Radiomics-Derived Brain Age Predicts Functional Outcome After Acute Ischemic Stroke

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Abstract

Background and Objectives
While chronological age is one of the most influential determinants of poststroke outcomes, little is known of the impact of neuroimaging-derived biological "brain age." We hypothesized that radiomics analyses of T2-FLAIR images texture would provide brain age estimates and that advanced brain age of patients with stroke will be associated with cardiovascular risk factors and worse functional outcomes.

Methods
We extracted radiomics from T2-FLAIR images acquired during acute stroke clinical evaluation. Brain age was determined from brain parenchyma radiomics using an ElasticNet linear regression model. Subsequently, relative brain age (RBA), which expresses brain age in comparison with chronological age-matched peers, was estimated. Finally, we built a linear regression model of RBA using clinical cardiovascular characteristics as inputs and a logistic regression model of favorable functional outcomes taking RBA as input.

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Glossary

AF = atrial fibrillation; **DM** = diabetes mellitus; **HTN** = hypertension; **MRI-GENIE** = MRI-GENetics Interface Exploration; **MAE** = mean absolute error; **mRS** = modified Rankin scale; **NIHSS** = NIH Stroke Scale; **RBA** = relative brain age; **WMH** = white matter hyperintensity.

Results

We reviewed 4,163 patients from a large multisite ischemic stroke cohort (mean age = 62.8 years, 42.0% female patients). T2-FLAIR radiomics predicted chronological ages (mean absolute error = 6.9 years, $r = 0.81$). After adjustment for covariates, RBA was higher and therefore described older-appearing brains in patients with hypertension, diabetes mellitus, a history of smoking, and a history of a prior stroke. In multivariate analyses, age, RBA, NIHSS, and a history of prior stroke were all significantly associated with functional outcome (respective adjusted odds ratios: 0.58, 0.76, 0.48, 0.55; all p-values < 0.001). Moreover, the negative effect of RBA on outcome was especially pronounced in minor strokes.

Discussion

T2-FLAIR radiomics can be used to predict brain age and derive RBA. Older-appearing brains, characterized by a higher RBA, reflect cardiovascular risk factor accumulation and are linked to worse outcomes after stroke.

While chronological age is one of the most influential determinants of poststroke outcomes,[1] little is known about the impact of neuroimaging-derived brain age, a recently developed biomarker of personalized brain health.[2] Stroke has devastating effects on both functional and cognitive outcomes.[3] However, the resilience of an individual to ischemic insults might vary depending on the status of the underlying brain. In fact, older-appearing brains on MRI, defined by a higher neuroimaging-predicted brain age rather than chronological age, have been associated with diverse diseases, risk factors, lifestyles, and cognitive performances.[4,5] By contrast, patients with younger-appearing brains are believed to undergo a healthier aging process with better brain maintenance, featuring a decreased pathologic age-related structural degeneration.[6] While a variety of studies focused on the brain age of patients suffering from neurodegenerative or psychiatric diseases, the aging process of the brains of patients with stroke and its impact on stroke outcomes remain largely undescribed.[2]

Although chronological time passes at the same speed for everyone, individuals age at different paces; thus, individuals can be more sensitive or, on the contrary, more resilient to the effects of biological aging. Quantifying the deviation from an expected brain aging distribution could prove relevant for assessing brain health and health prognoses, especially in diseases heavily influenced by age, such as stroke. Some authors showed that the brains of stroke survivors appeared older than those of age-matched healthy controls, highlighting the detrimental impact of the ischemic insult on the aging trajectory of the brain.[7,8] Moreover, other authors found an association between higher brain age and a greater risk of stroke, trapping stroke survivors in a vicious circle.[9] However, the clinical determinants of brain age in patients with stroke are currently unknown, warranting further imaging studies in stroke populations to identify potentially preventable risk factors.

The resilience of a brain to an ischemic insult varies between individuals and depends on numerous factors which overall describe individuals' brain health. Nevertheless, while good brain health might help to withstand a circumscribed stroke, this benefit could become insignificant when suffering from a more severe stroke. The influence of brain age on functional outcome should consequently be examined as a function of stroke severity to better understand the extent to which brain health plays a role in ischemic lesion mitigation. This could help select patients before acute therapeutic interventions. Indeed, identifying good responder patients lying at the borders of the therapeutic indication's spectrum is the central question of ongoing clinical trials, namely minor strokes (NIH Stroke Scale [NIHSS] less than 5). For instance, patients suffering from a minor stroke on a vulnerable brain might potentially benefit more from revascularization therapies than patients with better brain health. Identifying new noninvasive biomarkers available on admission, such as brain age, could help select additional patients for acute stroke treatment.

Capturing radiologic hallmarks of aging has been a dynamic field of neuroimaging research over the past few decades.[2] Nevertheless, established methods to quantify this process mainly leveraged atrophy, disregarding other cerebral imaging manifestations of age-related degeneration. Radiomics, an emergent method of image quantification providing standardized quantitative variables describing the global texture of an image, could provide a better estimate of age-related imaging alterations.[10] However, performances of radiomics to produce brain age biomarkers are unknown, a fortiori from acute MRI scans of patients with stroke.

In this large multicentric retrospective imaging study of patients with ischemic stroke, we aimed to (1) assess performances of brain T2-FLAIR MRI radiomics to predict brain age from clinical imaging, (2) understand the clinical determinants of brain age, and (3) study its relevance to poststroke outcome. We hypothesized that patients with stroke with a higher radiomics-predicted brain age than their chronological age would have more cardiovascular risk factors and worse poststroke functional outcomes, especially as observed in minor strokes.

Methods

Participants

We reviewed all neuroimaging data of patients with stroke included in a large international multisite collaborative effort: the MRI-GENetics Interface Exploration (MRI-GENIE) study. Sites shared clinical, MRI imaging, and genetic data. Both study design, data collection protocols, and populations have been previously published.[11-13]

Standard Protocol Approvals, Registrations, and Patient Consents

All participants or health care proxies provided signed informed consent. The MRI-GENIE project has been approved by the MGH Institutional Review Board (IRB, Protocol No.: 2001P001186 and Protocol #: 2003P000836) and the ethics boards of the collaborating institutions.

Data Collection and Neuroimaging Preprocessing

We reviewed a total of 4,163 patients across 17 different sites, for which cardiovascular risk factor phenotypes, T2-FLAIR imaging, and successful brain and ventricles segmentations were available.[14,15] Demographic and cardiovascular phenotypes included age, sex, hypertension (HTN), history of smoking, diabetes mellitus (DM), atrial fibrillation (AF), and a history of prior stroke. Acute stroke severity was measured with the NIHSS. Functional outcome was measured with the modified Rankin scale (mRS) at 60–180 days after stroke.

Axial T2-FLAIR images were acquired between 2003 and 2011 within 48 hours of the hospital admission, mostly on 1.5 T MRI scanners. Mean in-plane resolution was 0.7 mm (range: 0.3–1.0 mm), and the mean through-plane resolution was 6.2 mm (range: 3.0–30.0 mm). Total brain, ventricle, and white matter hyperintensities (WMH) were automatically segmented using dedicated state-of-the-art deep-learning frameworks; raw values were reported. Thorough control of the quality of the segmentations was performed and is already published.[14,15] To reduce interscanner unwanted variance, T2-FLAIR images intensities were normalized using a mean-shift algorithm.[14] We computed parenchymal masks by subtracting the ventricle masks from the total brain masks. Then, we performed a morphologic opening operation with a 3×3 kernel to each axial slice to prevent any segmentation noise from perturbating radiomics extraction.

Radiomic Feature Extraction

Radiomic features were extracted using the open-source toolbox PyRadiomics V2.2.0 from brain parenchyma on T2-FLAIR.[10] In brief, 760 features were extracted describing the shape, histogram, and texture of the brains. To reduce interscanner variability, images were downsampled to a $1 \times 1 \times 6$ mm matrix. The list of the extraction parameters can be found in the supplemental materials (eMethods, links.lww.com/WNL/C494).

Chronological Age, Brain Age, and Relative Brain Age

Radiomics-derived predictions of patients' chronological age were performed by an ElasticNet linear regression model in a 5-fold nested stratified cross-validation scheme (eFigure 1, links.lww.com/WNL/C494). First, the whole data set was split into 5 equivalent training and test samples (80/20%) to produce one single out-of-training-sample age prediction for every patient. Then, for each of the 5 train-test splits, feature selection was performed on the training set by an ElasticNet linear regression model in a 3-fold cross-validation scheme (inner loop). Selected features were subsequently entered into another ElasticNet model that was fitted on the entire training set where its L1 and L2 hyperparameters were optimized and then finally tested on the unseen test set (outer loop). Radiomics-based predicted ages are subsequently referred to as "brain age." Prediction performances were evaluated with Pearson correlation (r) and coefficient of determination (R^2). Intercenter variability in brain age prediction performances was studied (eAppendix 1, eFigure 2, eTable 1). To better understand which radiomics variables were relevant for brain age prediction, we recorded radiomics selected across all folds of the nested cross-validation and their respective ElasticNet linear regression coefficients (eAppendix 2, eTable 2). The results of the radiomics and machine learning results were reported according to the RQS and CLAIM statements (eAppendices 3 and 4).[16,17]

To evaluate the specific added value of brain age to chronological age, we calculated the residuals of predictions (brain age—chronological age). However, these residuals are known to be negatively correlated with chronological age because of a regression dilution bias induced by the accumulation of random measurement errors, which can be encountered in radiomics analyses.[18] An established solution suggested by the authors of a study[4] is to calculate relative brain age (RBA) by regressing out any correlation with chronological age as follows:

RBA = Predicted Age – Expected (Predicted Age | Chronological Age)

The expected predicted age as a function of chronological age is obtained by fitting a linear regression model with chronological age as an input and the predicted age as a response variable. RBA represents the appearance of an individual brain in comparison with chronological age-matched peers within the cohort: A higher brain age at a given chronological age will have a positive RBA and will reflect an older-looking brain,

whereas a younger-appearing brain on neuroimaging will have a negative RBA.

To evaluate the added value of detailed textural brain information on top of simple volumetric information of the brain mask, an ancillary analysis was performed: We here predicted brain age using only those radiomics features describing the size and the shape of the parenchyma but not the more detailed texture. This analysis was performed to produce brain age biomarkers based only on the cerebral parenchymal volumetric data and to compare it with the ones predicted from both volumetric and T2-FLAIR intensity profile data. No prediction was done using only advanced textural radiomics because they are inherently correlated to shape radiomics. To further help the interpretation of the neuroimaging underpinnings of radiomics RBA, we calculated the correlation between RBA and brain volume and WMH burden.

Identifying Clinical Determinants of Accelerated Aging

To quantify the impact of patients' clinical phenotypes on their brain, RBA were compared using a two-sided t-test for each categorical clinical variable (sex, HTN, DM, AF, CAD, history of smoking, history of prior stroke) and using Pearson correlation for continuous variables (age) (level of significance: $p < 0.05$). Variables for which RBA significantly differed in univariate analyses were then entered into a multiple linear regression model of RBA.

Evaluating the Impact of Accelerated Brain Aging on Poststroke Functional Outcome

Good functional outcome was defined as an mRS ≤ 2 at follow-up. Comparison of patients' RBA by dichotomized outcome groups was performed using a two-sided t-test. To compare the effect of RBA on functional outcome with traditional variables, a multiple logistic regression of dichotomized functional outcome was built. Feature selection for this model was performed using a 5-fold cross-validated recursive feature elimination process. Candidate predictors were age, sex, HTN, DM, AF, CAD, history of smoking, prior stroke, brain volume, WMH volume, NIHSS at index stroke, and RBA. The final model's coefficients were estimated, and odds ratios were calculated. To further evaluate the impact of RBA beyond dichotomized functional outcome (good vs bad), full-scale mRS distributions (0–6) were examined by quartiles of RBA.

In ancillary analyses, we investigated the hypothesis that RBA would only be impactful on functional outcomes in minor strokes because severe strokes may lead to unfavorable outcomes regardless of the underlying brain status. To explore this hypothesis, we studied the effect sizes of RBA on dichotomized outcome groups by incrementally adding patients by the rank of NIHSS (0, 0–1, 0–2, 0–3, etc.) and estimated the effect sizes by calculating the standardized adjusted odds ratios of multiple logistic regression models built with the variables previously identified as significantly associated with good functional outcome.

Data Availability

On reasonable request to the corresponding author and pending approval from local IRBs, data will be made available to replicate the results presented in this article. Radiomic features extraction, feature selection, and machine learning analyses were performed in Python 3.7.6 using the toolbox *scikit-learn* and *pyradiomics*.[10,19] Logistic regression coefficients estimations were performed using *statsmodels*.[20]

Results

Population

All included patients had suffered an ischemic stroke. Population demographics are shown in Table 1. There were 42% female patients, and the mean age was 62.8 (standard deviation 15.0) years. Admission NIHSS scores and follow-up mRS scores were available for 2,234 and 1,871 patients, respectively. Exhaustive ordinal mRS scale (0–6) data were available for 871 patients. Median NIHSS was 3 (interquartile range: 1–6); good functional outcome was achieved by 72.5% of patients.

Radiomics Brain Age Predictions and RBA

The mean predicted brain age was 62.8 years with a mean absolute error (MAE) of 6.9 years. Pearson correlation and coefficient of determination between predicted brain age and chronological age were $r = 0.81$ $p < 0.001$ and $R^2 = 0.65$, respectively (Figure 1). Prediction performances using only radiomics describing the shape and size of the brain parenchyma were lower: $r = 0.66$ $p < 0.001$, $R^2 = 0.45$, mean predicted brain

**Table 1** Clinical and Radiological Characteristics of the Study Population (n = 4,163)

Age	Mean (SD)	62.8 (15.0)
Female	n (%)	1,748 (42.0%)
Hypertension	n (%)	2,825 (67.9%)
Diabetes mellitus	n (%)	687 (16.5%)
Atrial fibrillation	n (%)	595 (14.3%)
Coronary artery disease	n (%)	772 (18.5%)
History of smoking	n (%)	1,331 (32.0%)
Prior stroke	n (%)	539 (12.9%)
WMH volume	Median (IQR)	4.2 mL (1.4–11.2)
Brain volume	Mean (SD)	1,467.5 mL
Brain ventricular volume	Median (IQR)	31.8 (18.9–42.6)
NIHSS at baseline[a]	Median (IQR)	3 (1–6)
Good functional outcome at 60–180 d[b]	n (%)	1,356 (72.5%)

[a] NIHSS was available for 2,234 patients.
[b] Dichotomized functional outcome (mRS ≤ 2 vs mRS > 2) was available for 1,871 patients.
Abbreviations: IQR = interquartile range; mRs = modified Rankin scale; NIHSS = NIH Stroke Scale; WMH = white matter hyperintensities.

Figure 1 Brain Age Prediction Performances and Relative Brain Age
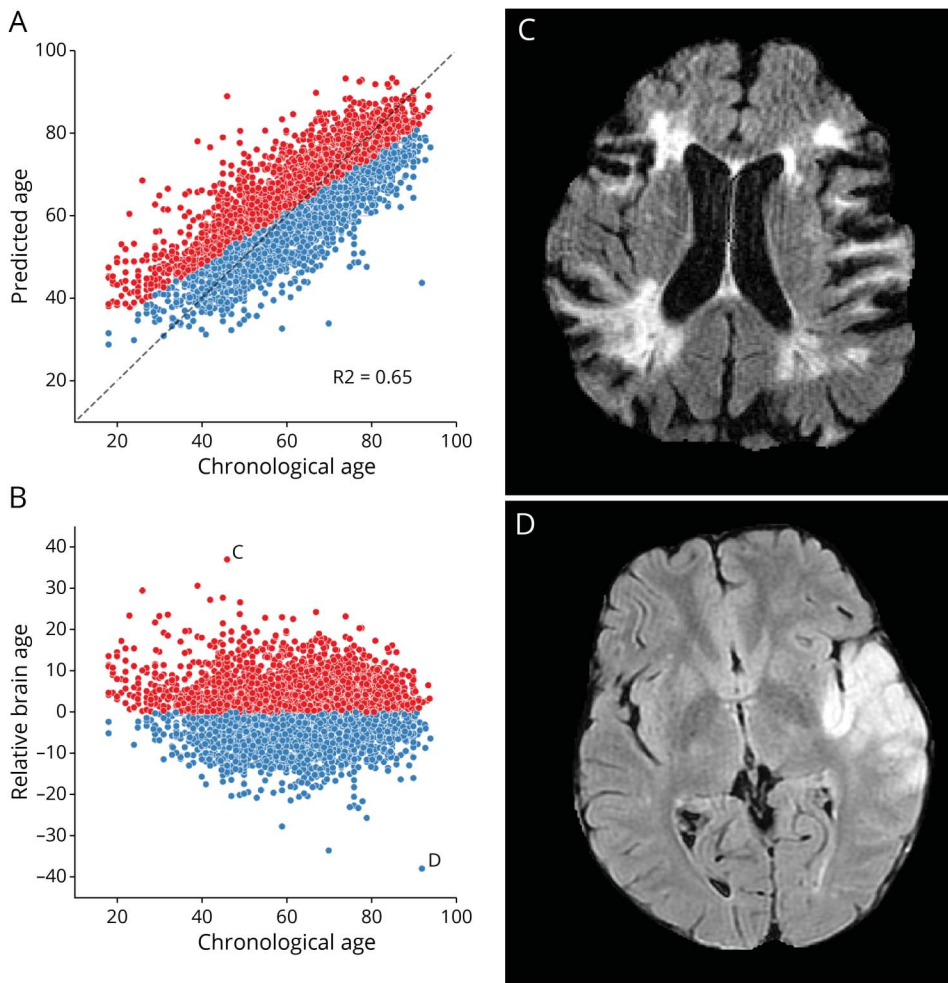
Scatter plots of the T2-FLAIR radiomics (A) predicted brain age and (B) relative brain age (RBA) per chronological age. Patients were colored in red if they had a positive RBA and thus a brain that appeared older to their age-matched peers or in blue if they had a negative RBA and a younger-looking brain. (C) T2-FLAIR axial image of a patient with a positive RBA: predicted brain age = 88, chronological age = 46, RBA = 36.2; this patient's brain exhibits multiple cortical and subcortical sequelae, moderate-to-severe parenchymal atrophy with enlarged ventricles and sulci, and confluent white matter hyperintensities, which extents are unexpectedly large for a 46-year-old patient. (D) T2-FLAIR axial image of a patient with a negative RBA: predicted brain age = 43, chronological age = 92, RBA = −38.6; notwithstanding the left middle cerebral artery lesion, this patient's brain trophicity is maintained; the cortex and the deep gray nuclei are sharply defined, overall describing a healthy brain for this 92-year-old patient.

age: 62.8 years, and MAE = 9.0 years. Additional radiographic examples of brain age predictions are shown in eFigure 3 (links.lww.com/WNL/C494). Relevant radiomics for brain age prediction, their correlation with imaging characteristics, and the results of the intersite prediction performances are presentedal materials (eAppendices 2 and 4). In brief, brain age prediction performances were lower when producing brain age in a site where patients' age significantly differed from the training sites. T2-FLAIR radiomics that captured neuroimaging aspects of atrophy, hyperintensities, and heterogeneity were predictive of higher brain age and therefore older-appearing brain, whereas radiomics representative of parenchymal trophicity and homogeneity were predictive of lower brain age and thus, younger-appearing brain. Moreover, this was confirmed by analyzing RBA with more traditional radiological hallmarks of brain aging: patients with older-appearing brains had a higher WMH burden and a lower brain volume.

Clinical Phenotype and Brain Aging

In univariable analysis, patients with HTN, DM, AF, CAD, a history of smoking, and a history of prior stroke had a significantly higher RBA. RBA did not differ between male

patients and female patients (Table 2). As expected, there was no significant correlation between chronological age and RBA: $r = 0.03$, $p = 0.145$.

Table 2 Comparison of Patients' Relative Brain Age (RBA) by Clinical Phenotype (n = 4,163)

	No	Yes	*p* Value
Female	0.02 ± 7.16	−0.02 ± 7.23	0.863
Hypertension	−0.61 ± 7.45	0.29 ± 7.05	<0.001
Diabetes mellitus	−0.18 ± 7.16	0.92 ± 7.03	<0.001
Atrial fibrillation	−0.10 ± 7.14	0.60 ± 7.48	0.034
Coronaropathy	0.13 ± 7.29	0.58 ± 6.74	0.014
History of smoking	−0.15 ± 7.07	0.33 ± 7.43	0.045
Prior stroke	−0.42 ± 7.07	2.85 ± 7.33	<0.001

Two-sided *t*-test, alpha = 5%. RBA values are expressed by their mean ± standard deviation. Patients with positive RBA have older-looking brains, whereas patients with negative RBA have younger-looking brains.

Table 3 Multivariable Linear Regression of the Clinical Predictors of Relative Brain Age (RBA) (n = 4,163)

	RBA coefficient	95% CI Lower	95% CI Upper	p Value
Hypertension	0.5615	0.085	1.038	0.021
Diabetes mellitus	0.9098	0.318	1.502	0.003
Atrial Fibrillation	0.4911	−0.133	1.115	0.123
Coronary artery disease	0.1824	−0.387	0.752	0.530
History of Smoking	0.5367	0.07	1.003	0.024
Prior Stroke	3.2134	2.566	3.861	<0.001

Two-sided t-test, alpha = 5%. A positive coefficient implies older-looking brains.

In multiple regression analyses, RBA was higher and therefore expressed accelerated brain aging in patients with HTN, DM, a history of smoking, and a history of prior stroke (Table 3).

RBA and Poststroke Functional Outcome

Patients who achieved a good functional outcome had a significantly lower RBA (−0.44 vs 1.45, p < 0.001) and therefore a younger-looking brain than their chronological age-matched peers.

Among the evaluated predictors of poststroke outcome, the automated cross-validated recursive feature elimination process selected 4 clinical variables to enter the final logistic regression model: age, baseline NIHSS, prior stroke, and RBA. The results of the logistic regression of good functional outcomes are summarized in Table 4. In brief, in multivariable analysis, higher chronological age, higher RBA, higher baseline NIHSS score, or the presence of a history of prior stroke was independently associated with worse poststroke outcomes (respective adjusted odds ratios for good outcome: 0.58, 0.76, 0.48, 0.55; all p-values < 0.001). Distributions of mRS scores by quartile of RBA are shown in Figure 2. There was a higher

Table 4 Logistic Regression of Good Functional Outcome

Variables	Unstandardized aOR — aOR	95% CI for aOR Lower	95% CI for aOR Upper	Standardized aOR — aOR	95% CI for aOR Lower	95% CI for aOR Upper	p Value
Age	0.96	0.95	0.97	0.58	0.51	0.65	<0.001
NIHSS	0.87	0.85	0.89	0.48	0.43	0.54	<0.001
Prior stroke	0.55	0.41	0.74	0.55	0.41	0.74	<0.001
RBA	0.96	0.95	0.98	0.76	0.68	0.86	<0.001

NIHSS = NIH Stroke Scale; RBA = relative brain age; aOR = adjusted odds ratio.

proportion of favorable mRS in the lower quartiles of RBA in patients exhibiting younger-looking brains.
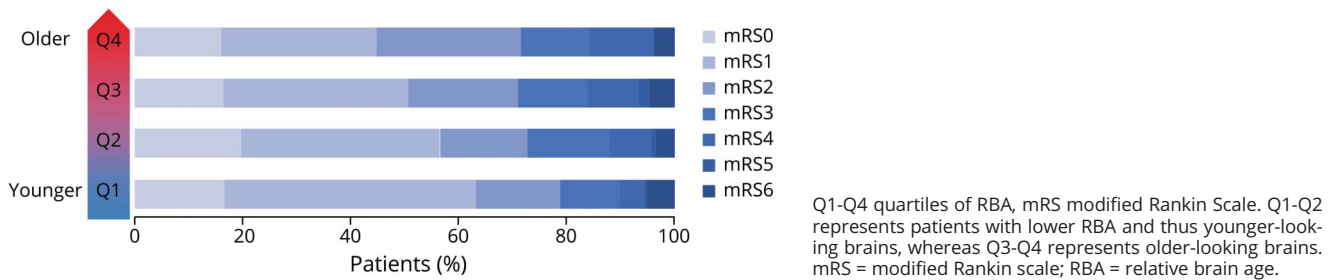
Multivariable effect sizes of RBA on the dichotomized poststroke outcome by the rank of baseline NIHSS are shown in Figure 3. After adjustment for covariates (age, NIHSS, history of prior stroke), the detrimental effect size of RBA on achieving a good functional outcome was maximal for NIHSS = 0 (aOR = 0.61, n = 295) and decreased until NIHSS ≤ 9 (aOR = 0.75, n = 1,642).

Discussion

By leveraging a large ischemic stroke clinical imaging cohort, we successfully used brain MRI T2-FLAIR radiomics to predict brain age and derived RBA, a biomarker describing patients' brain health relative to their peers. Older-appearing brains were associated with cardiovascular risk factors, highlighting their detrimental impact on brain health. Finally, we showed that high RBA had a negative impact on poststroke functional outcomes. This effect was especially pronounced in patients presenting with lower stroke severity.

Chronological age quantifies the length of time a person has lived but is unlikely to affect stroke prognosis directly. It may best serve as a surrogate marker for age-related cerebral parenchymal alterations. In some patients, such deleterious alterations accumulate more rapidly or more slowly than the expected pace. Our results suggest that quantifying the deviation from expected brain age in patients with stroke can be relevant for assessing brain health and prognostication. Indeed, in our cohort, patients who did not achieve a favorable outcome had brains that appeared older on T2-FLAIR compared with their chronological age-matched peers. Moreover, our results show that RBA affected stroke outcomes independently from chronological age, NIHSS, and history of prior stroke. Indeed, patients with an older-appearing brain were more likely to develop an unfavorable poststroke outcome at any given age. This finding indicates that radiomics-derived RBA could assess the brain health of patients with stroke and quantify the resilience of brains in a way that chronological age cannot. In previous analyses of randomized control trials, chronological age–defined older patients (older than 80 years) were identified as a subgroup that benefitted more from endovascular recanalization than their younger counterparts, with the hypothesis that they had less brain reserve to withstand ischemia.[21,22] Future studies could evaluate whether patients with older-appearing brains would benefit more from recanalization[23] and assess whether brain age imaging biomarkers can help to identify new candidates for reperfusion therapies. For instance, patients with an NIHSS lower than 5 are currently not eligible for mechanical thrombectomy and are the topic of numerous randomized controlled trials. Our results could suggest that in this specific stroke population, patients with an older-appearing brain are less likely to reach a good functional poststroke outcome and could maybe benefit more from reperfusion therapies.

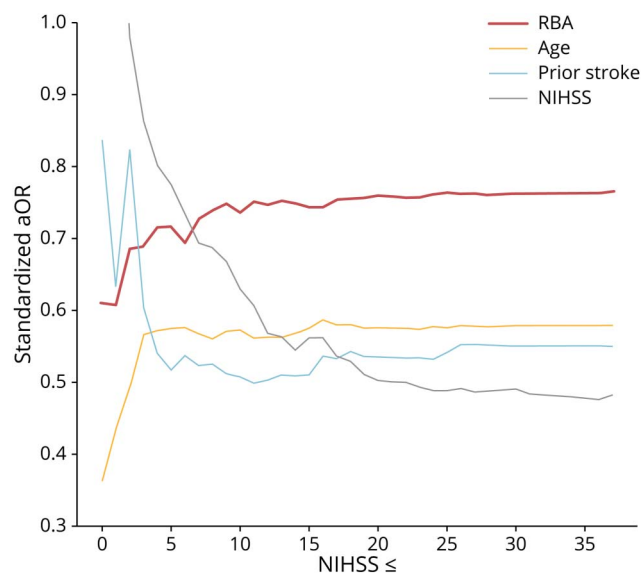**Figure 2** mRS Shift Plot per Quartile of RBA

Q1-Q4 quartiles of RBA, mRS modified Rankin Scale. Q1-Q2 represents patients with lower RBA and thus younger-looking brains, whereas Q3-Q4 represents older brains. mRS = modified Rankin scale; RBA = relative brain age.

Individual lifestyles, genetics, and environment can also set a different course for brain aging.[4,24] We found that high RBA was associated with HTN, DM, and a history of smoking, in line with the results based on large cohorts such as UK Biobank and Whitehall II.[4,5,9,24] This adds to the body of evidence that cardiovascular health and brain health are intertwined and stresses the importance of preventative medicine.[25] Our results also showed that a history of prior stroke was the most influential clinical factor affecting RBA, with an effect size 3-fold larger than other clinical variables. The second most detrimental clinical trait for brain aging in our sample was diabetes, which also emerged as a significant condition accelerating brain aging in previous work.[26] Identifying potentially modifiable factors affecting brain health yields relevance for prevention interventions.[27] For instance, body mass index and daily exercise were previously identified as predictive of younger brain age and are

Figure 3 Effect Sizes of the Predictors of Good Functional Outcome by Rank of Baseline NIHSS

RBA had a detrimental impact on achieving a good functional outcome especially in patients with low NIHSS. aOR = adjusted odds ratio; NIHSS = NIH Stroke Scale; RBA = relative brain age.

potentially modifiable.[24,28] RBA and brain age could furthermore be used as follow-up brain health biomarkers.

Translation of the brain age biomarker to clinical care remains challenging. Indeed, most of the available neuroimaging brain age prediction methods include spatial registration to an anatomic template, which requires high-quality research-grade imaging.[2,4,24] Moreover, T1-weighted imaging is predominantly used in these pipelines but is uncommonly acquired during acute stroke MRI imaging workup. Therefore, there is a need for frameworks compatible with clinical care settings, especially in time-sensitive diseases such as stroke, featuring T2-FLAIR, given its common utilization in both the acute phase and during the follow-up.[29] Radiomics, an emerging image quantifying technology, could represent a potential solution because they require little computational power and can be applied to any digitalized medical imaging.[16] Radiomics were never assessed to predict brain age. While in previous literature, brain age is mostly predicted by volumetric information, radiomics description encompasses information that goes beyond volume, characterizing the shape and the texture of an image; consequently, radiomics can potentially capture more information. Analyses of T2-FLAIR images using radiomics are especially relevant in patients with stroke because this sequence reflects both higher age and cerebral burden of diseases.[30] Moreover, most published studies have trained their models on healthy brains, which have a uniform aging distribution unlike stroke cohorts. This aspect might be reflected by the greater errors of our predictions than in published literature, which ranges in adult cohorts from around 2.5 years, for recent complex deep learning–based methods,[31] to between 4.3 and 13.5 years for more traditional methods.[2] Moreover, there is a trend in brain age prediction literature to incorporate more and more complex and multimodal data, such as diffusion tensor imaging or functional MRI and process it within high-end deep learning frameworks.[24,32,33] We deliberately chose to tackle the challenge of leveraging clinical imaging and a lighter methodological framework with the idea of developing models that are more interpretable and may have a better chance of translating brain age biomarkers to routine clinical care.

This work has several limitations. First, our cohort included patients from 2003 to 2011, whose management might not have been fully representative of patients treated in modern stroke

care settings. Future work will assess the impact of brain age on the outcome of patients treated with up-to-date reperfusion therapies. Second, despite being drawn from a multicentric cohort using nested cross-validation, future validation of our preliminary findings in an independent cohort will further ensure the generalizability of the brain age biomarker in stroke care. Third, we could not benchmark our method against other published methods such as BrainAGE or Brain age delta[2,18] because we did not have T1-weighted images; further work could evaluate our method on reference data sets if they include T2-FLAIR imaging. Fourth, our work leveraged segmentation masks and therefore suffers from limitations related to segmentation steps. Moreover, the impact of motion artifacts or of early hemorrhagic transformation on RBA was not specifically assessed. Finally, we could not explore the relationship between T2-FLAIR radiomics-derived brain age biomarkers with more detailed outcome metrics, such as cognitive and language outcomes, or with other neuroimaging biomarkers of brain health, such as brain reserve or effective reserve.[34,35] Future studies could indeed study the relationship between radiomics brain age and cognitive reserve in patients with stroke.

To conclude, in this cohort study of 4,163 patients with ischemic stroke, using radiomics extracted from clinically acquired T2-FLAIR images, we derived RBA, a chronological age–independent biomarker describing individual biological brain age. A higher RBA was linked to the presence of cardiovascular risk factors and worse poststroke outcomes. Therefore, this newly radiomics-derived RBA may capture previously unidentified prognostic information.

Study Funding

Disclosures

Publication History

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