MOSAIC: Multimodal Stroke Assessment Using Computed Tomography

 Novel Diagnostic Approach for the Prediction of Infarction Size and Clinical Outcome

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Background and Purpose—With new CT technologies, including CT angiography (CTA), perfusion CT (PCT), and multidetector row technique, this method has regained interest for use in acute stroke assessment. We have developed a score system based on Multimodal Stroke Assessment Using CT (MOSAIC), which was evaluated in this prospective study.

Methods—Forty-four acute stroke patients (mean age, 63.8 years) were enrolled within a mean of 3.0±1.9 hours after symptom onset. The MOSAIC score (0 to 8 points) was generated by results of the 3 sequential CT investigations: (1) presence and amount of early signs of infarction on noncontrast CT (NCCT; 0 to 2 points), (2) stenosis (>50%) or occlusion of the distal internal carotid or middle cerebral artery on CTA (0 to 2 points), and (3) presence and amount of reduced cerebral blood flow on 2 adjacent PCT slices (0 to 4 points). The predictive value of the MOSAIC score was compared with each single CT component with respect to the final size of infarction and the clinical outcome 3 months after stroke by use of the modified Rankin Scale (mRS) and the Barthel Index (BI).

Results—Among the CT components, PCT showed the best correlation to infarction size (r=0.75) and clinical outcome (r=0.60 to 0.62) compared with NCCT (r=0.43 to 0.58) and CTA (r=0.47 to 0.71). The MOSAIC score showed consistently higher correlation factors (r=0.67 to 0.78) and higher predictive values (0.73 to 1.0) than all single CT components with respect to outcome measures. A MOSAIC score <4 predicted independence with 89% to 96% likelihood (mRS ≤2, BI ≥90); a MOSAIC score <5 predicted fair outcome with 96% to 100% likelihood (mRS ≤3, BI ≥60).

Conclusions—The MOSAIC score based on multidetector row CT technology is superior to NCCT, CTA, and PCT in predicting infarction size and clinical outcome in hyperacute stroke. (Stroke. 2002;33:2819-2826.)

Key Words: angiography ■ brain stem infarction ■ cerebral blood flow ■ computed tomography ■ outcome

Despite major advances in MRI technology, CT still represents the most frequently used imaging modality in acute stroke patients. Widespread availability and rapid accessibility are the main advantages of CT over MRI in the acute stroke setting in many centers. Besides pure exclusion of brain hemorrhage, however, early data about site and severity of brain ischemia and their respective pathogenesis are clinically requested. By this means, thrombolysis and other invasive therapies such as decompressive surgery should be selected on a more solid basis. Hence, the ultimate goal of acute stroke imaging is a robust patient stratification to achieve individualized treatment strategies.3-5 With the advent of recent-generation scanners, the diagnostic potential of CT with regard to this demand has dramatically increased.6

It has been shown that early signs of infarction on noncontrast CT (NCCT) have significant prognostic impact with respect to future infarction and clinical course. With sufficient expertise, these infarction signs can be detected with satisfactory reliability and reproducibility.7,10 Moreover, CT angiography (CTA) is a well-recognized method for evaluating extracranial11 and intracranial brain-supplying arteries.12 Therefore, the status of the major cerebral arteries can readily be assessed in stroke patients without significant delay.13 Within the last years, perfusion CT (PCT) has been established as the third CT component enabling depiction of the perfusion deficit beyond the major arteries, ie, on the tissue level.14-20 With the recent introduction of multidetector row CT technology, volume coverage of PCT can be extended to include further parts of the brain.21,22

Thus, with the 3 main CT modalities (NCCT, CTA, PCT), profound knowledge about brain anatomy, vessel status, and tissue hemodynamics can be acquired in acute stroke patients.
within several minutes. However, no diagnostic algorithm exists that integrates information from these supplementary CT modalities for acute patient stratification. We propose the Multimodal Stroke Assessment Using CT (MOSAIC), which is a novel multimodal CT. In this study, we evaluate the predictive value of a specific MOSAIC score with respect to (1) occurrence and size of cerebral infarction and (2) clinical outcome 3 months after symptom onset.

Methods

Patients
Forty-four patients (14 women) 63.8±13.8 years of age of 48 primarily screened patients were enrolled in this prospective study that was approved by the local ethics committee. Four patients were excluded from the analysis because of insufficient-quality of CTA or PCT maps (n=3) and missing data on follow-up because of voluntary discharge from hospital (n=1). All patients had clinical signs of acute hemispheric brain ischemia, and brain hemorrhage had been excluded by NCCT. There was no evidence of allergies against contrast agents, hyperthyroidism, or renal insufficiency in any of the patients. The severity of clinical deficits at admission was measured by the National Institutes of Health Stroke Scale (NIHSS). The mean±SD NIHSS on admission was 10.4±6.8 (range, 0 to 27).

After completion of the study procedure, all patients were admitted to the local stroke unit for further therapy and diagnostic workup. In 7 patients (15.9%), systemic thrombolysis with recombinant tissue plasminogen activator was performed within 3 hours after symptom onset. The remaining patients were treated with heparin or platelet inhibitors. Suspected stroke causes consisted of cardiogenic (n=12) and arterial (n=14) cerebral thromboembolism or cerebral microangiopathy (n=3). In 6 patients, ≥1 cause was found; 9 patients remained without any detectable source of ischemia.

Three months after stroke onset, a structured questionnaire was performed for all patients by telephone to assess the level of independence at home. If the patient was unable to answer the questions, relatives were interviewed after informed consent was obtained. As outcome measures, we used 2 established score systems, the modified Rankin Scale (mRS) and Barthel Index (BI). The mRS is a 7-point scoring system that distinguishes patients from 0 (no symptoms) to 6 (death).23 According to previous studies, dependency was defined by mRS >2, and bad outcome was defined by mRS >3.24 The BI has a range of points from 0 (totally independent) to 100 (completely independent) according to a 10-item list of daily tasks in the household.25 Dependency is reflected by a BI of ≤90; bad outcome is defined by a BI <60.24

Principle of PCT Measurement
The theoretical basis of the applied PCT technique has been described in detail. It contains the continuous CT data acquisition during first passage of a peripherally administered bolus of contrast medium. Subtle changes in CT density over the brain tissue can be detected to generate time-density curves on a pixel-by-pixel basis. Based on the indicator-dilution theory and the maximum slope model described elsewhere, the Perfusion CT software package (Siemens Medical Solutions) provides high-resolution maps of relative cerebral blood flow (CBF), relative cerebral blood volume (CBV), and time to peak (TTP). In this study, only PCT-derived CBF maps (PCTCBF) were used for further analysis.

Multimodal CT Imaging and Follow-Up Examination
CT imaging studies were performed with a slip-ring, multidetector row CT scanner (SOMATOM VolumeZoom, Siemens) that allows continuous scanning at up to 4 anatomic levels. First, an NCCT of the entire brain was performed with a slice thickness of 4 mm infratentorially and of 7 mm supratentorially. PCT measurements were performed in 2 adjacent CT slices with a slice distance and slice thickness of 10 mm. According to others, the lower slice was defined at the level of the basal ganglia including parts of the anterior, middle, and posterior cerebral artery territory.28 The second slice was 1 cm above, containing upper parts of the basal ganglia. Contrast agent (40 mL, Ultravist 300, Schering) was injected intravenously as a sharp bolus (8 mL/s) into an antecubital vein via 16- to 18-gauge needle with an automatic injector. Simultaneously, dynamic CT scanning was performed at a sampling rate of 1 image per second for a 40 seconds. Technical parameters for the dynamic scan were as follows: 80 kVp, 180 mA, 512×512 matrix size, and a 25-cm field of view. CTA was performed from the level of the sixth cervical body (C6) up to the lateral ventricles with 100 mL of contrast agent (Ultravist 300, Schering). For CTA, 140 kVp and 120 mA were applied. Maximum-intensity projections were reconstructed in axial, sagittal, and coronal views. Figure 1 shows an example of multimodal CT imaging in acute stroke.

Follow-up imaging was performed to measure the size and localization of cerebral infarction with MRI (n=16; diffusion-weighted, fluid-attenuated inversion recovery and T2-weighted sequences) or non-contrast CT (n=28) within the next 10 days after stroke.

Data Analysis
For further analysis, all data were transferred to a PC workstation. NCCT was analyzed for early signs of infarction by 2 experienced neuroradiologists (S.P.K., C.G.G.) who were completely blinded to clinical data. They were also unaware of the side of the affected hemisphere. For this purpose, the optimum-density CT window was used to discriminate normal and hypoattenuated tissue. For quantification of the infarction signs, the methods described in the Alberta Stroke Program Early CT Score Study (ASPECTS) was used. In this method, the territory of the middle cerebral artery (MCA) was divided into 10 standardized regions: caudate nucleus, internal capsule, lentiform nucleus, insular ribbon, and 6 cortical MCA.
territories at the level of the basal ganglia (n=3) and centrum semiovale (n=3). For each ASPECTS region, a decision was made as to whether early signs of infarction were visible, and the number of regions affected were subsequently counted. In 3 patients, infarction signs were falsely visualized on the unaffected hemisphere without infarction signs on the affected side. In these patients, absence of infarction signs was considered in further analyses. CTA and PCT data were analyzed by at least 1 experienced neuroradiologist and 1 vascular neurologist in consensus (D.G.N., S.P.K., E.M.N., C.G.G.). Results of the CTA were examined in all 3 projections. The status of the major intracranial cerebral arteries at the circle of Willis was differentiated into no stenosis or mild stenosis (<50%), stenosis ≥50%, and vessel occlusion. PCT$_{\text{infarct}}$ maps were generated on a specially designed workstation as explained elsewhere. The first decision of whether tissue ischemia was present was visually made. If present, the area of visible perfusion deficit and the area of the entire ipsilateral hemisphere were manually outlined. Then, the relative size of the perfusion deficit was given in percent of the affected hemisphere. To obtain the level of relative CBF reduction through this visual approach and to assess its consistency, the outlined area was mirrored over the midline to the contralateral hemisphere. From measurements over the contralateral homologue, the relative CBF in the ischemic tissue was given in percent of the contralateral values. For statistical comparison among the single CT components, results of the first CBF map were used. Assessment of the follow-up images was performed by 2 neuroradiologists in consensus (S.P.K., C.G.G.). The size of infarction was measured on those slices of the follow-up scans that corresponded best to the level of the perfusion measurements. The area with tissue infarction and the area of the entire hemisphere were manually outlined. In accordance with the analysis of the perfusion maps, the size of infarction was given in percent of the affected hemisphere. Additionally, the overall infarction size was assessed on the slice with maximum extension by measuring its maximum length and width, which, in some cases, was located outside the measurement level. For further statistical analysis, the maximum infarction size was summarized within 5 groups: (1) no infarction, (2) maximum infarction diameter <2 cm, (3) 2 to 5 cm, (5) 5 cm up to one third of the MCA territory, and (5) more than one third of the MCA territory.

Definition of the MOSAIC Score

According to the results of the NCCT, CTA, and PCT$_{\text{infarct}}$, patients were given 0 to 8 points as explained in Table 1. The PCT$_{\text{infarct}}$ cutoff of 20% of the entire hemisphere to categorize the amount of ischemia was chosen because it approximates at best one third of the MCA territory. Accordingly, the lowest MOSAIC score of 0 represents (1) early infarction signs in at least 4 ASPECTS regions, normal findings in all 3 modalities, and the highest score of 8 points was chosen because it approximates at best one third of the MCA territory, and (5) more than one third of the MCA territory.

<table>
<thead>
<tr>
<th>Early signs of infarction on NCCT</th>
<th>MOSAIC Study Patients, n (%)</th>
</tr>
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<tbody>
<tr>
<td>No infarction signs</td>
<td>0</td>
</tr>
<tr>
<td>1–3 ASPECTS regions infarcted</td>
<td>1</td>
</tr>
<tr>
<td>≥4 ASPECTS regions infarcted</td>
<td>2</td>
</tr>
<tr>
<td>Ipsilateral pathology on CTA</td>
<td></td>
</tr>
<tr>
<td>Normal or stenosis &lt;50%</td>
<td>0</td>
</tr>
<tr>
<td>ICA/MCA stenosis ≥50%</td>
<td>1</td>
</tr>
<tr>
<td>ICA/MCA occlusion</td>
<td>2</td>
</tr>
<tr>
<td>PCT$_{\text{infarct}}$ slice-1</td>
<td></td>
</tr>
<tr>
<td>No perfusion deficit</td>
<td>0</td>
</tr>
<tr>
<td>Perfusion deficit &lt;20%</td>
<td>1</td>
</tr>
<tr>
<td>Perfusion deficit ≥20%</td>
<td>2</td>
</tr>
<tr>
<td>PCT$_{\text{infarct}}$ slice-2</td>
<td></td>
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<tr>
<td>No perfusion deficit</td>
<td>0</td>
</tr>
<tr>
<td>Perfusion deficit &lt;20%</td>
<td>1</td>
</tr>
<tr>
<td>Perfusion deficit ≥20%</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 1. Definition of the MOSAIC Score and Distribution of the Study Patients

*The threshold size of the PCT$_{\text{infarct}}$ perfusion deficit is given as percentage of the ipsilateral hemisphere as described in the Methods section.

Results

Clinical Characteristics and Follow-Up

Multimodal CT imaging was started 3.0±1.9 hours (range, 0 to 8 hours) after symptom onset. During the acute in-hospital phase, 2 patients (4.5%) died, and 3 patients (6.8%) underwent decompressive surgery to prevent incipient cerebral herniation. In all but 2 patients, brain infarction was visible on follow-up imaging. In 30 patients, the infarction affected 1 (n=4) or both (n=26) target slices of the PCT measurements. At the level of the measurement slices, the relative size of the infarction was 11.9±20.6% (slice 1) and 14.5±22.3% (slice 2) of the hemisphere, with an overall mean size of 13.6±21.6%. The infarction size comprised <5% of the hemisphere in 11 patients, 5% to 20% of the hemisphere in 7 patients, and >20% of the hemisphere in 12 patients. In 11 patients, small cortical and subcortical infarctions located above the measurement slices (n=8) or infratentorial infarction in the brain stem (n=2) or cerebellum (n=1) occurred. Ten of these infarctions were <2 cm, and only 1 infarction was 4 cm in maximum diameter. On 3-months follow-up, 2 additional patients had died (total mortality rate, 9.1%). The mean±SD follow-up values of mRS and BI were 2.4±1.7 and 77.2±34.4, respectively. According to cutoff values of mRS and BI, the dependency rates after 3 months were 38.6% and 36.4%, respectively. Frequencies of bad outcome were 25.0% and 22.7% according to mRS and BI, respectively. All patients except 1 with infarctions outside the measurement slices were independent on follow-up with good outcome measures of 1.3±0.9 (mRS) and 97.7±4.7 (BI), respectively.
Multimodal CT Imaging

Basic data are summarized in Table 1. Of 44 patients, 21 (47.7%) showed early signs of cerebral infarction on NCCT. In 18 patients (40.9%), these infarction signs were visible at the level of the PCT slices; in 3 patients, they were located only in slices above. Using the ASPECTS scoring system, an overall mean number of 1.7±2.3 areas (range, 0 to 8) showed signs of cerebral infarction most frequently involving the lentiform nucleus (n=17), caudate nucleus (n=9), internal capsule (n=5), and insular cortex (n=6). On CTA, ipsilateral pathological findings were noted in 24 patients, revealing occlusion of the M1 (n=9) or the M2 (n=3) segment of the MCA, stenosis (n=4) or occlusion (n=13) of the distal internal carotid artery (ICA), and additional occlusion of the anterior cerebral artery (n=1). In 7 patients, a combined pathology of the ICA and MCA was found. With PCT_CBF-brain ischemia was visible in 30 patients (68.1%), affecting both slices in 26 (59.1%) and a single slice only in 4 patients (9.1%). Including all patients, the mean±SD size of the ischemic area was 12.9±18.2%, with 11.9±20.6% on slice 1 and 14.5±22.3% on slice 2. In 2 patients, additional ischemic areas within the territory of the anterior and posterior cerebral arteries were detected. The relative CBF within the visually identified ischemic tissue was 38.6±10.8% compared with the contralateral homolog. The average MOSAIC score was 3.6±2.9 (see also Table 1). Nine patients (20.4%) had a score of 0, 15 patients (34.1%) had a moderate score of 1 to 3, and the remaining 20 patients (45.5%) had a score ≥4.

Impact of the Type of Acute Treatment

We compared patients who underwent systemic thrombolysis with those who received heparin or antiplatelet drugs only. Patients undergoing thrombolysis had significantly larger neurological deficits according to the NIHSS (median, 16 versus 8; P=0.02), showed a significantly higher number of early infarction signs according to the ASPECTS regions (median, 2 versus 0 affected; P=0.01), had a higher proportion of vessel obstruction on CTA (median, 2 versus 0; P=0.01), and had larger perfusion deficits on PCT_CBF (median size, 22.4% versus 3.1%; P=0.04) than those who received heparin or antiplatelet therapy only. Accordingly, the MOSAIC score was likewise significantly higher in patients subjected to thrombolysis compared with the remaining patients (median, 7 versus 3; P=0.008). Despite clear evidence of more severe strokes in the thrombolysis group, after treatment, patients who had undergone thrombolysis showed only a trend toward more unfavorable outcome. They had a trend toward larger brain infarctions (median, 8.7% versus 2.5%; P=0.07) and showed nonsignificantly more clinical deficits as assessed with the BI (median, 90 versus 60; P=0.3) and mRS (median, 3.0 versus 2.3; P=0.4) compared with the conservative treatment group.

Correlation Between CT Data and Follow-Up

Linear regression analysis between CT results and outcome measures revealed consistent differences among the 4 CT components for all target parameters (Figure 2). Of the 3 single CT components, the ASPECTS score on NCCT showed lowest correlation coefficients (r=0.42 to 0.58), whereas PCT_CBF consistently showed highest values (r=0.52 to 0.75) with respect to clinical status and infarction size. With respect to the correlation coefficients on linear regression analysis, MOSAIC was superior to all single CT components (r=0.59 to 0.78). When occurrence of any supratentorial infarction regardless of its size is considered the outcome measure, we similarly found a difference in sensitivity values among the CT parameters: NCCT showed lowest values (58.9%), followed by CTA (66.7%) and PCT_CBF (71.8%), whereas the MOSAIC score showed highest values (87.1%). The specificity with respect to occurrence of infarction was 100% for all parameters because no false-positive values were noted.

The results of the sensitivity, specificity, PPV, and NPV with respect to final clinical outcome for each CT component and the MOSAIC score are given in Table 2. The MOSAIC score showed a better efficiency than all single CT modalities in predicting dependency during daily life and bad clinical outcome. As given in Table 2, the predictive superiority of the MOSAIC score over the single CT parameters consistently reached statistical significance over NCCT (all P<0.05), was close to statistical significance over CTA (P=0.06 to 0.1), and showed a trend over PCT_CBF (P=0.1). Figure 3 illustrates the superiority of the MOSAIC score over all single CT components in predicting outcome through ROC curve analysis.

Discussion

The value of PCT in assessing the amount of cerebral ischemia has been evaluated in several clinical17,19,27,29 and experimental studies.32–34 It has been shown that occurrence of cerebral infarction can be predicted with high sensitivity and specificity15,17,18 and that pathophysiological aspects can be derived from the respective perfusion pattern.19,20 However, as mentioned by most authors, a major limitation of the PCT technique is the restriction of perfusion measurements to a single slice. Even with the advent of multidetector row CT scanners to cover up to 2 cm of the brain,21,22 it is likely that hemodynamic alterations distant to the measurement levels will be missed. Remarkably, although early signs of infarc-
significantly be expanded. A further limitation of the current
and CTA, the diagnostic window of PCT measurements could
could be hypothesized that by adding the results of NCCT
that integrates the entire body of diagnostic information. It

literature on PCT in acute stroke is the lack of studies
investigating its prediction of the parameter of highest med-
ical and socioeconomic relevance, ie, clinical outcome. In
this prospective study, we evaluated the value of MOSAIC, a
multimodal, multidetector row CT imaging, in predicting
infarction size and clinical outcome 3 months after stroke. We
sought to compare the prognostic impact of a multimodal
score system with each single CT modality.

Therefore, we developed a MOSAIC score that is clearly
structured and easy to apply. To quantify the amount of tissue
infarction on NCCT, we used the ASPECTS scoring system
that has been shown to have good reliability and predictive
value in acute stroke. This scoring system counts in 10
well-defined areas of the MCA territory the number of
regions in which infarction signs can be visualized. This
contrasts to the purely dichotomized approach to discriminate
whether infarction signs cover more than one third of the
MCA territory.10,34 We believe that using the ASPECTS
scoring system allows more structured quantification of early
infarction signs. For CTA, we differentiated between patients
without significant stenosis, those with stenosis of \( \geq 50\% \),
and those with vessel occlusion. For clarity, we did not
further differentiate as to whether the distal ICA or the M1 or
M2 segment of the MCA was affected. In fact, patency of
the proximal MCA segment has a more significant impact on the
tissue hemodynamics than the status of the distal ICA or
distal MCA. However, we did not introduce a weighing factor
based on nonvalidated assumptions that would further com-
plicate the scoring system. Because CBF measurements have

**TABLE 2. Sensitivity, specificity, PPV, and NPV for CT Parameters With Respect to Clinical
Outcome at 3 Months**

<table>
<thead>
<tr>
<th>Dependency at 3 months (mRS &gt; 2)</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOSAIC score ( \geq 4 )</td>
<td>83.3 (58.6–96.2)</td>
<td>92.3 (74.8–98.8)</td>
<td>88.2</td>
<td>88.9</td>
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<tr>
<td>PCT ( \geq 5% )</td>
<td>76.5 (50.1–93.0)</td>
<td>88.0 (68.8–97.3)</td>
<td>80.0</td>
<td>81.5</td>
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<tr>
<td>CTA</td>
<td>72.2 (46.5–90.2)</td>
<td>76.9 (56.3–91.0)</td>
<td>68.4</td>
<td>80.0</td>
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<tr>
<td>NCCT</td>
<td>77.8 (52.4–93.5)</td>
<td>73.1 (52.2–88.4)</td>
<td>66.7</td>
<td>82.6</td>
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<tr>
<th>Dependency at 3 months (mRS &gt; 3)</th>
<th>Sensitivity (95% CI)</th>
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<th>PPV</th>
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<tr>
<td>MOSAIC score ( \geq 5 )</td>
<td>93.8 (69.7–99.0)</td>
<td>89.3 (71.1–97.6)</td>
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<td>96.2</td>
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<tr>
<td>PCT ( \geq 10% )</td>
<td>84.6 (54.5–97.6)</td>
<td>77.8 (57.7–91.3)</td>
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<td>91.3</td>
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<td>CTA</td>
<td>81.3 (54.3–95.7)</td>
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<td>57.1</td>
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<th>Bad outcome (mRS &gt; 3)</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>PPV</th>
<th>NPV</th>
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<tbody>
<tr>
<td>MOSAIC score ( \geq 5 )</td>
<td>100 (100–100)</td>
<td>87.9 (71.8–96.5)</td>
<td>73.3</td>
<td>100</td>
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<tr>
<td>PCT ( \geq 10% )</td>
<td>90.0 (55.5–98.3)</td>
<td>81.3 (63.6–92.7)</td>
<td>60.0</td>
<td>96.3</td>
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<td>CTA</td>
<td>90.9 (58.7–98.5)</td>
<td>72.7 (54.5–86.7)</td>
<td>52.6</td>
<td>96.0</td>
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<td>42.9</td>
<td>91.3</td>
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<td>70.6 (52.5–84.9)</td>
<td>47.4</td>
<td>96.0</td>
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<tr>
<td>NCCT</td>
<td>80.0 (44.4–96.9)</td>
<td>61.8 (43.6–77.8)</td>
<td>38.1</td>
<td>91.3</td>
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**Figure 3.** Survey of ROC curves for NCCT, CTA, PCT, and
MOSAIC score with regard to prediction of clinical dependency
3 months after stroke as indicated by BI \( \leq 90 \). True positive rate (sensitivity) is plotted as a function of the true negative rate (100–specificity) for different cutoff points. According to ROC curve analysis, optimum efficacy with respect to true positive and true negative rate is reached in the upper left corner, whereas the lower right corner reflects the least efficacy. Area under the ROC curve reflects the overall efficacy of the parameter including all cutoff points. The highest efficacy is provided by MOSAIC score (area, 0.90), followed by PCT (area, 0.86; \( P = 0.4 \)) and CTA (area, 0.81; \( P = 0.07 \)). Lowest efficacy was found for NCCT (area, 0.73; \( P = 0.001 \)).
been shown to be more accurate than CBV or TTP in predicting tissue outcome in acute stroke,\textsuperscript{17,18} this parameter was chosen to enter the MOSAIC score as the third CT component. This decision is corroborated by similar findings on MRI perfusion imaging, indicating that CBF rather than CBV or TTP provides the optimum compromise between sensitivity and specificity in predicting infarction size in acute cerebral ischemia.\textsuperscript{35,36} To provide good reproducibility, we did not introduce CBF thresholds but rather used the visible size of the ischemic area to quantify ischemia. This is in accordance with studies on PET\textsuperscript{37} and single photon emission tomography\textsuperscript{38} demonstrating the extension of ischemia rather than the exact amount of CBF reduction to be highly predictive of final infarction size. Interestingly, using our purely visual approach to identify the ischemic tissue, we found a consistent relative CBF of $\approx 39\%$ compared with the mirrored tissue on the contralateral hemisphere. Because both PCT slices contributed separately to the MOSAIC score, up to 4 points were possible by PCT$_{\text{CBF}}$ but only 2 points by NCCT and CTA.

Throughout the analysis, the MOSAIC score was superior to all single CT components with respect to the various outcome measures (Table 2 and Figure 3). The MOSAIC score showed a strong correlation to the size of infarction ($r=0.78$) and clinical outcome ($r=0.69$). Likewise, high predictive values with respect to clinical outcome were found. Depending on the outcome scale applied, patients with a MOSAIC score $<4$ had an $89\%$ to $96\%$ likelihood of independence, and those with a MOSAIC score of $<5$ had a $96\%$ to $100\%$ likelihood of fair outcome. As hypothesized, the predictive values of the MOSAIC score were higher compared with the single CT modalities. However, this superiority reached statistical significance only over NCCT, and a consistent trend was also found toward CTA and PCT (Table 2). The latter was due to the still-large confidence intervals of the predictive values as an effect of the still-limited amount of data. Of these, PCT$_{\text{CBF}}$ proved to be the CT modality with best prediction of infarction size and clinical outcome. This is in accordance with a recent finding by Ezzeddine et al.,\textsuperscript{20} who found perfusion measurements to be diagnostically more beneficial than NCCT and CTA in classifying stroke subtype.

Furthermore, advantages of the multidetector row PCT measurements became evident for this first time in our study. In $13\%$ of the patients with evidence of tissue ischemia (ie, $9\%$ of all patients), visualization of hemodynamic alterations was possible only in 1 of the 2 slices. Thus, 1 of 11 patients would have had false-negative perfusion results if only single-slice PCT measurements were performed. Until now, no systematic studies have been available that assessed the diagnostic contribution of a dual or multislice approach over single-slice CT measurements. In the only other study using a multidetector row CT system by Wintermark et al.,\textsuperscript{22} a comparison of single and multislice perfusion measurements was not in the scope of their article. Although quite conceivable, it needs to be demonstrated by controlled investigations that the multislice CT approach is superior to the single-slice technique in terms of diagnostic sensitivity and specificity.

The lesion volume defined as the area with reduced CBF showed a good correlation to infarction size ($r=0.75$) and clinical outcome ($r=0.62$). In contrast, findings of NCCT and CTA were only of moderate predictive value. In particular, the positive prediction of outcome by NCCT ($38\%$ to $67\%$) and by CTA ($47\%$ to $68\%$) was limited. Strong differences among parameters were also found when occurrence of any supratentorial infarction was used as a dichotomized outcome variable. Although all parameters had $100\%$ specificity in detecting cerebral infarctions (no false-positive ratings), their sensitivity was only $59\%$ for NCCT and $67\%$ for CTA. Thus, normal findings on NCCT or CTA do not exclude the development of small cortical infarcts with sufficient reliability. This is in accordance with a large study that evaluated the predictive value of early NCCT for ischemic brain damage.\textsuperscript{9} This study likewise found high values for specificity ($85\%$) and PPV ($96\%$) but only moderate to low values for sensitivity ($64\%$) and NPV ($27\%$). Even PCT$_{\text{CBF}}$ had only $72\%$ sensitivity in detecting all supratentorial infarctions, which reflects the restriction of PCT measurements to a limited amount of brain tissue. When all CT information was extracted into the MOSAIC score, this sensitivity increased to $87\%$. Thus, even a completely normal multimodal CT status is unable to reliably exclude the existence of tissue ischemia. However, all infarctions missed were small and mostly functionally irrelevant. Thus, prediction of functional outcome was affected only slightly by this limitation.

The correlation of the CT parameters with clinical status at admission was less strong. The correlation factors with the NIHSS were highest for the MOSAIC score and lowest for the NCCT findings. This is in accordance with previous studies using early neuroradiological predictors based on CT and MRI technology. Lev et al.\textsuperscript{16} used 3-dimensional helical CT scanning to discriminate between perfused and nonperfused tissue in 22 patients undergoing intra-arterial thrombolysis. Their lesion volume showed a good correlation to clinical outcome ($r=0.53$) but only a weak correlation to the initial NIHSS ($r=0.33$). Thijs et al.\textsuperscript{39} found a correlation factor of 0.68 between lesion volume on diffusion-weighted imaging and BI at 1 month but only a moderate correlation of 0.45 between diffusion-weighted imaging and NIHSS on admission.

Several issues in the present study and the proposed technique need to be addressed. First, our follow-up imaging to detect and quantify cerebral infarction consisted of CT and MRI. This reflects clinical obstacles and structural limitations, which is in agreement with other studies reporting on similarly heterogeneous compositions.\textsuperscript{15,17,29,40} Because the same investigators analyzed both CT and MRI follow-up images, the error, if relevant, should be limited and consistent in direction. Second, in 3 patients, the clinically blinded investigators noted early signs of infarction on the unaffected hemisphere. Although these results did not enter the MOSAIC score, they may reflect remaining diagnostic uncertainty in the detection of these subtle CT changes.\textsuperscript{10,34} Lev et al.\textsuperscript{16} stated that many of their early infarction signs on NCCT were only retrospectively identified after visualization of coregistered contrast-enhanced CT images. Indeed, knowledge of clinical or hemodynamic details facilitates the detec-
tion of early infarction signs. Still, we believe that for scientific purposes our approach with totally blinded investigators is preferred. Nevertheless, knowledge of clinical symptoms may have led to a higher ASPECTS score in some of our cases with better predictability of this component. This issue further underscores the need for more reliable parameters for early patient stratification. Third, in 3 patients, small infarcts in the brain stem and cerebellum occurred that were missed by the multimodal CT workup. This indicates a fundamental limitation of the CT technique in general. Because many infratentorial strokes can be recognized clinically, early MRI is preferred in such cases. Finally, the radiation dose and the amount of contrast agent used for the proposed MOSAIC technique need to be discussed. The effective dose equivalent of the entire CT procedure using the technique parameters as described in the Methods section amounts to ∼6 mSv, which is reasonable for an emergency procedure. This is in accordance with a recent calculation given by Wintermark et al. 22 For PCT and CTA, only 140 mL of contrast agent is needed. Thus, subsequent intra-arterial catheter angiography is still possible, eg, if local thrombolysis is indicated. Furthermore, it has been shown that nonionic contrast, even in much higher doses than applied in this study, is not detrimental in acute cerebral ischemia. 41 Thus, we believe that technical parameters do not constitute a significant restriction of the proposed technique.

In this study, we did not investigate to what extent the multimodal CT approach is useful in predicting the early clinical course because of infarction growth or development of cerebral edema, nor did we investigate if and how patient selection for thrombolytic therapy can be improved by this approach. Besides the number of early CT signs of cerebral infarction, 24 proof is lacking that novel CT modalities truly contribute to this selection process. With regard to CTA, there is still controversy about whether vessel status on CTA represents an exclusion criterion for thrombolysis. 13, 42 With respect to PCT, Lev et al. 16 using a simplified measurement technique, found the ischemic volume to be predictive of outcome after intra-arterial thrombolysis. Whereas patients with lesion volumes >100 mL had poor outcome, most patients with smaller lesion volumes showed good improvement after local thrombolysis. Wintermark et al defined irreversibly infarcted tissue by strongly reduced CBV values and defined potentially salvageable tissue with additional CBF measurements. 22 Thus, current evidence suggests that PCT measurements have greater potential than CTA to select suitable candidates for thrombolysis. Because all patients in our study with normal NCCT, CTA, and PCT (MOSAIC score=0) had unanimously good outcome, they are unlikely to benefit from thrombolysis. On the other hand, in patients with large areas of severe ischemia on PCT\textsubscript{CBV} in which irreversible tissue necrosis is likely to exist, 22 the benefit from thrombolysis is likewise questionable. More work is needed to establish a CT-based “mismatch imaging” to improve patient selection for aggressive treatment approaches. In this respect, the MOSAIC approach may help to discriminate patients unlikely to benefit from thrombolysis with either brain ischemia that is too mild or too severe. It further needs to be evaluated whether the integration of other CT-derived perfusion parameters (ie, CBV, TTP) into this scoring system allows more sensitive and specific prognostication of tissue viability and infarction size.

In summary, we have shown that the multimodal CT concept optimizes the diagnostic exploitation of this technique in predicting infarction size and clinical outcome in hyperacute stroke. In needs to be addressed to what extent a CT algorithm is comparable to the MRI technique, which, if available, has become the gold standard of acute stroke imaging.

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