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BRAIN ATROPHY PREDICTS MORTALITY AFTER MECHANICAL THROMBECTOMY OF PROXIMAL ANTERIOR CIRCULATION OCCLUSION

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ABSTRACT

Background. Brain atrophy is associated with an inferior functional outcome in patients undergoing mechanical thrombectomy (MT) for acute ischemic stroke. We hypothesized, that brain atrophy determined from pre-interventional non-contrast-enhanced computed tomography scans would also be linked to increased mortality in this cohort.

Methods. A total of 204 patients treated with MT for acute occlusions of the internal carotid artery (ICA) or the M1-segment of the middle cerebral artery (M1) at Tampere University Hospital, Finland, between 2013 and 2017 were retrospectively studied. Brain atrophy index (BAI), masseter muscle surface area and density, chronic ischemic lesions and white matter lesions were evaluated from pre-interventional computed tomography studies. Logistic regression was applied in analyzing the association of BAI with three-month mortality.

Results. Median age at baseline was 69.9 years (IQR 15.6) and mortality at three months was 13.2% (n=27). BAI, measured with excellent reproducibility (intraclass correlation coefficient ≥ 0.894 , $P < 0.001$), was significantly associated with age ($r = 0.54$), white matter lesions ($r = 0.43$), dental status ($r = -0.31$), masseter area ($r = -0.24$), masseter density ($r = -0.28$), and chronic ischemic lesions ($r = 0.24$) ($P \leq 0.001$ for all). In univariable analysis, BAI demonstrated a strong association with mortality (OR 2.02, 95% CI 1.34-3.05, per 1-SD increase) and none of the other factors associated with mortality remained as significant when included in the same multivariable model. The results remained similar when extending the follow-up up to 2.5 years.

Conclusions. Brain atrophy predicts three-month mortality after MT of the ICA or the M1 independent of age, masseter sarcopenia, chronic ischemic lesions, or white matter lesions.

INTRODUCTION

Mechanical thrombectomy (MT) is regarded as the treatment of choice for patients suffering from acute ischemic stroke (AIS) due to proximal anterior circulation occlusion.[1–4] Despite the introduction of this method as well as the overall development of interventional techniques, medical therapy, and preventive measures, there is still potential for improvement in the postinterventional survival of AIS patients, whereby it is crucial to identify key prognostic markers applicable for clinical practice.

Identified predictors of mortality after a large vessel ischemic stroke include stroke severity, time to treatment after symptom onset, unsuccessful recanalization, poor collateral circulation, age, sex, diabetes, atrial fibrillation, renal insufficiency, frailty, and the presence of symptomatic intracranial hemorrhage. Furthermore, in the general stroke population, the presence of white matter lesions (WML) has been linked to poorer outcome, but a similar association has not yet been demonstrated in patients treated with MT.[5–8] Chronic ischemic lesions (CILs), in turn, were linked to postinterventional outcome after MT in our previous study.[9] The Alberta stroke program early computed tomography score (ASPECTS) has also been established as a prediction tool in this cohort.[10]

Brain atrophy can be easily measured by determining the bicaudate index or brain atrophy index (BAI) from CT scans.[11] It is independently associated with increased mortality in older individuals, patients with manifest arterial disease, and elderly trauma patients.[11–14] Furthermore, in AIS patients undergoing MT, cerebral atrophy has been linked to inferior functional outcome.[15] Moreover, brain atrophy is associated with physical frailty,[16,17] and in our previous study we showed that sarcopenia, represented by masseter muscle area and

density, is associated with poor three-month survival after MT.[18] The potential predictive value of BAI and its dependence on sarcopenia as well as other risk factors in AIS patients treated with MT remains poorly defined. We hypothesized that including BAI in multivariable models could improve the prediction of mortality after MT due to AIS.

METHODS

Patients

We retrospectively investigated patients treated with MT at Tampere University Hospital between January 2013 and December 2017 (n=432). Non-contrast-enhanced computed tomography (NECT), computed tomography angiography (CTA), and in most cases, computed tomography perfusion (CTP) scanning were included in the imaging protocol. Individuals transferred for treatment from other hospitals were re-evaluated upon arrival. Patient selection for MT was conducted by a stroke neurologist and a neurointerventional radiologist. Absence of extensive irreversible ischemic changes and hemorrhage in NECT, presence of a proximal occlusion in the CTA and a sufficient amount of salvageable tissue in CTP imaging when available were prerequisites for MT. Even patients arriving after 6 hours from symptom onset or suffering from a wake-up stroke were treated with MT on the condition that no large infarct could be detected and there was salvageable tissue.[19,20] In patients with a history of moderate or severe dementia, MT was withheld.

Patients with a thrombus of the internal carotid artery (ICA) or the M1-segment of the middle cerebral artery (M1), sufficient quality digitally stored pre-interventional NECT and CTA scans, an ASPECT-score of >7 at the 24-hour CT, absence of substantial parenchymal hematoma after MT, and surviving a minimum of 24 hours after the intervention were analyzed. Patients with main thrombus in a location other than ICA or M1 (n=100) were excluded. Seven patients, originally diagnosed with an ICA thrombus, had a high-grade stenosis of the ICA or the common carotid artery and were therefore left out of the analyses. Furthermore, nine patients were excluded due to CT artifacts caused by metallic dental fillings which inhibited muscle measurements. Those with larger infarcts (n=102), parenchymal

hematoma 2, or remote parenchymal hematoma 2 (n=9) at 24 hours were excluded because of the high likelihood of having poor three-month outcome thus masking potential weaker predictive signals.[21,22] Additionally, one patient died within 24 hours and was hence excluded from the study. Supplementary Figure 1 presents the inclusion/exclusion of study patients. Altogether 228 patients (52.8% of individuals treated with MT) were excluded.

Thrombus locations in the excluded cohort were as follows: ICA in 78, M1-segment in 111, M2-segment in 81, M3-segment in 11, basilar artery in 24, P1-segment in 7, A1-segment in 1, A2-segment in 1, A3-segment in 3, and major vein thrombi in 7 cases. Fifty-two of the excluded patients had occlusions in multiple locations. The excluded patients did not significantly differ from the study subjects with respect to age, sex, or a history of hypertension, diabetes, or atrial fibrillation. Coronary artery disease was significantly less and brain edema more prevalent in the excluded patients compared to the included patients (9.2% vs 16.2% [$P=0.029$] and 49.1% vs 28.9% [$P<0.001$], respectively).

Imaging parameters and radiological assessment

CT imaging was conducted with a 64-row multidetector CT scanner (General Electric LightSpeed VCT, GE Healthcare, Milwaukee, WI, USA). The parameters 120 kV with AUTO mA and SMART mA technic, noise index 3.3, 40% adaptive statistical iterative reconstruction (ASIR), collimation 4x5 mm, and rotation 0.5 s were applied for NECT. Images were obtained axially (0.625 mm slices). Subsequently, adjacent axial slices were reconstructed to the thickness of 5 mm and coronal slices to the thickness of 2 mm. The CTA scanning range extended from the aortic arch to the vertex of the skull and a helical technique was utilized. The following imaging parameters were applied: 100 kV with AUTO mA and SMART-mA, noise index 9, 40% ASIR, collimation 40 x 0.625 mm, rotation 0.5 s, and pitch factor 0.984.

Automatic bolus triggering of the contrast agent (iomeprol, 350 mg I/ml, IOMERON, Bracco, Milan, Italy) from the aortic arch was used and it was administered with 18-gauge cannula via an antecubital vein applying a double-piston power injector with a 5 ml/s flow rate (70 ml of contrast agent followed by a 50 ml saline flush).

One radiologist (S.P.) determined BAIs from NECT images. The measurements were performed at the same axial level as the heads of the caudate nuclei: the shortest distance between these (intercaudate distance) and the distance between the inner skull surfaces (interskull distance) were measured in the same coronal plane (Figure 1). BAI values were obtained by dividing the intercaudate distance by the interskull distance. Sarcopenia was evaluated from CTA scans by measuring the masseter muscle area (MA, mm²) and mean radiodensity (MD, Hounsfield Unit, HU) as described in our previous study.[23] The presence of teeth was classified in three categories: 1) no teeth, 2) any missing teeth, and 3) no evidence of missing teeth. Average Masseter area (MAavg, mean of left and right MA) and Masseter density (MDavg, mean of left and right MD) were calculated. The presence of WMLs was assessed from NECT images according to the Fazekas scale and scored followingly: 0 – absence of lesions, 1 – small caps or pencil-thin lining in the periventricular white matter or punctate foci in other white matter areas, 2 – smooth halo in the periventricular white matter or beginning confluence of focal lesions, and 3 – irregular periventricular hyperintensity extending into deep white matter or large confluent lesions in other white matter areas.[24] Admission NECT was also evaluated for the presence, region and side of CILs entailing territorial infarcts and lacunar infarcts (including branched atheromatous disease type lesions). The excellent inter- and intra-observer reliability of masseter area and density measurements have been demonstrated by independent observers in previous studies.[18,23] The same reproducibility analyses were performed for BAI and Fazekas in order to confirm inter-

observer reliability. Consequently, 30 CT scans of the MT patients were randomly selected and evaluated by two independent radiologists. The technical outcome was evaluated with the modified Thrombolysis In Cerebral Ischemia (mTICI) -grading from digital subtraction angiography studies at the end of the procedure. Modified Rankin Scale (mRS) was assessed by a neurologist three months after MT over the phone or during a follow-up visit.

Statistical analysis

The statistical analyses were performed with SPSS 25 for Mac OS X. Normality distributions of parameters were observed using histograms and Kolmogorov-Smirnov test with Lilliefors Significance Correction. Medians with interquartile range were reported for noncategorical variables. For generalizability, BAI, MAavg, and MDavg were reported as means and standard deviations. Counts with frequencies were used for categorical variables. The cohort was divided into three subgroups based on BAI tertiles and the risk factors were reported accordingly. Based on normality, parametric or non-parametric tests were selected for comparisons. For two independent groups, the Mann-Whitney U-test was selected for non-gaussian continuous variables. For three independent groups, the Kruskal-Wallis test was used for non-gaussian and the One-way ANOVA for normally distributed variables. The Chi-square test was used for categorical comparisons. Intraclass correlation coefficient (ICC) was applied to estimate reproducibility i.e. inter-observer variability of the BAI measurements and Fazekas scale. ICC over 0.75 was classified as excellent reproducibility using two-way random single measurements with consistency and absolute agreements along with 95% confidence intervals.

Pairwise association between the risk factors or other clinical variables and BAI were evaluated with Pearson correlation coefficient analysis. The association between BAI and risk factors significantly correlated with it was further examined with multivariable linear regression

analysis. Multicollinearity was also tested by calculating the variance inflation factor (VIF) values for the significantly correlating factors. Univariable and multivariable logistic regression analyses were used to investigate the associations between three-month mortality and each risk factor. Parameters associated with mortality ($P < 0.1$) in univariable analyses were selected as covariates in the multivariable analyses. Multivariable models with BAI were therefore created for age, WML, MAavg, and MDavg. Kaplan-Meier survival analysis was performed to describe the association between BAI tertiles and overall mortality. The Log rank test was used to compare the survival distributions between the tertiles. BAI, MAavg, and MDavg were z-scored and reported odds ratios (ORs) correspond to a 1-SD increase in the parameter value. Good technical outcome of treatment was defined as mTICI score ≥ 2 and good clinical outcome as mRS 0-2 at three months. The sample size of the study is sufficient (80% power with a two-sided alpha value of 0.05) for detecting continuously distributed risk factors that correlate with $r \geq 0.24$ with mortality (effect size estimate medium by Cohen's d value 0.483).

Ethical considerations

The study was conducted following the ethical principles of the Declaration of Helsinki and approved by the Pirkanmaa Hospital District Science Center. As this study was conducted retrospectively based on patient records, ethics committee approval or informed patient consent were not required.

RESULTS

Patient characteristics

The demographics of the study patients (n=204) are shown in Table 1. Patients were predominantly male (61.3%) and median age was 69.9 years (IQR 15.6). Altogether 157 patients (77.0%) had M1-thrombus, 68 patients (33.3%) ICA-thrombus, and 21 patients (10.3%) both. There were significant differences in age, WMLs, CILs, dental status, MAavg, and MDavg among the BAI tertiles. Patients within the highest tertile were older and had more WMLs and CILs than patients in the other tertiles. Furthermore, patients within the lowest tertile had fewer missing teeth than other patients. MAavg and MDavg values decreased as BAI increased. Good procedural success was achieved in 186 patients (91.2%). The three-month mRS was available for 179 patients (87.7%) of which 114 (63.7%) experienced good clinical outcome.

Table 1. Characteristics of acute ischemic stroke patients subjected to mechanical thrombectomy.

Risk factor, n (%)	All (n = 204)	BAI tertile			P Value
		Lowest (n = 61)	Middle (n = 76)	Highest (n = 67)	
Age (years), median (IQR)	69.9 (15.6)	60.1 (18.9)	70.4 (10.9)	76.5 (12.8)	<0.001*
Male	125 (61.3)	36 (59.0)	51 (67.1)	38 (56.7)	0.405
Hypertension	89 (43.6)	21 (34.4)	39 (51.3)	29 (43.3)	0.140
Diabetes mellitus	35 (17.2)	8 (13.1)	13 (17.1)	14 (20.9)	0.507
Coronary artery disease	33 (16.2)	9 (14.8)	10 (13.2)	14 (20.9)	0.427
Atrial fibrillation	113 (55.4)	31 (50.8)	41 (53.9)	41 (61.2)	0.474
M1-thrombus	157 (77.0)	47 (77.0)	57 (75.0)	53 (79.1)	0.844
ICA-thrombus	68 (33.3)	22 (36.1)	28 (36.8)	18 (26.9)	0.389
M1- and ICA-thrombus	21 (10.3)	8 (13.1)	9 (11.8)	4 (6.0)	0.354
Edema	59 (28.9)	15 (24.6)	24 (31.6)	20 (29.9)	0.655
Collateral Score, < 2	47 (23.0)	17 (27.9)	16 (21.1)	14 (20.9)	0.564
ASPECTS 24h					0.763
8 points	49 (24.0)	17 (27.9)	16 (21.1)	16 (23.9)	
9 points	73 (35.8)	21 (34.4)	30 (39.5)	22 (32.8)	
10 points	82 (40.2)	23 (37.7)	30 (39.5)	29 (43.3)	
Arrival hemoglobin (g/L), median (IQR)	133 (25)	132 (18)	133 (31)	134 (23)	0.628
Creatinine level (μ mol/L), median (IQR)	77 (28)	76 (27)	77 (29)	79 (32)	0.421
NIHSS 0h, median (IQR)	15 (8)	16 (6)	15 (8)	15 (8)	0.655
WMLs (Fazekas), median (IQR)	0 (1)	0 (0)	0 (2)	1 (1)	<0.001*
CILs	64 (31.4)	9 (14.8)	25 (32.9)	30 (44.8)	0.001*

Multiple CILs	46 (22.5)	7 (11.5)	18 (23.7)	21 (31.3)	0.026*
Lacunar CILs	27 (13.2)	3 (4.9)	8 (10.5)	16 (23.9)	0.005*
Dental status					<0.001*
No teeth	37 (18.1)	4 (6.6)	19 (25.0)	14 (20.9)	
Any missing teeth	122 (59.8)	31 (50.8)	47 (61.8)	44 (65.7)	
No evidence of missing teeth	45 (22.1)	26 (42.6)	10 (13.2)	9 (13.4)	
Masseter average area (mm ²), mean (SD)	429.7 (119.3)	460.8 (117.2)	435.5 (119.5)	394.8 (113.6)	0.006*
Masseter average density (Hounsfield units), mean (SD)	64.1 (12.8)	68.1 (11.8)	65.0 (11.7)	59.5 (13.5)	<0.001*
Brain atrophy index, mean (SD)	0.143 (0.033)	0.106 (0.015)	0.140 (0.008)	0.180 (0.022)	<0.001*

Abbreviations: ASPECTS, the Alberta stroke program early computed tomography score; CIL, Chronic ischemic lesion; ICA, internal carotid artery; IQR, interquartile range; M1, M1-segment of the middle cerebral artery; NIHSS, NIH Stroke Scale; SD, standard deviation; WML, White matter lesion.

* Statistical significance.

Determinants of BAI

Age ($r=0.54$, $P<0.001$), WMLs ($r=0.43$, $P<0.001$), dental status ($r=-0.31$, $P<0.001$), MAavg ($r=-0.24$, $P=0.001$), MDavg ($r=-0.28$, $P<0.001$), and CILs (CIL: $r=0.24$, $P=0.001$; lacunar: $r=0.23$, $P=0.001$; multiple: $r=0.19$, $P=0.008$) correlated significantly with BAI in Pearson coefficient analysis (Supplementary Table 1). According to linear regression analysis adjusted with all significant correlating factors, only age, WMLs, and lacunar CILs were independently associated with BAI ($P<0.01$ for all).

Reproducibility of the CT measurements

Inter-observer variability was determined for BAI measurement and Fazekas scale with excellent reproducibility as tested by ICC analysis (ICC 0.894-0.956, $P<0.001$) (Supplementary Table 2).

Association of preoperative brain atrophy with three-month mortality

The follow-up lasted until December 31st 2018 with a median duration of 30.8 months (IQR 28.9, range 0-70.4 months). Three-month mortality was 13.2% ($n=27$, 62.8% of all deaths) for all patients. The mortality at three months differed significantly between BAI tertiles: mortality was 4.9% ($n=3$) in the lowest tertile, 11.8% ($n=9$) in the middle tertile and 22.4% ($n=15$) in the highest tertile ($P=0.013$). No patients were lost to follow-up.

In univariable analyses, BAI was significantly associated with increased three-month mortality (OR 2.02, 95% CI 1.34-3.05, per 1-SD increase) (Table 2). Other statistically significant predictors were age (OR 1.05, 95% CI 1.01-1.09, per one year increase), WMLs (Fazekas scale) (OR 1.66, 95% CI 1.15-2.41, per one grade increase), MAavg (OR 0.52, 95% CI 0.31-

0.86, per 1-SD increase) and MDavg (OR 0.55, 95 % CI 0.36-0.83, per 1-SD increase). Other demographic characteristics or comorbidities were not significantly associated with mortality.

Table 2. Unadjusted and adjusted associations between risk factors and three-month mortality using logistic regression in acute ischemic stroke patients subjected to mechanical thrombectomy.

Risk factor	Unadjusted		BAI adjusted	
	Odds ratio (95% CI)	P Value	Odds ratio (95% CI)	P Value
Age, per year increase	1.05 (1.01–1.09)	0.026*	1.02 (0.98–1.07)	0.375
M1-thrombus	0.55 (0.23–1.31)	0.177		
ICA-thrombus	1.21 (0.52–2.80)	0.662		
M1- and ICA-thrombus	0.30 (0.04–2.35)	0.252		
Edema	1.85 (0.80–4.26)	0.150		
Collateral score, < 2	1.83 (0.76–4.40)	0.177		
ASPECTS 24h, per point increase	1.30 (0.76–2.21)	0.341		
Creatinine level, per $\mu\text{mol/L}$ increase	1.00 (1.00–1.01)	0.245		
NIHSS 0h, per point increase	1.04 (0.96–1.12)	0.401		
WMLs, per Fazekas grade increase	1.66 (1.15–2.41)	0.007*	1.37 (0.91–2.06)	0.137
CILs	1.34 (0.58–3.12)	0.497		
Multiple CILs	1.54 (0.63–3.79)	0.347		
Lacunar CILs	1.60 (0.55–4.66)	0.388		
Dental status, per grade increase	0.58 (0.30–1.11)	0.101		
MAavg, per SD greater than mean	0.52 (0.31–0.86)	0.012*	0.59 (0.35–1.00)	0.050*
MDavg, per SD greater than mean	0.55 (0.36–0.83)	0.004*	0.63 (0.41–0.97)	0.036*

BAI, per SD greater than mean	2.02 (1.34–3.05)	0.001*	1.81–1.87 (1.16–2.93) ^a	0.004– 0.009* ^a
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Abbreviations: ASPECTS, the Alberta stroke program early computed tomography score; BAI, brain atrophy index; CI, confidence interval; CIL, chronic ischemic lesion; ICA, internal carotid artery; MAavg, masseter average area; MDavg, masseter average density; M1, M1-segment of the middle cerebral artery; NIHSS, NIH Stroke Scale; WML, white matter lesion.

* Statistical significance.

^a Calculated by adjusting BAI with each significant risk factor individually. Reported as a range of point estimates.

In multivariable analyses, BAI persisted as a predictor of elevated mortality (OR range 1.81-1.87, 95% CI 1.16-2.93, per 1-SD increase) independent of age or WMLs. In addition to BAI, both MAavg (OR 0.59, 95% CI 0.35-1.00, per 1-SD increase) and MDavg (OR 0.63, 95% CI 0.41-0.97, per 1-SD increase) were significantly associated with mortality. Further analyses indicated that multicollinearity was not a concern (age, Tolerance=0.57, VIF=1.76; WML, Tolerance=0.70, VIF=1.43; MAavg, Tolerance=0.68, VIF=1.47; MDavg, Tolerance=0.67, VIF=1.50). The association between arrival hemoglobin and three-month mortality was evaluated in additional analyses showing significance both in the univariable (OR 0.95, 95% CI 0.92-0.98, per g/L increase) and multivariable models (OR 0.95, 95% CI 0.93-0.98, per g/L increase). Arrival hemoglobin did not weaken the odds ratio (OR=1.99) or statistical significance of BAI (95% CI 1.28-3.09) in the multivariable model. Overall mortality during the follow-up was 21.1% (n=43). When extending the follow-up up to 2.5 years the results of Kaplan-Meier analysis remained similar: patients in the highest and middle BAI tertiles had a significantly worse survival compared to the lowest tertile according to the log rank comparisons ($P<0.01$ for both) (Figure 2).

DISCUSSION

We found that BAI measured from admission NECT-scans with excellent reproducibility is an independent predictor of three-month mortality after MT in patients presenting with ICA or M1 occlusions. A 1-SD increase in BAI is associated with a twofold increase in three-month mortality. None of the other parameters associated with mortality remained as significant as BAI in the multivariable analyses.

To the best of our knowledge, the association between brain atrophy and postinterventional survival in patients undergoing invasive procedures has not been thoroughly investigated. A recent study on trauma patients by Tanabe et al.[11] demonstrated a 1.5 times higher risk of 1-year mortality per each 1-SD increase in BAI, which persisted after adjusting for covariates. Although Tanabe et al.[11] did not find a significant difference in 30-day mortality, their Kaplan-Meier survival curves show a trend resembling our survival curves: most of the deaths occurred within the first three months, after which the curves continue to run more parallel. In the aforementioned study, masseter sarcopenia also had a cumulative effect on mortality.[11] Similarly, in our previous work, we demonstrated that MDavg and MAavg are independent predictors of three-month survival after MT of the ICA or M1.[18] Masseter muscle parameters remained as significant predictors of mortality when included as covariates in the model along with BAI also in the present study. This finding suggests that both BAI and masseter sarcopenia are predictors of three-month mortality in MT patients.

Earlier studies have established age as a predictor of survival after ischemic stroke[25,26] and that brain atrophy increases mortality among the elderly.[12,13] In consensus with prior research, we also found age to be an important factor predicting mortality but in the present

study we additionally ascertained that age loses its significance as a predictor when considered together with BAI. Conversely, Tanabe et al.[11] found age to be significant even after adjusting for BAI and masseter area. This discrepancy could be explained by the differences in the study populations: the Tanabe et al.[11] study included only patients aged 65 years or older and studied a wide range of trauma patients. Furthermore, Tanabe et al.[11] examined mortality over a one-year period, in which the effect of age is likely to be greater. Our results suggest that both age and BAI are important prognostic factors for patients undergoing MT, although BAI appears to be more relevant in predicting short-term mortality.

In addition to age, our results showed that BAI is also strongly associated with the presence of WMLs and CILs. The association between WMLs and clinical outcome in MT patients is contradictory in prior research.[7,8] In our study, we showed that the presence of WMLs does not persist as a significant predictor of three-month mortality in the same model with BAI. Our results do not resolve the predictive value of WMLs on the clinical outcome at three months. However, they do suggest that BAI is a distinctly stronger predictor of mortality than WMLs in the same time frame. Moreover, WML evaluation is more reliable from magnetic resonance images compared to CT scans,[27,28] whereas BAI measurements from CT images have shown excellent reliability.[11] Hence, compared to WMLs, BAI could be a more useful prognostic tool for clinical practice. In earlier research, CILs have been associated with poor clinical outcome at three months after MT in sexagenarians and older.[9] The study time frame may explain the lack of significant results between CILs and mortality in our analyses: even though the presence of CILs is associated with poor functional outcome at three months, its effect on mortality may appear after a longer period. Our analyses on overall mortality, however, suggest that BAI may also have long-term predictive value. The associations between BAI and CILs and mortality in MT patients in the long-term would require additional research.

In our study, hemoglobin persisted as a significant predictor of mortality after adjusting for covariates, whereas serum creatinine did not reach statistical significance at any point. Our results on the effect of hemoglobin and creatinine are in line and corroborated by previous studies in stroke patients.[29,30]

Mortality after MT is still relatively high considering the high reperfusion rates. The full picture of factors contributing to the higher mortality risk despite successful recanalization is unclear. In our previous studies, we have demonstrated the excellent feasibility and reliability of MAavg and MDavg measurements from routine CTA images in clinical work and their relation with survival in carotid endarterectomy and MT patients.[18,23] In the present study, we found that brain atrophy is associated with an increased risk of three-month mortality after MT. Although magnetic resonance imaging is frequently used for detection of degenerative brain changes, it is often not available in acute situations unlike CT. BAI measured from routine CT images with excellent reproducibility, similar to masseter parameters, could therefore provide an additional prognostic tool in identifying which patients with a large-vessel occlusion will benefit from MT. Identifying patients more susceptible to poor outcomes would enable, for example, better resource allocation for post-procedural rehabilitation. In future studies, severe brain atrophy would even be worth considering when assessing the appropriateness of MT for patients in poor condition.

Our study has some limitations. Firstly, the population of the study only consists of single-center AIS patients undergoing MT due to ICA or M1 occlusions, which may limit the generalizability of the results. Secondly, the retrospective nature of part of the data collection and measurements may further limit the generalizability and expose the results to selection bias

as well as potential non-evaluated confounders. Another potential source of confounding is the post hoc exclusion of patients with large strokes (ASPECT-score ≤ 7) or large post-procedural parenchymal hematoma at 24 hours. Exclusion by such strong predictors will probably enhance the effect of BAI on mortality. In addition, high quality data on the pre-stroke functional and nutritional status, or all relevant previous medications of the study subjects at the time of the MT were not available.

CONCLUSIONS

Brain atrophy determined from routine pre-interventional non-contrast-enhanced computed tomography scans predicts mortality in acute ischemic stroke patients suffering from occlusions of the internal carotid artery or the M1-segment of the middle cerebral artery treated with mechanical thrombectomy independent of age, masseter sarcopenia, or the severity of chronic ischemic or white matter lesions.

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COMPETING INTERESTS

None declared.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

AUTHOR STATEMENTS

I. Lauksio: Participated in research conception and design, analyzed data and wrote and revised the manuscript.

I. Lindström: Participated in research conception and design, data collection, wrote the statistical analysis plan, analyzed data and wrote and revised the manuscript.

N.K.: Participated in research conception and design and wrote and revised the manuscript.

N.S.: Participated in research conception and design, data collection and interpretation and wrote and revised the manuscript.

J.H.: Participated in research conception and design, data collection, statistical analysis and interpretation and wrote and revised the manuscript.

N.O.: Participated in research conception and design, data collection, analysis and interpretation and wrote and revised the manuscript and he is guarantor.

S.P.: Participated in research conception and design, data collection and wrote and revised the manuscript and she is guarantor.

All authors agree to be accountable for all aspects of the work.

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FIGURE LEGENDS

Figure 1. Representative preoperative non-contrast-enhanced computed tomography image of a mechanical thrombectomy patient demonstrating the measurement of brain atrophy index.

Figure 2. Kaplan-Meier survival curves of acute ischemic stroke patients treated with mechanical thrombectomy: comparing different brain atrophy index (BAI) tertiles. Patients in the highest and middle BAI tertiles had a significantly worse survival compared to the lowest tertile according to the log rank test ($P < 0.01$ for both comparisons).

Patients at risk

Lowest BAI tertile	61	58	43	33	20	15	0
Middle BAI tertile	76	65	46	31	15	6	0
Highest BAI tertile	67	50	35	22	7	3	0

SUPPLEMENTARY TABLES

Supplementary Table 1. Pearson correlation coefficient analysis of risk factors in acute ischemic stroke patients subjected to mechanical thrombectomy.

Variable	R	P Value
Brain atrophy index	1	
Age	0.543	<0.001
WMLs (Fazekas)	0.431	<0.001
CILs	0.240	0.001
Multiple CILs	0.186	0.008
Lacunar CILs	0.227	0.001
Dental status	-0.314	<0.001
Masseter average area	-0.241	0.001
Masseter average density	-0.284	<0.001

Abbreviations: CIL, Chronic ischemic lesion; WML, White matter lesion.

Supplementary Table 2. Intraclass correlation coefficient (ICC) analysis of BAI measurements and Fazekas scale.

Variable	ICC ^a	95% CI	ICC ^b	95% CI	P Value
BAI	0.932	0.861-0.967	0.894	0.598-0.961	<0.001
Fazekas scale	0.955	0.907-0.989	0.956	0.910-0.979	<0.001

Abbreviations: BAI; Brain atrophy index

^a Model: Intraclass correlation coefficient (ICC) two-way random consistency.

^b Model: Intraclass correlation coefficient (ICC) two-way random absolute.

SUPPLEMENTARY FIGURES

Supplementary Figure 1. Flow chart of the inclusion and exclusion criteria of the study.

ASPECTS, The Alberta stroke program early computed tomography score; ICA, internal carotid artery; M1, M1-segment of the middle cerebral artery.