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Radiomics-Based Intracranial Thrombus Features on CT and CTA Predict Recanalization with Intravenous Alteplase in Patients with Acute Ischemic Stroke

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ABSTRACT

BACKGROUND AND PURPOSE: Thrombus characteristics identified on non-contrast CT (NCCT) are potentially associated with recanalization with intravenous (IV) alteplase in patients with acute ischemic stroke (AIS). Our aim was to determine the best radiomics-based features of thrombus on NCCT and CT angiography associated with recanalization with IV alteplase in AIS patients and proximal intracranial thrombi.

MATERIALS AND METHODS: With a nested case-control design, 67 patients with ICA/M1 MCA segment thrombus treated with IV alteplase were included in this analysis. Three hundred twenty-six radiomics features were extracted from each thrombus on both NCCT and CTA images. Linear discriminative analysis was applied to select features most strongly associated with early recanalization with IV alteplase. These features were then used to train a linear support vector machine classifier. Ten times 5-fold cross-validation was used to evaluate the accuracy of the trained classifier and the stability of the selected features.

RESULTS: Receiver operating characteristic curves showed that thrombus radiomics features are predictive of early recanalization with IV alteplase. The combination of radiomics features from NCCT, CTA, and radiomics changes is best associated with early recanalization with IV alteplase (area under the curve = 0.85) and was significantly better than any single feature such as thrombus length ($P < .001$), volume ($P < .001$), and permeability as measured by mean attenuation increase ($P < .001$), maximum attenuation in CTA ($P < .001$), maximum attenuation increase ($P < .001$), and assessment of residual flow grade ($P < .001$).

CONCLUSIONS: Thrombus radiomics features derived from NCCT and CTA are more predictive of recanalization with IV alteplase in patients with acute ischemic stroke with proximal occlusion than previously known thrombus imaging features such as length, volume, and permeability.

ABBREVIATIONS: AUC = area under the curve; GLCM = gray-level co-occurrence matrix; LSW = level-spot waves; ROC = receiver operating characteristic

Acute ischemic stroke treatment using intravenous alteplase, a tissue-type plasminogen activator, is primarily focused on dissolving thrombus within the arterial tree. Thrombus charac-

teristics such as length, burden, and permeability identified on multitechnique CT are potentially associated with recanalization with IV alteplase.¹ For example, a shorter length of middle cerebral artery M1 segment thrombus is associated with successful recanalization with IV alteplase treatment.^{2,3} It is hypothesized that thrombus length along with collateral status and angioarchitecture within the cerebral arterial tree may be related to lysis with IV alteplase.⁴ Patients with short-but-permeable thrombi are more likely to be recanalized with intravenous alteplase than those without.⁵ Thrombus permeability, measured by attenuation characteristics on noncontrast CT and CT angiography, is associated with improved functional outcome, smaller final infarct volume, and higher recanalization rates.⁶ Nonetheless, the ability of these imaging constructs to reliably predict recanalization with IV alteplase in patients with proximal intracranial thrombi is still limited.

Radiomics is an emerging field that converts imaging data into a high-dimensional feature space using a large number of auto-

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Radiomics features used in the analysis

	Method	No. of Features
Set 1: First-order statistics	Voxel intensity distribution	34
Set 2: Shape and size	Thrombus length, surface, and volume	6
Set 3: Textural features	Gray-level co-occurrence matrix	78
	Gray-level run length matrix	66
	Neighborhood gray-level difference matrix	10
	Law texture	105
	Local binary pattern	27

matically extracted data-characterization algorithms.⁷⁻⁹ Compared with measuring intracranial thrombus characteristics such as length, volume, and permeability, radiomics features distill multiple-but-subtle variations within the thrombus environment that cannot be appreciated by the human eye. We hypothesized that radiomics-based features of intracranial thrombus on NCCT and CTA are capable of measuring distinct characteristics of thrombus associated with recanalization with IV alteplase better than known thrombus characteristics measured on NCCT and CTA.

MATERIALS AND METHODS

Patient Selection

The primary objective of the study was to identify radiomics-based thrombus characteristics associated with recanalization of thrombus with IV alteplase in patients with intracranial ICA or M1 MCA segment thrombi. Because recanalization of thrombus with IV alteplase within these proximal intracranial arterial segments is rare, we used a case-control study design nested within the precise and rapid assessment of collaterals using multi-phase CTA in the triage of patients with acute ischemic stroke for IV or IA Therapy (PROVe-IT).¹⁰ We only included patients who had thin-slice NCCT (slice thickness ≤ 2.5 mm) and CTA (slice thickness ≤ 0.625 mm) performed on the same scanner. The study included all patients fulfilling study inclusion criteria with ICA/M1 MCA segment thrombi treated with IV alteplase who achieved recanalization as assessed on the first angiographic acquisition in patients undergoing endovascular therapy or on repeat CTA within 4 hours of baseline imaging in patients who did not undergo endovascular therapy. This time point for assessment of recanalization gives us a clinically relevant measure of recanalization with intravenous tPA that is relatively early. Patients were matched for age, sex, and stroke severity with controls (patients who also had ICA/M1 MCA segment thrombi treated with IV alteplase but without successful recanalization). After excluding 22 patients with excessive motion ($n = 3$), poor image quality ($n = 9$), and image coregistration failure ($n = 10$), we identified 30 patients and 37 controls for inclusion in the current study. The study was approved by the Conjoint Health Research Ethics Board at the University of Calgary.

Thrombus Segmentation

CTA images were automatically aligned with NCCT images using rigid registration with 3D Slicer (<http://www.slicer.org>), a publicly available software.¹¹ The quality of the registration was checked by visual inspection; manual correction was performed whenever the algorithm registration results were suboptimal. A senior neuroradiology fellow (J.N.) performed manual contour-

ing of thrombi in a slice-by-slice manner from axial views of NCCT images using ITK-SNAP (www.itksnap.org),¹² while viewing the corresponding coregistered CTA images for guidance. This manual segmentation was used for the primary analysis. To analyze the variability introduced by manual segmentation, another neuroradiology fellow (Z.A.) manually segmented the same data. The results

based on this segmentation were compared with the primary analysis. Pearson correlation analysis was also performed regarding the thrombus length and volume of 2 manual segmentations.

Radiomics Feature Extraction of Thrombus

Three hundred twenty-six predefined radiomics image features that describe thrombus characteristics were extracted in an automated manner from the above images.^{7,13} These features can be divided into 3 sets: 1) first-order statistics, 2) shape and size, and 3) high-order statistical textural information (Table). The first set quantifies thrombus-intensity characteristics using first-order statistics calculated from all voxels within the thrombus region. Set 2 consists of features such as thrombus length, volume, and compactness.² Set 3 consists of textural features that can quantify textural heterogeneity within the thrombus.¹³ More details on feature definition are in the On-line Appendix. These features were calculated in 3D, thereby taking spatial information compared with the neighboring voxels into account. To obtain a single-feature vector per thrombus, we calculated the mean value of each feature across all the voxels within the thrombus. Radiomic features were extracted from NCCT and CTA images independently. A third group, radiomics change features between NCCT and CTA, was generated additionally by subtracting NCCT features from CTA features. Besides the 3 groups described above, a combination of any 2 or 3 feature groups by concatenation was also used for analysis. All calculations were implemented in Matlab (R2016b; MathWorks, Natick, Massachusetts). For more implementation details about the support vector machine, please refer to the On-line Table 3.

Feature Selection and Classification

Linear discriminative analysis was applied to the 3 groups of features and all possible combinations of the 3 groups of features to rank them in order of importance. Receiver operating characteristic (ROC) analysis was used to compare features in each group and in all the various group combinations generated above; these features were then ranked from the highest-to-lowest importance in each group. The optimum number of features for each group was thereby determined by the feature combination yielding the highest area under the curve (AUC) value using a recursive feature-elimination strategy. To decrease the impact of overfitting, we performed experiments using selected features by 5-fold cross-validation with subjects randomly divided into 5 equally sized groups. Within cross-validation experiments, the support vector machine model for optimizing radiomics features and parameters was built on 4 of the 5 folds and evaluated on the subjects in the

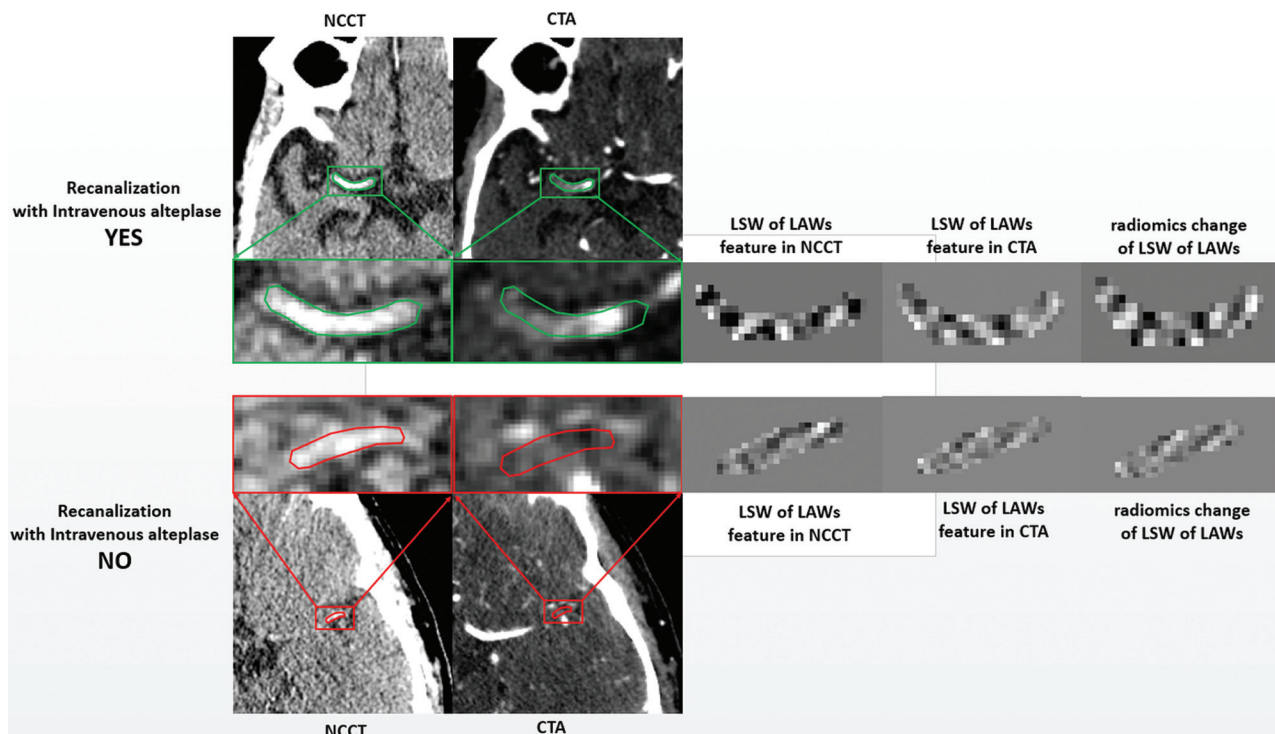


FIG 1. Visualized feature images of thrombus of 2 patients, one with early recanalization and another without recanalization. The selected feature, Laws SD of LSW, is demonstrated. The LSW value (gray-level) of each pixel in the feature map is measuring the heterogeneity in the local region of each pixel.

fifth fold. All cross-validation experiments were repeated 10 times to evaluate the stability of the selected features.

In addition, the selected features were compared with a clinically used feature, residual flow, subjectively graded using consensus by 2 experts from CTA images,⁵ with ROC analysis. The selected features were also compared with thrombus permeability defined as a mean attenuation increase from NCCT to CTA, maximum attenuation in CTA, and a maximum attenuation increase from NCCT to CTA. The mean and maximum Hounsfield units of thrombus in NCCT and CTA were manually measured by placing 1–3 ROIs (area of 1–3 mm²) on the thrombus (1 in each third of the thrombus) on NCCT and CTA.^{14,15} However, in this study, the mean and maximum Hounsfield units of thrombus in NCCT and CTA were automatically calculated from the segmented whole thrombus in registered NCCT and CTA images. Finally, we created a multivariable support vector machine model for the clinically used features, such as thrombus length, volume, residual flow, and the 4 permeability measurements, for classification accuracy comparisons.

RESULTS

Patient Characteristics

Baseline demographics and other characteristics of the 67 patients included in this study are summarized in On-line Table 1. The difference regarding baseline clinical variables, etiology of ischemic stroke, and intracranial thrombus imaging characteristics was assessed using the Wilcoxon rank sum test for nonparametric data and the Fisher exact test of proportions for categorical data separately between patients who received intravenous alteplase with and without recanalization. There were no statis-

tically significant differences between the 2 groups by the etiology of ischemic stroke ($P > 0.05$), clinical ($P > 0.05$), and imaging parameters ($P > 0.05$), excluding the occlusion site in internal carotid artery ($P < 0.01$) and proximal M1 segment MCA ($P < 0.01$), and CT imaging ($P < 0.01$) and IV alteplase to recanalization assessment time ($P < 0.01$).

Determining the Best Radiomics Features

The most discriminative features from each feature group associated with recanalization with IV alteplase are shown in On-line Table 2. In particular, the mean of Laws level-spot waves (LSW)⁷ ranked high in NCCT (third), radiomics change (second), and the group combining 3 feature groups (third). Figure 1 demonstrates the radiomics feature map of LSW for 2 patients from the case and control groups, one from each group. The feature value (gray-level in this feature map) measures the heterogeneity in the local neighboring region of each pixel. The higher the feature values are, the less heterogeneous is the signal from the thrombus. The 2 thrombi in Fig 1 are different in appearance, as seen by the distribution of gray levels in the feature image. The thrombus that recanalized with intravenous alteplase appears more heterogeneous in terms of Laws LSW feature values compared with the thrombus that did not recanalize.

To determine the radiomics features that best discriminate patients from controls, we used the top 5 features from the NCCT feature group, 15 features from the CTA feature group, 6 features from the radiomics change group, and 12 features from the combination of 3 feature groups listed in On-line Table 2, individually, to generate ROC curves using 10 × 5-fold cross-validation. AUC values for different feature combinations were demon-

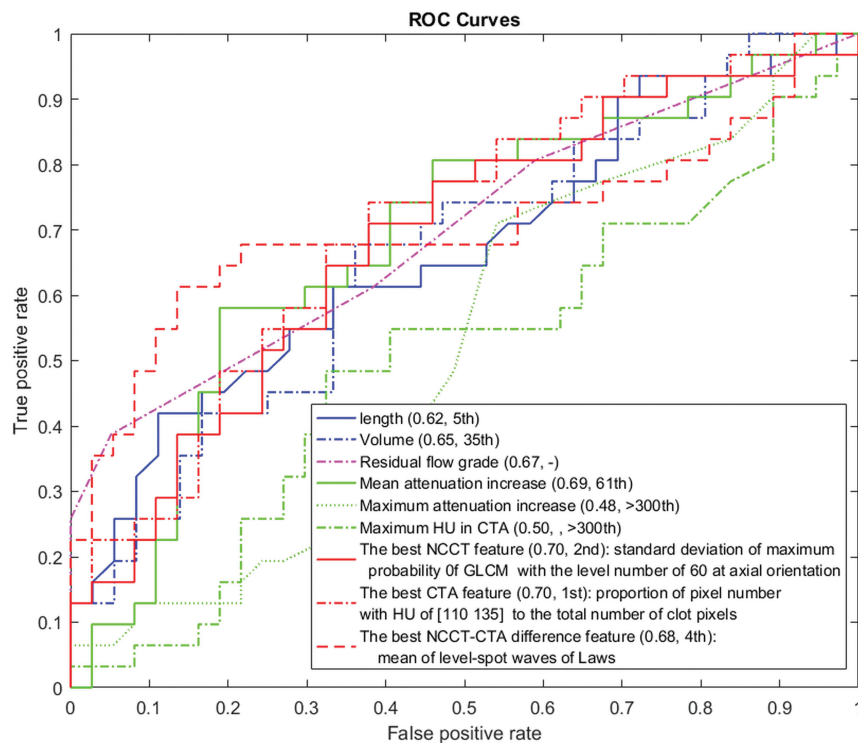


FIG 2. ROC results of the best radiomics features from different feature groups, compared with clinically relevant currently measurable features such as thrombus length, volume, and permeability measurements, as well as subjective assessment of the residual flow grade. The numbers in the parentheses following legend names denote AUC values and ranking after linear discriminative analysis.

strated in On-line Figure 1. The ROC curves of the best features from each group are plotted in Fig 2. The AUCs are 0.69 ± 0.01 for the best NCCT feature (ie, the SD of maximum probability of the gray-level co-occurrence matrix with the level number of 60 at sagittal orientation), 0.69 ± 0.01 for the best CTA feature (the proportion of pixel numbers with 110–135 HU to the total number of clot pixels), and 0.69 ± 0.03 for the best radiomics change (ie, the proportion of pixel numbers with 110–135 HU to the total number of thrombus pixels, respectively). The ROC curves of the top 5 features from each feature group are additionally demonstrated in the On-line Figure 2. An ANOVA test showed that there were no statistically significant differences among these features ($P = .15$). The prediction accuracy of these features is similar to that of biologically relevant features, such as thrombus length^{4,16} (AUC = 0.66 ± 0.01 , $P = .27$), thrombus volume (AUC = 0.66 ± 0.003 , $P = .19$), thrombus permeability measured as¹⁴ mean attenuation increase from NCCT to CTA (AUC = 0.68 ± 0.03 , $P = .16$) (Fig 2), but significantly better than the thrombus permeability measurement that uses maximum attenuation in CTA¹⁴ (AUC = 0.49 ± 0.01 , $P < .001$) and a maximum attenuation increase from NCCT to CTA (AUC = 0.48 ± 0.07 , $P < .001$). Additionally, a nonradiomics feature, residual flow grade, was compared with all the selected radiomics features and generated a similar prediction accuracy (AUC = 0.68 ± 0.03 , $P = .21$).

Classification Accuracy

Figure 3 shows ROC curves using different feature combinations with 10×5 -fold cross validation. In Fig 3A, the selected 5 NCCT features are most predictive with an AUC = 0.78 ± 0.02 , followed by the 6 radiomics change features with an AUC = 0.77 ± 0.04 ,

while the 15 CTA features are least predictive with AUC = 0.74 ± 0.03 . However, combining these features further into different groups increases the prediction accuracy greatly (Fig 3B). In particular, 12 features selected from the combination group of NCCT, CTA, and radiomics change features provide the best prediction accuracy (AUC = 0.85 ± 0.03) and were significantly better than features such as thrombus length ($P < .001$), thrombus volume ($P < .001$), thrombus permeability as measured by a mean attenuation increase from NCCT to CTA ($P < .001$) or by maximum attenuation in CTA ($P < .001$) or by a maximum attenuation increase from NCCT to CTA ($P < .001$), and the nonradiomics feature of residual flow grade ($P < .001$). No evidence was found that a combination of the clinically used features improved prediction accuracy (AUC = 0.68 ± 0.03).

Because manual segmentation of thrombus could introduce variability in the analysis, a second manual segmentation of the same data was performed by

another neuroradiology fellow (Z.A.). Pearson correlation coefficients regarding the thrombus length and volume of 2 manual segmentations were 0.95 and 0.94, respectively, between the 2 observers. When the analyses were replicated for the second manual segmentations as seen above, the same combination of the NCCT, CTA, and radiomics change features generated an AUC = 0.83 ± 0.02 , not significantly different from the results of the first manual segmentation ($P = .27$).

DISCUSSION

Using a nested case-control study design, we show that intracranial thrombus heterogeneity on NCCT and CTA as captured by radiomics is associated with recanalization with intravenous alteplase. Radiomics-based feature analysis of intracranial large-vessel thrombi demonstrably increases our ability to predict recanalization with intravenous alteplase compared with current clinically measurable thrombus characteristics such as length, volume, and thrombus permeability.

Whether IV alteplase will likely result in recanalization in patients with proximal intracranial thrombus is, in our opinion, an important piece of information that can help physicians make appropriate decisions on triage, transport, and treatment of patients, especially when the risk of administering alteplase (intracranial and otherwise) is considered.¹⁷ Patients in whom the probability of recanalization with intravenous alteplase is likely very low and who may have a higher risk of bleeding may benefit from direct transport to the angi suite for endovascular treatment. Patients in whom the probability of recanalization with intravenous alteplase is very high and in whom endovascular ac-

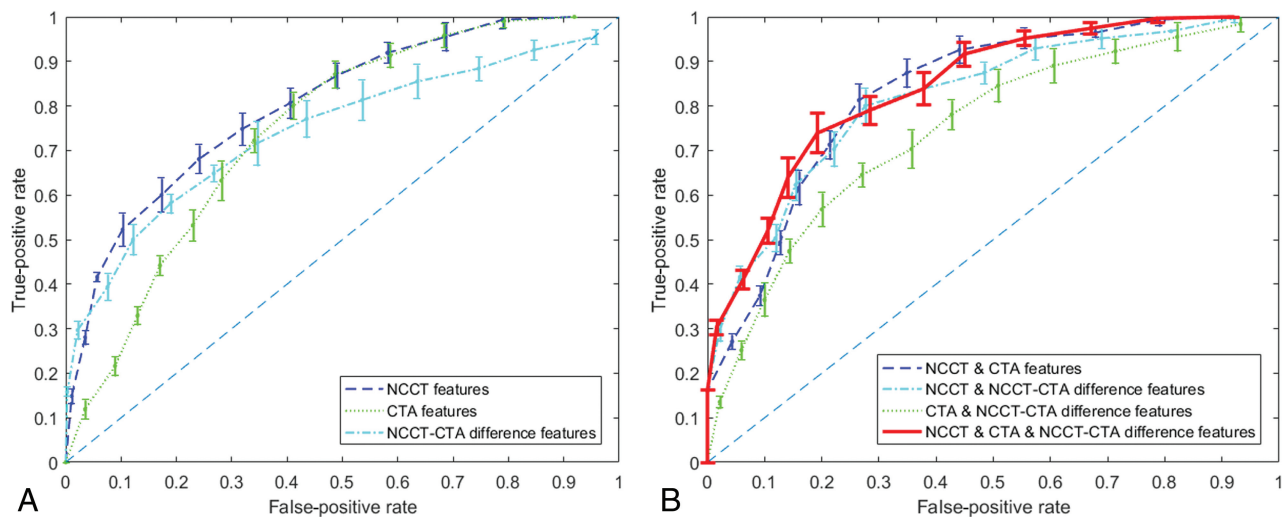


FIG 3. ROC curves for the prediction of early recanalization with IV alteplase using 67 patients (30 patients versus 37 controls). The bars on the curves represent the SDs of 10 repetitions. A, ROC curves for each feature group. B, ROC curves for different combinations of feature groups.

cess is difficult or risky could be given intravenous alteplase and observed for improvement. One may also weigh these considerations when deciding on transport in patients who are imaged at primary stroke centers and await transport to comprehensive stroke centers. We acknowledge that these decisions will not, however, be taken in isolation and that multiple clinical factors will also influence such decisions. Moreover, subgroup analysis of ongoing and future trials testing direct endovascular treatment versus intravenous alteplase followed by endovascular treatment in patients with proximal intracranial thrombus may also benefit to be informed by information that help determine likelihood of early recanalization with lytic agents. In addition, trials that test newer thrombolytic agents and augmented thrombolytic techniques may find this information useful in learning about optimal trial designs.

Radiomics features are computational in a high-dimensional feature space that is converted from imaging data using many data-characterization algorithms. In this study, 326 predefined radiomics features that describe thrombus characteristics, such as first-order statistics, shape and size, and high-order statistical textural feature, were automatically extracted from manually segmented thrombus in NCCT and CTA images. These radiomics features capture subtle variations within the thrombus environment not easily perceived by the human eye. Individually, our analysis shows that these features are as good as known thrombus imaging biomarkers such as thrombus length and permeability.^{4,14} However, when these radiomics features are combined into a statistical model, the ability for predicting recanalization with intravenous alteplase is significantly improved ($P < .001$).

Variability in image acquisition across hospitals and scanners in clinical practice affects image analysis and therefore the expert reader's ability to identify thrombus characteristics such as density, length, and permeability. The imaging data used in our analysis were acquired from scanners at multiple centers, and the radiomics features were directly computed from the imaging data, without any preprocessing or normalization. Our analysis demonstrates that the extracted radiomics features are stable under various image-acquisition parameters. Our results therefore sug-

gest the potential generalizability of our results. In our opinion, radiomics-based models predicting recanalization of thrombus with intravenous alteplase can be further improved with better standardization of imaging protocols.

Among 67 patients receiving IV alteplase, the patients with successful recanalization nearly doubled compared with the patients without recanalization, on the basis of a history of diabetes and smoking and anticoagulation therapy (On-line Table 1). Although no statistically significant differences were observed from the limited data in this study, it would be interesting to explore this trend further with a larger dataset. Another finding from On-line Table 1 is that longer times from alteplase start to recanalization and from CT to recanalization are associated with successful recanalization, and the patients with ICA and proximal M1 MCA occlusion have significantly low rates of recanalization (all $P < .01$), even from these limited data. These results are consistent with the results in Menon et al.¹⁷ With a plasma half-life of 6–7 minutes, alteplase is not likely to be biologically active 6 hours after administration. However, it is possible that the early thrombus debulking effects of alteplase translate to less overall thrombus, allowing endogenous tissue plasminogen activator to complete the remaining lysis required.¹⁷

This study has some limitations. Our sample size was small, primarily because recanalization of proximal intracranial thrombus with intravenous alteplase within a clinically relevant time is relatively rare. To address this limitation, we used a case-control study design. We do, however, acknowledge that such a design informs us about associations but not causality. To address overfitting of data, we used a series of steps, including the use of i) a feature-selection approach to first select the best features associated with recanalization, ii) a linear support vector machine with fewer parameters to be derived compared with more complicated nonlinear machine learning models such as random forests and deep neural networks, iii) L2 norm regularization to constrain the model fitting and decrease the effective df without reducing the actual number of parameters in the model, iv) and a 10×5 -fold cross-validation strategy to generate a more accurate indication of how well the model generalizes to unseen data.

To address variability in thrombus segmentation between experts, a second neuroradiology fellow manually contoured all thrombi using the same processing pipeline. Results were similar to those in the primary analysis. Feature representation influences classification accuracy. In this work, the mean value was used to represent the feature along all voxels within a thrombus,^{7,13} without taking feature distribution into account. Feature ranking using linear discriminative analysis was applied on the whole dataset before cross-validation, which might introduce a selection bias,¹⁸ thereby overestimating performance. More extensive validation on an independent test dataset is required to evaluate the stability of the selected features. We were unable to explore the underlying biologic meaning of the radiomics-based imaging. This type of correlation will need in vitro studies that look at radiomics and thrombus pathology together.

CONCLUSIONS

This proof-of-principle case-control study shows that statistical models using radiomics-based imaging features of intracranial large-vessel thrombi can help identify patients who are likely to achieve recanalization with intravenous alteplase. Future work on automating image thrombus segmentation and image analysis along with further validation of our results can potentially lead to the development of computer-aided image-analysis software that could help physicians determine whether patients with proximal occlusions would recanalize in a reasonable timeframe with intravenous alteplase. This knowledge may be useful in the design and testing of novel thrombolytic agents or enhanced thrombolysis strategies. Until then however, this method cannot be used for decision-making in acute stroke care, a time-sensitive situation in which intravenous thrombolysis has to be administered to eligible patients promptly and with minimal delay.

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