessments of white matter lesions. *Neuroepidemiology*. 2013;40(1):13–22. doi:10.1159/000341859. [PubMed: 23075702]
46. Raza SA, Barreira CM, Rodrigues GM, Frankel MR, Haussen DC, Nogueira RG et al. Prognostic importance of CT ASPECTS and CT perfusion measures of infarction in anterior emergent large vessel occlusions. *Journal of neurointerventional surgery*. 2018. doi:10.1136/neurintsurg-2018-014461.

Figure 1.

Association between leukoaraiosis and time to recanalization. (A) Histogram of the time from symptom onset to recanalization for the entire cohort of patients stratified by absent-to-mild (blue, n=122) versus moderate-to-severe (red, n=22) leukoaraiosis. (B) Time from symptom onset to recanalization (OTR) as stratified by the van Swieten scale (VSS) score indicates an inverse association between the OTR and VSS with overall shorter OTR among subjects with worse leukoaraiosis (p=0.006; ANOVA on Ranks).

Figure 2.

Association between leukoaraiosis and 90-day functional outcome. Subjects with moderate-to-severe leukoaraiosis (van Swieten Scale [VSS] 3–4) had a significantly worse 90-day functional outcome than subjects with absent-to-mild leukoaraiosis (VSS 0–2; Fisher's Exact test).

Figure 3.

Association between leukoaraiosis, time from symptom onset to recanalization (OTR), and 90-day outcome. (A) In the entire cohort (n=144), there was no significant linear association between the OTR and the 90-day modified Rankin Scale score (mRS) ($p>0.05$; unadjusted). (B) Representation of the association between leukoaraiosis severity (as assessed by the van Swieten scale [VSS]), OTR, and 90-day mRS. On average, for subjects with similar 90-day outcomes, the OTR was inversely associated with leukoaraiosis severity as indicated by a gradient from shorter (cold colors) to longer (warm colors) OTR with increasing leukoaraiosis severity across all mRS-categories. (C-D) Absolute difference in OTR (min) to achieve a similar functional outcome by day 90 as assessed by the (C) 90-day mRS as well as (D) the degree of mRS improvement from baseline to 90 days as shown by linear regressions (with their 95%-confidence intervals) and stratified according to leukoaraiosis severity (individual 95% prediction bands are omitted from this panel for clarity). Crossing slopes of the regression lines indicate leukoaraiosis-by-OTR interaction. Note that because of the non-normal distribution of the data in (A, C, and D) confidence intervals are likely biased (either too wide or small) and should not be used to estimate significance cut-offs.

Table 1

Baseline characteristics (unadjusted) of the studied patient population as stratified by leukoaraiosis severity

Characteristics	All patients (n=144)	VSS 0–2 (n=122)	VSS 3–4 (n=22)	P-value
Age, years	68 (57–81)	66 (54–76)	82 (78–86)	<0.001
Female gender	71 (49%)	57 (47%)	14 (64%)	0.169
Admission SBP, mmHg	141 (123–158)	140 (121–156)	147 (132–171)	0.113
Admission DBP, mmHg	76 (65–90)	78 (66–91)	72 (59–90)	0.491
Neuroimaging				
Admission NIHSS	18 (14–22)	18 (13–21)	21 (18–25)	0.012
ASPECTS 6–10	128 (89%)	107 (88%)	21 (96%)	0.467
Good DSA collaterals	106 (74%)	91 (75%)	15 (68%)	0.600
Perfusion CT obtained	50 (34.7)	44 (36.1)	6 (27.3)	0.476
Treatment				
Thrombolysis with rtPA	84 (58%)	68 (56%)	16 (73%)	0.163
Time to rtPA, min	110 (76–150)	118 (83–162)	68 (53–111)	0.009
OTR, mm	381 (304–586)	397 (312–681)	303 (201–404)	<0.001
OTR <8 hours	97 (67%)	75 (62%)	22 (100%)	<0.001
Procedure duration, min	91 (60–147)	95 (60–149)	80 (51–122)	0.207
TICI 3 (versus TICI 2b)	24 (17%)	23 (19%)	1 (5%)	0.125
Laboratory data				
Admission glucose (random), mg/dL	124 (110–144)	123 (110–143)	137 (111–159)	0.306
Platelet count, 10 ³ /μL	204 (163–248)	210 (163–254)	185 (157–234)	0.216
International normalized ratio	1.0 (1.0–1.1)	1.0 (1.0–1.1)	1.0 (1.0–1.1)	0.562
Stroke mechanism				0.002
Large artery atherosclerosis	30 (21%)	27 (22%)	3 (14%)	
Cardioembolic	74 (51%)	55 (45%)	19 (86%)	
ESUS	27 (19%)	27 (22%)	0 (0%)	
Other determined	13 (9%)	13 (11%)	0 (0%)	
Preexisting risk factors				
Atrial fibrillation	64 (44%)	46 (38%)	18 (82%)	<0.001
Coronary artery disease	34 (24%)	28 (23%)	6 (28%)	0.785
Diabetes	26 (18%)	23 (19%)	3 (14%)	0.801
Heart failure	22 (15%)	21 (17%)	1 (5%)	0.198
Hyperlipidemia	75 (52%)	63 (52%)	12 (55%)	0.821
Hypertension	105 (73%)	88 (72%)	17 (77%)	0.796
Prior stroke or TIA	13 (9%)	6 (5%)	7 (32%)	0.001
Peripheral artery disease	7 (5%)	5 (4%)	2 (9%)	0.290
Preadmission medications				
Statin	59 (41%)	51 (42%)	8 (36%)	0.814
Antihypertensive	99 (69%)	83 (68%)	16 (73%)	0.805
Antiglycemic	19 (13%)	16 (13%)	3 (14%)	1.000
Antiplatelets	54 (38%)	45 (37%)	9 (41%)	0.812

Characteristics	All patients (n=144)	VSS 0–2 (n=122)	VSS 3–4 (n=22)	P-value
Oral anticoagulants	31 (22%)	23 (19%)	8 (36%)	0.089
mRS worsening by 90 days	2 (1–4)	2 (1–3)	4 (1–6)	0.016
Good 90-day mRS (0–2)	74 (51%)	69 (57%)	5 (23%)	0.005

ASPECTS indicates Alberta Stroke Program Early CT Score, DBP=diastolic blood pressure; DSA=digital subtraction angiography, ESUS=Embolic stroke of undetermined source, mRS=modified Rankin Scale, NIHSS=National Institutes of Health Stroke Scale, OTR=symptom onset-to-reperfusion time, TIA=transient ischemic attack, rtPA=recombinant tissue-type plasminogen activator, SBP=systolic blood pressure;

TICI=thrombolysis in cerebral infarction; VSS= van Swieten scale. Data are n (%) or median (25th–75th quartile). Data was complete for all included variables.

Table 2

Multivariable ordinal logistic regression analyses of the leukoaraiosis $\times$ time interaction-association with the 90-day modified Rankin Scale score

Independent variable	Odds ratio (95% confidence interval)	P-value
Model 1 [†]		
OTR (per 10 minutes)	1.14 (1.03–1.27)	0.009
Leukoaraiosis severity	11.10 (0.54–227.42)	0.118
OTR $\times$ Leukoaraiosis	0.87 (0.78–0.97)	0.011
Model 2 [‡]		
OTR (per 10 minutes)	1.13 (1.02–1.26)	0.019
Leukoaraiosis severity	5.00 (0.24–103.35)	0.298
OTR $\times$ Leukoaraiosis	0.90 (0.81–1.00)	0.042

Significant onset-to-reperfusion time (OTR) $\times$ leukoaraiosis interaction indicating that the association of the OTR with the 90-day mRS depended on the degree of pre-existing leukoaraiosis.

[†]Model 1, unadjusted (Goodness-of-fit statistics: $\chi^2=644.6$, $p=0.575$; proportional odds assumption $p=0.165$).

[‡]Model 2, adjusted for pre-stroke mRS, admission National Institutes of Health Stroke Scale score, collateral status, hypertension, and treatment with recombinant tissue-type plasminogen activator (Goodness-of-fit statistics: $\chi^2=666.9$, $p=0.857$; proportional odds assumption $p=0.379$).