Quantitative Collateral Grading on CT Angiography in Patients with Acute Ischemic Stroke

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Abstract. Reliable assessment of collateral blood supply is important in acute ischemic stroke. We propose a quantitative method for evaluation of collateral status on CT angiography (CTA). We collected CTA images of 70 patients from MR CLEAN with an occlusion in the M1 branch. Our proposed quantitative collateral score (qCS) consisted of atlas-based territory-at-risk identification and vessel segmentation using a Hessian-based filter. Ground truth was obtained by manual collateral scoring (mCS). Accuracy was evaluated by analysis of Spearman ρ and one-way ANOVA. Correlation of mCS and qCS with tissue death and functional outcome was assessed. Receiver operating characteristics curves of mCS and qCS were analyzed to distinguish favorable from unfavorable outcome. qCS strongly correlated with mCS and showed reliable correlations with tissue death and functional outcome. qCS showed higher discriminative power between favorable and unfavorable compared to mCS, indicating potential clinical value.

Keywords: Collateral status · Automatic assessment · Acute ischemic stroke · CT angiography · Endovascular therapy

1 Introduction

In stroke patients with acute proximal large vessel occlusion, endovascular therapy (EVT) and intravenous thrombolysis are the only two effective treatment options used in routine practice [1]. Many studies have emphasized the relevance of collateral assessment on baseline imaging to quickly identify patients who potentially benefit from EVT

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[2, 3]. Some studies even utilized the collateral status as an inclusion criteria for their randomized control trial [4]. Collaterals maintain blood flow via alternative routes in the brain and good collateral supply is associated with smaller infarct volumes and improved clinical outcome [5, 6]. To achieve information on the collateral status in the acute setting, single-phase CT angiography (CTA) is the most widely used imaging modality. Single-phase CTA is a snapshot of vascular contrast enhancement over time. Although information on dynamic filling of the leptomeningeal collaterals is lacking, CTA allows visualization of the extent of collateral capacity.

Many collateral grading systems on CTA have been proposed, but a consistent and easy to interpret standard score has yet to be found [7]. There is a need for objective and accurate collateral capacity assessment since current grading methods are susceptible to poor interobserver agreement and are often scored on coarse ordinal scales. An automated and quantitative collateral scoring method holds the promise to overcome these problems and aid in rapid triaging of patients for EVT. The aim of this study is to introduce a quantitative method for the evaluation of collateral status on CTA. We investigate the correlation of our proposed method with tissue and functional outcome and assess the predictive value for favorable functional outcome as compared to standard visual scoring.

2 Materials and Methods

2.1 Patient Selection

Study data was acquired from the MR CLEAN [8] database. Patient eligibility and methods of MR CLEAN have been described previously [9]. All patients or their legal representatives provided written informed consent. For this post-hoc analysis, we included 70 consecutive patients from the MR CLEAN database who received baseline thin-sliced single-phase CTA imaging (approximately 1 mm) and who had follow-up non-contrast CT (NCCT) imaging to allow follow-up infarct volume (FIV) assessment. No fixed CTA protocols were used in MR CLEAN, and protocols varied per center. We only included patients with an occlusion in the middle cerebral artery (MCA) M1 segment. Patients with large diffuse haemorrhagic transformations (PH2) and image data with extreme artifacts or insufficient scan quality were excluded. A summary of the clinical patient information is given in Table 1.

Table 1. Clinical baseline characteristics stratified by favorable and unfavorable outcome.

Parameter	All (N = 59)	mRS 0–2 (N = 22)	mRS 3–6 (N = 78)
Age (yr) (mean ± SD)	63.8 (13.5)	64.5 (15.1)	63.0 (13.5)
Sex (female) (No.,%)	24 (40.7)	6 (46.2)	18 (39.1)
NIHSS (median, IQR)	17 (14–21)	14 (9–17)	19 (16–22)
Onset to randomization (min) (median, IQR)	194 (145–282)	166 (132–233)	205 (148–291)

Note: NIHSS indicates National Institutes of Health Stroke Scale; IQR, interquartile range; mRS, modified Rankin Scale

2.2 Outcomes

The primary clinical outcome parameter was the patient's functional outcome at 90 days as captured by the mRS. The mRS is a 7-point scale ranging from no symptoms (score 0) to dead (score 6). Primary radiological outcome is the tissue outcome in terms of FIV assessed on follow-up NCCT. Secondary clinical outcome was the dichotomized mRS score of 0–2, which indicates functional independence and is considered a favorable outcome.

2.3 Manual Collateral Score

The presence of leptomeningeal collaterals on CTA was defined as relative differences in appearance of vasculature between hemispheres, distal to the proximal artery occlusion. In this study, the collateral status was scored manually on an existing commonly used ordinal scale by Tan et al. [10] as part of MR CLEAN and in a quantitative fashion using automatic analysis. In MR CLEAN, a central imaging committee assessed the manual collateral score (mCS) on baseline CTA. Image evaluators had more than 10 years of experience and were blinded to all clinical findings, except symptom side. All CTA images were independently graded by two neuroradiologists. A third reader resolved discrepancies between the initial two readers. The mCS was assessed on a commonly used 4-point scale, with 0 for absent collaterals (0% filling of the occluded territory), 1 for poor collaterals (>0% and ≤50% filling of the occluded territory), 2 for moderate (50% and <100% filling of the occluded territory), and 3 for good collaterals (100% filling of the occluded territory) [10]. Readers used the non-ischemic hemisphere as normal reference. A mixture of CTA images with NCCT window-level and maximum-intensity-projections were used for collateral grading, including all available slices. An example is shown in Fig. 1A. If different slices expressed different collateral capacities, an average collateral score over all slices was determined. No fixed CTA acquisition protocols were used in MR CLEAN and protocols varied per center. Inter-observer reliability for mCS assessment in MR CLEAN has previously been reported (kappa = 0.60) [5].

2.4 Quantitative Collateral Score

Quantitative collateral score (qCS) was obtained using an automatic method. This method uses CTA images as input and consisted of the following steps; (1) identification of affected territory at risk; (2) segmentation of vessels; and (3) comparison of vessel presence between hemispheres.

The location and extent of the territory at risk depends on the location of the intracranial occlusion. Inclusion of all vessels in the entire MCA territory might lead to overestimation of the collateral capacity. It is well-known that variation in cerebroarterial structures between patients is common, making precise territory at risk localization impossible without additional imaging. Therefore, the patient-specific territory at risk is estimated. Topographic probability maps as presented previously by Boers et al. [11] allow for identification of the area likely to infarct for a given occlusion location. These

probability maps are created by the co-registration of individual follow-up NCCT images into the coordinate space of a healthy subject. FIVs per occlusion location were segmented, and mapped onto each other. The sum of the FIV masks represented the frequency of infarction for each voxel. Co-registration was performed to align the probability maps with each patient's CTA by a subsequent rigid and affine transformation. Mutual information was set as similarity measure. In this study, we focused on M1 occlusions and defined the territory at risk as the area that has >5% prevalence of infarction. This region is used as Region of Interest (ROI) and was mirrored to cover both the ipsilateral and contralateral side for further analysis (Fig. 1B).

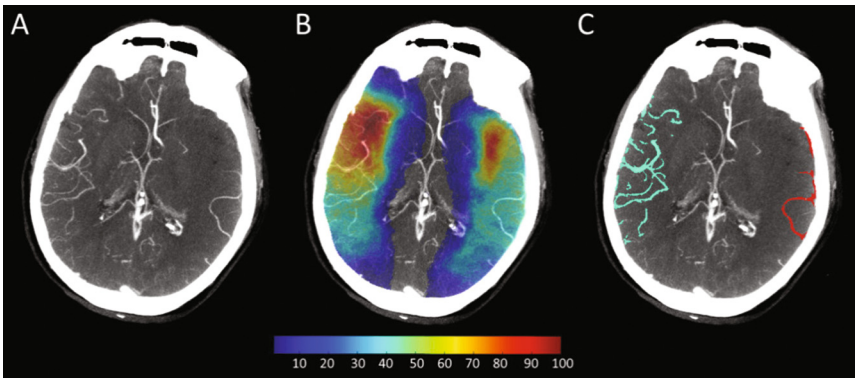

Fig. 1. **A**: Maximum intensity projection (MIP) of a CTA image with an occlusion in the left M1 branch and mCS of poor collaterals (>0% and ≤50% filling of the occluded territory). **B**: MIP with overlay of co-registered distribution map of infarct prevalence. Area of >5% is used as region of interest for the Hessian-based filter. **C**: MIP with segmented vessels distal to the M1 branch used for collateral capacity calculation. For this patient, the qCS was 27%.

After obtaining the ROIs in both hemispheres, a Hessian-based filter introduced by Frangi et al. [12] was applied to enhance tube-like structures (vessels) and suppress disk-like and blob-like structures. Because this filter is known for its sensitivity near edges, and thus the skull, a previously described skull-stripping algorithm was applied prior to filtering [13]. It is important to use a multi-scale approach to capture the variation in vessel size. For this, a detailed statistical cerebroarterial atlas that was derived from 700 normal MRA datasets [14] was used to obtain the mean vessel diameter distal to the M1 segment, ranging from 0.9 to 3.1 mm. This range was used as the input scale range for the filter. The step size for the multi-scale approach was set to 1.1 mm. The required parameters that control the sensitivity of the filter were chosen based on visual inspection and were set as $\alpha = 0.5$, $\beta = 0.5$, and $c = 500$. Filtering resulted in a 3D-image with a vesselness measure; each voxel in the output volume indicated the similarity of the local structure to a vessel. Applying a patient-specific threshold within the ROI on the vesselness image resulted in a binary image of the vessels. This threshold was defined as the mean + SD vesselness measure of the background; the area outside the ROI with a

density of less than 200 Hounsfield units. A morphological closing operator using a disk-shaped structuring element with a radius of 0.4 mm was applied as post-processing step to correct for disconnected segments (Fig. 1C).

To ensure that only the vessels distal to the proximal M1 segment were measured, vessels with a diameter of >3.1 mm were excluded. Hereafter, the segmented vessels distal to the M1 segment in both hemispheres were extracted and multiplied by its density values (in Hounsfield units), where the sum represented the vascular presence (*VP*) of each hemisphere. The qCS was calculated as the percentage of the *VP* of the affected and healthy hemisphere via the following equation:

$$qCS = \max\left(100, \frac{VP_{ipsi}}{VP_{contra}}\right); 0 \leq qCS \leq 100$$

where VP_{ipsi} and VP_{contra} is the vascular presence of the affected and contralateral side respectively.

2.5 Assessment of Tissue Outcome

Tissue outcome was assessed on follow-up NCCT imaging, acquired 5–7 days after stroke onset. If 5–7 day NCCT was not available due to death or discharge, 24 h follow-up NCCT was used. In case of hemicraniectomy, the last scan prior to surgery was selected. The ischemic lesions were segmented using previously developed and validated software, resulting in a binary mask of the FIV [13]. Adjacent hyperdense areas suspected for hemorrhagic transformation were considered part of the FIV. All FIVs were inspected and adjusted if necessary by a trained observer (AMB) with more than 4 years of experience and at least one neuroradiologist (WvZ, LFB or CBM) with more than 15 years of experience. A consensus reading with 2 neuroradiologists was performed to resolve cases with any discrepancies. FIV was calculated in milliliters (mL) by multiplying the number of voxels of the segmented ischemic lesions with its voxel size.

Table 2. Tissue outcome and collateral scores

Variable	All (N = 59)	mRS 0–2 (N = 22)	mRS 3–6 (N = 78)
FIV (median, IQR)	88 (31–215)	23 (9–30)	116 (34–249)
mCS (mean ± SD)	1.8 (1.0)	2.5 (0.8)	1.6 (0.9)
qCS (mean ± SD)	47.9 (31.9)	40.6 (30.9)	73.3 (21.2)

Note:– FIV indicates follow-up infarct volume; mCS, manual collateral score; qCS, quantitative collateral score; mRS, modified Rankin Scale

2.6 Statistical Analysis

Dichotomous variables were presented as proportion of population. Continuous variables were tested for normality (Kolmogorov–Smirnov test) and presented as mean and SD if normally distributed or as median and interquartile range (IQR) otherwise. The mCS was

used as a reference standard to evaluate the accuracy of the proposed qCS method. The accuracy was assessed by constructing boxplots and calculation of the Spearman rank correlation coefficients. One-way ANOVA analysis was performed to test for differences in qCS between mCS groups.

Receiver operating characteristics (ROC) curves were created and the area under the curve (AUC) was calculated to quantify the discriminative power of mCS and qCS to distinguish between favorable and unfavorable functional outcome (mRS 0–2 versus mRS 3–6). Sensitivity and specificity were calculated. All statistical analyses were performed in SPSS v.24.0 (IBM Corp., Armonk, NY, USA). A p-value of <0.05 indicated statistical significance in all analyses.

3 Results

We included 70 patients with an M1 occlusion in the MCA territory. We additionally excluded 11 patients due to incomplete head scans (n = 7), extreme movement artifacts (n = 2) and errors in co-registration (n = 2), resulting in a total of 59 patients for analysis. Mean age was 63.8 (SD ± 13.4), mean slice thickness was 0.89 mm (SD ± 0.17), and median FIV was 81 mL (IQR:31-214.5).

The correlation between qCS and mCS was significant with a Spearman ρ of 0.68, $p < 0.001$. Boxplots are displayed per mCS grade in Fig. 2. The qCS was significantly different between all mCS groups, except for absent collaterals (grade 0) versus poor collaterals (grade 1). Imaging parameters are shown in Table 2.

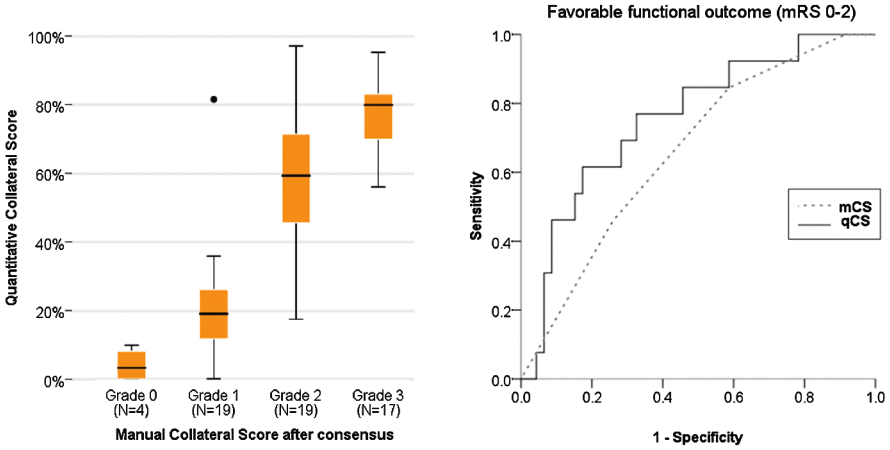

Fig. 2. Left: distribution of quantitative collateral score (qCS) per manual collateral score (mCS) grade, ranging from absent collaterals (0% filling of the occluded territory) to good collaterals (100% filling of the occluded territory). The qCS was significantly different between all mCS groups, except for absent collaterals (grade 0) versus poor collaterals (grade 1). Right: ROC curve analysis of mCS and qCS for discriminating favorable outcome (mRS 0–2) from unfavorable outcome (mRS 3–6).

The correlation of qCS and mCS with FIV were similar (both Spearman $\rho = -0.61$, $p < 0.001$). Correlation with mRS as outcome measure was also significant for both collateral scores; qCS showed Spearman $\rho = 0.36$, $p = 0.006$; and mCS showed Spearman $\rho = 0.28$, $p = 0.03$. ROC curves are displayed in Fig. 2. The discriminative power of mCS to distinguish between favorable and unfavorable functional outcome was poor with an AUC of 0.66. The proposed qCS showed an AUC of 0.76, representing a fair discriminative power, with a sensitivity and specificity of respectively 0.77 and 0.67.

4 Discussion

We have presented a new quantitative method to estimate the collateral capacity on CTA imaging of patients with an acute ischemic stroke. We have shown that the quantitative score strongly correlates with the manual collateral score. In our population, the associations of the quantitative collateral score with clinical and radiological outcome is identical to the common manual score, indicating the great potential clinical value.

To our knowledge, this is the first study that quantifies collateral capacity on CTA imaging. Visualization of the collateral capacity is not limited to CTA, and grading methods on various imaging modalities have been introduced. Four-vessel Digital subtraction angiography (DSA) is considered the gold standard for assessment of collateral supply. However, in the process of rapidly triaging patients for stroke therapy, DSA is seldom used because of its invasiveness and time-consuming nature [3, 15, 16]. Ernst and colleagues [17] previously introduced an atlas-based method for TOF- and contrast-enhanced MRA imaging to score collateral abundance in a quantitative fashion. Despite promising results, it might be challenging to translate these results to other types of imaging protocols.

Our study has some limitations. We only selected patients with a proven M1 occlusion for this study, resulting in a selection bias. Though the M1 segment of the MCA territory is the most common location for a large vessel occlusion, our proposed method should prove accurate for other occlusion types as well to be utilized in the total EVT eligible population. Furthermore, this study suffers from a relative small number of subjects which impedes multivariable regression analysis. Important prognostic factors, such as age, baseline National Institutes of Health Stroke Scale (NIHSS) score and treatment allocation should be included in future studies to further investigate the role of qCS assessment in acute stroke. We used thin-slice CTA to proof our concept of quantitative collateral scoring and applying our method on CTA images with thicker slices might result in suboptimal vessel segmentation, impairing the final qCS.

Our method heavily depends on the output of the Hessian-based filter introduced by Frangi et al. [12], the so-called vesselness filter. It is known that traditional Hessian-based filters often fail in preserving the vessel structure during smoothing, and small vessels and bifurcations might be characterized as background. Despite these disadvantages, we chose to use Frangi's vesselness filter for several reasons: (1) it was designed to detect vessels in angiography images; (2) it addresses the multiscale character of artery trees, thereby accounting for variations in vessel diameters; and (3) small flaws in detecting vascular structures would only result in minimal loss of accuracy, since our

approach compares hemispheres to obtain the final qCS. In this study, we did not compare other Hessian-based filters or other filter types such as linear and non-linear anisotropic filters. Furthermore, the optimal sensitivity parameters for the vesselness filter were set according to visual inspection. Exploring the output of different setting and filters might result in an even more robust and accurate method, and will be addressed in a future study.

In this study, a quantitative method to estimate the collateral capacity in automated fashion on CTA is presented. There is a strong correlation with the manual reference score and our method showed strong correlations with tissue death and functional outcome. Quantitative scoring showed higher discriminative power between favorable and unfavorable outcome after stroke in comparison to manual assessment, and might be helpful in future patient selection models for EVT.

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