Aneurysmal subarachnoid hemorrhage (SAH) is a serious disease with high case fatality and morbidity. A high rate of hypodense lesions consistent with cerebral infarctions has been evident on delayed computed tomographic (CT) scanning among survivors. Delayed cerebral infarction (DCI) was proposed to be the preferred surrogate outcome in SAH, to vasospasm or delayed cerebral ischemia. Although some studies suggested deep DCI and high infarct volume were poor prognostic factors, the literature was unclear on the outcome impact of quantitative DCI load according to location. These knowledge would help us to understand better the pathological process and assess the severity of delayed cerebral ischemia.

Objectives
In this study, we aimed to assess the significance of the presence of DCI, DCI load, and location in patients with SAH among cognitive and functional outcomes at 3 months.

Methods
We prospectively enrolled patients with SAH presenting to an academic neurosurgical unit in Hong Kong during a 3-year period. DCI was defined by new hypoattenuation on computed tomography at 4 to 6 weeks, which was not present in the postaneurysm-treatment computed tomography at 24 to 48 hours. DCI was assessed for location according to cerebral artery territories and load semiquantitatively. Cognitive and functional outcome assessments were carried out 3 months after ictus.

Results
One hundred twenty-six patients with subarachnoid hemorrhage consented for this study. DCI occurred in 56 (44%) patients and was associated with poorer cognitive and functional outcomes (Montreal Cognitive Assessment, Mini-Mental State Examination, modified Rankin Scale, and Lawton Instrumental Activity of Daily Living) at 3 months. In patients with DCI, the presence of perforator zone infarct was associated with poorer cognitive and functional outcomes, and cortical middle cerebral artery infarct was associated with poorer modified Rankin Scale. After adjustment for age, admission World Federation of Neurosurgical Societies Grade and mode of aneurysm treatment, both middle cerebral artery cortical infarct load and perforator infarct load were independently associated with poor cognitive outcomes (Montreal Cognitive Assessment and Mini-Mental State Examination) and modified Rankin Scale.

Conclusions
Middle cerebral artery cortical and perforator zone infarct loads are potential surrogate marker to assess the severity of delayed cerebral ischemia. (Stroke. 2015;46:3099-3104. DOI: 10.1161/STROKEAHA.115.010844.)

Key Words: aneurysm • cerebral infarction • middle cerebral artery • stroke • subarachnoid hemorrhage
within 96 hours after ictus; (3) between 21 and 75 years of age; (4) a speaker of Chinese (Cantonese); (5) a CT of brain done at 4 to 6 weeks; and (6) informed consent from the patients or their next of kin. The patient exclusion criteria were (1) a history of previous cerebrovascular or neurological disease other than unruptured intracranial aneurysm or (2) a history of neurosurgery before ictus.

All CT scans were performed on a 64-slice CT (Lightspeed VCT; GE Healthcare), with axial images acquired in 5-mm thick sections, which were reviewed for image analysis. Delayed CT was defined as post treatment 4 to 6 weeks. DCI was defined as new parenchymal hypoattenuation on delayed CT, which was not present in early and post treatment (after 24–48 hours) CT, and cannot be accounted by hydrocephalus.

Standard of Care
Ruptured aneurysms would usually be treated within 24 hours after admission. Nimodipine would routinely be started on admission and continued for 21 days. When symptomatic vasospasm (delayed ischémie neurological deficit) developed, hypertensive treatment with elevated mean arterial blood pressure of ≥120 mm Hg would be started. CT perfusion would be performed for diagnosis. Cerebral digital subtraction angiography was not usually performed and no balloon angioplasty and other intra-arterial treatment were done within the cohort.

Infarct Load and Location of DCI
The affected territories of the anterior circulation were graded by a systematic quantitative scoring system modified from Alberta Stroke Program Early CT Score (ASPECTS) as m-ASPECTS. The m-ASPECTS value was calculated from 2 standard axial CT cuts, 1 at the level of the thalamus and basal ganglia, and 1 just rostral to the ganglionic structures. The territory of the middle cerebral artery (MCA) is allocated 10 points. We modified by adding 1 point for each anterior cerebral artery territory for each cuts. One point is subtracted for an area of parenchymal hypoattenuation, for each of the defined regions. The m-ASPECTS thus allocated the anterior circulation 24 points.

For posterior circulation infarct, posterior circulation Acute Stroke Prognosis Early CT Score (pc-ASPECTS) is used. pc-ASPECTS allocated the posterior circulation 10 points. A pc-ASPECTS score of 10 indicates the absence of visible posterior circulation ischemia, a score of 0 indicates parenchymal hypoattenuation in all pc-ASPECTS territories.

Infarct Load Was the Sum Scores of the m-ASPECTS and pc-ASPECTS. The Sum Scores Ranged From 0 to 34 (No Parenchymal Hypoattenuation)
Location was calculated from the axial CT cuts, at the level of the thalamus and basal ganglia, and 1 just rostral to the ganglionic structures. Locations were classified into perforator zone, cortical anterior cerebral artery (ACA), cortical MCA, and cortical posterior cerebral artery (PCA). Perforator zone infarct was defined as 1 attributable to perforating arteries from the anterior, middle, and posterior cerebral arteries, including those located in the putamen, caudate head, corpus callosum, subependymal area of lateral ventricle, and thalamus.

All images were reviewed independently by 2 radiologists (R.C.H.N. and J.C.M.S.). A third radiologist adjudicator (D.Y.W.S.) assessed the infarct extent when discrepancy arose.

Clinical Outcome Assessments
Assessments were carried out 3 months after ictus by trained research assistants (psychology graduates) trained blinded to other clinical data.

Montreal Cognitive Assessment
The Montreal Cognitive Assessment (MoCA) is a 1-page 30-point test that is usually administered within 15 minutes, and evaluates the following 7 cognitive domains: visuospatial/executive functions, naming, verbal memory registration and learning, attention, abstraction, 5-minute delayed verbal recall, and orientation. One point would be added for education <12 years. MoCA had been previously validated to assess cognitive dysfunction and deficits in patients with SAH.

Mini-Mental State Examination Chinese (Cantonese) Version
The Mini-Mental State Examination (MMSE) comprises 5 sections (orientation, registration, attention and calculation, recall, and language). The maximum total score is 30 and the test can usually be completed within 10 minutes.

Modified Rankin Scale
The modified Rankin Scale (mRS) is a valid and clinically relevant disability scale to assess recovery and is commonly used in stroke trials. mRS identifies activity limitation.

Chinese Lawton Instrumental Activity of Daily Living Scale
The Lawton Instrumental Activity of Daily Living (IADL) Scale is an appropriate instrument to assess independent living skills. Items assessed include ability to use the telephone, go shopping, prepare food, do the housekeeping, do the laundry, the use of transportation, responsibility for own medications, and ability to handle finances.

Statistical Analysis
Statistical analyses were generated using SPSS for Windows version 18.0 (SPSS Inc, Chicago, IL). Categorical data are given as numbers (percentages), unless otherwise specified; numeric data are given as means and SDs; and ordinal data are given as medians and interquartile ranges. A difference with a P<0.05 was regarded as statistically significant (2-tailed test). Categorical data were analyzed using the Fisher exact test or χ2 test, with odds ratios and 95% confidence intervals (CIs) as appropriate. Correlations between numeric or ordinal data were assessed using Kendall rank correlation (Kendall τb coefficient).

Multiple regression analysis was performed to determine the factors associated with clinical outcome using the enter method, with the F probability of entry set at 0.05 and that of removal set at 0.10. Interactions between independent variables were assessed by tolerance value and variable inflation factor. Tolerance value is an indicator of the extent to which the variance of the specified independent variable is not explained by the other independent variables in the model and is calculated using the formula 1 R2 for each variable. A small value (<0.10) indicates that the multiple correlation with other variables is significant, suggesting the possibility of multicollinearity. The other value is the variable inflation factor, which is the converse of the tolerance value. Similarly, variable inflation factor >10 indicate multicollinearity. All analyses had tolerance value >0.10 and variable inflation factor <10, which indicated no multicollinearity. Thus, there was no significant interaction between independent variables in the analyses. Assumptions of normality, linearity, and homoscedasticity of residuals were checked with Normal P-P Plot and Scatterplot for all analyses, and there was no major deviation suggesting violation of assumptions.

Results
Patient Characteristics
We screened 167 patients with SAH and 126 (75%) patients consented for this study. There was no loss to follow-up at
3-month assessments. Patient characteristics are shown in Table 1. SAH patients with DCI tended to have poorer WFNS grade on admission (P=0.021) and require external ventricular drain for acute hydrocephalus (P<0.001). Symptomatic vasospasm occurred in 74 (59%) patients and DCI occurred in 56 (44%) patients. There was a trend toward association between symptomatic vasospasm and DCI (Kendall τb coefficient=0.44; P=0.068).

### Table 1. Patient Profile

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Patients With DCI</th>
<th>Patients Without DCI</th>
<th>OR (95% CI)</th>
<th>MD</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>126</td>
<td>56</td>
<td>70</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Age (y, mean±SD)</td>
<td>54±10</td>
<td>54±9</td>
<td>54±11</td>
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<td>0</td>
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<tr>
<td>Male</td>
<td>49 (39)</td>
<td>28 (50)</td>
<td>21 (30)</td>
<td>2.3 (1.1–4.9)</td>
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<td>0.022</td>
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<tr>
<td>Smoker</td>
<td>35 (28)</td>
<td>14 (25)</td>
<td>21 (30)</td>
<td>0.8 (0.4–1.7)</td>
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<td>0.534</td>
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<td>Hypertension</td>
<td>51 (41)</td>
<td>22 (39)</td>
<td>29 (41)</td>
<td>0.9 (0.4–1.9)</td>
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<td>Years of formal education (mean±SD)</td>
<td>8±4</td>
<td>8±4</td>
<td>9±5</td>
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<td>1</td>
<td>0.067</td>
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<td>WFNS grade on admission</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>I</td>
<td>44 (35)</td>
<td>18 (32)</td>
<td>26 (37)</td>
<td></td>
<td></td>
<td>0.021*</td>
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<td>II</td>
<td>44 (35)</td>
<td>15 (27)</td>
<td>29 (41)</td>
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<tr>
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<td>3 (4)</td>
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<tr>
<td>IV</td>
<td>14 (11)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>19 (15)</td>
<td>13 (23)</td>
<td>6 (9)</td>
<td></td>
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<td>Fisher CT grade</td>
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<td>I</td>
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<tr>
<td>III</td>
<td>52 (41)</td>
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<td>30 (43)</td>
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<tr>
<td>IV</td>
<td>73 (58)</td>
<td>34 (61)</td>
<td>39 (56)</td>
<td></td>
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<td>Intraventricular hemorrhage</td>
<td></td>
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<tr>
<td></td>
<td>71 (56)</td>
<td>34 (61)</td>
<td>37 (53)</td>
<td>1.4 (0.7–2.8)</td>
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<td>Location of ruptured aneurysm</td>
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<td>Vertebralbasilar system</td>
<td>20 (16)</td>
<td>7 (13)</td>
<td>13 (19)</td>
<td>1.7 (0.8–3.7)</td>
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<tr>
<td>Anterior communicating/cerebral artery</td>
<td>39 (31)</td>
<td>21 (38)</td>
<td>19 (26)</td>
<td>0.6 (0.2–1.7)</td>
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<td>Posterior communicating artery</td>
<td>12 (10)</td>
<td>3 (5)</td>
<td>9 (13)</td>
<td>0.4 (0.1–1.5)</td>
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<td>Internal carotid artery</td>
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<td>13 (23)</td>
<td>21 (30)</td>
<td>0.7 (0.3–1.6)</td>
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<td>Middle cerebral artery</td>
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<td>1.8 (0.7–4.8)</td>
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<tr>
<td>Endovascular embolization</td>
<td>75 (60)</td>
<td>33 (59)</td>
<td>42 (60)</td>
<td>1.0 (0.5–2.0)</td>
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<tr>
<td>Microsurgical clipping</td>
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<td>20 (36)</td>
<td>22 (31)</td>
<td>1.2 (0.6–2.6)</td>
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<td>Acute hydrocephalus requiring EVD</td>
<td>58 (46)</td>
<td>36 (64)</td>
<td>22 (31)</td>
<td>3.9 (1.9–8.3)</td>
<td>&lt;0.001**</td>
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<tr>
<td>Chronic hydrocephalus requiring VPS</td>
<td>14 (11)</td>
<td>8 (14)</td>
<td>6 (9)</td>
<td>1.8 (0.6–5.5)</td>
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<td>0.31</td>
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<tr>
<td>Modified Rankin Scale</td>
<td></td>
<td></td>
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<tr>
<td>0</td>
<td>18 (14)</td>
<td>6 (11)</td>
<td>12 (17)</td>
<td></td>
<td></td>
<td>0.006**</td>
</tr>
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<td>1</td>
<td>12 (10)</td>
<td>6 (11)</td>
<td>6 (9)</td>
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</tr>
<tr>
<td>2</td>
<td>43 (34)</td>
<td>10 (18)</td>
<td>33 (47)</td>
<td></td>
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<tr>
<td>3</td>
<td>12 (10)</td>
<td>8 (14)</td>
<td>4 (6)</td>
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<tr>
<td>4</td>
<td>7 (6)</td>
<td>5 (9)</td>
<td>2 (3)</td>
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</tr>
<tr>
<td>5</td>
<td>28 (22)</td>
<td>18 (32)</td>
<td>10 (14)</td>
<td></td>
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<tr>
<td>6</td>
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<tr>
<td>0–2</td>
<td>73 (58)</td>
<td>22 (39)</td>
<td>51 (73)</td>
<td>0.2 (0.1–0.5)</td>
<td>&lt;0.001**</td>
<td></td>
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<tr>
<td>0–1</td>
<td>30 (23)</td>
<td>12 (21)</td>
<td>18 (26)</td>
<td>0.8 (0.3–1.8)</td>
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<td>0.575</td>
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<tr>
<td>Instrumental ADL (median, interquartile range)</td>
<td>14, 0–18</td>
<td>6.5, 0–17</td>
<td>17.5, 7–18</td>
<td></td>
<td>5</td>
<td>0.001**</td>
</tr>
<tr>
<td>MMSE (median, interquartile range)</td>
<td>27, 24–29</td>
<td>25, 18.5–28</td>
<td>28, 26–29</td>
<td></td>
<td>5</td>
<td>0.001**</td>
</tr>
<tr>
<td>MoCA (median, interquartile range)</td>
<td>23, 19–26</td>
<td>20, 13–23</td>
<td>25, 22–27</td>
<td></td>
<td>6</td>
<td>&lt;0.001**</td>
</tr>
</tbody>
</table>

Number (%) unless specified. ADL indicates activity of daily living; CT, computed tomography of brain; DCI, delayed cerebral infarction; EVD, external ventricular drain; MD, mean difference; MMSE, mini-mental state examination; MoCA, Montreal Cognitive Assessment; OR, odds ratio; VPS, ventriculo-peritoneal shunt; and WFNS, World Federation of Neurosurgical Societies.

*P<0.05. **P<0.01.
Presence of DCI
On univariate analyses, DCI was associated with poorer mRS, IADL, MoCA, and MMSE. After adjustments for age, admission WFNS grade and mode of aneurysm treatment, DCI remained significantly associated with poorer mRS (odds ratio, 0.6; 95% CI, 0.0–1.2; \( P=0.041 \)), IADL (odds ratio, −3.6; 95% CI, −6.0 to −1.1; \( P=0.004 \)), MoCA (odds ratio, −4.6; 95% CI, −6.8 to −2.3; \( P<0.001 \)), and MMSE (odds ratio, −4.6; 95% CI, −7.1 to −2.1; \( P<0.001 \)).

Locations of DCI
In the 56 SAH patients with DCI, we divided the locations into perforator zone, cortical ACA, cortical MCA, and cortical PCA. Perforator zone DCI was found in 20 (54%) patients with DCI; cortical ACA DCI was found in 17 (30%) patients; cortical MCA DCI was found in 35 (63%) patients; and cortical PCA DCI was found in 5 (9%) patients.

On univariate analyses, perforator zone was associated with poorer mRS, MoCA, and MMSE; cortical MCA location was also associated with poorer mRS. There was no difference in outcomes between the presence of right and left DCI. After adjustments for age, admission WFNS grade and mode of aneurysm treatment, perforator zone remained significantly associated with mRS (odds ratio, 1.5; 95% CI, 0.5–4.2; \( P=0.003 \)), MoCA (odds ratio, −6.0; 95% CI, −11.3 to −6.0; \( P=0.027 \)), and MMSE (odds ratio, −7.1; 95% CI, −13.4 to −0.8; \( P=0.027 \)); Cortical MCA location showed a trend of association with mRS (odds ratio, 0.9; 95% CI, 0.0–1.9; \( P=0.058 \)). Perforator zone also showed a trend of association with IADL in both univariate analysis and after adjustments for age, admission WFNS grade, and mode of aneurysm treatment (odds ratio, −3.8; 95% CI, −8.1 to 0.6; \( P=0.086 \)).

Infarct Load of DCI
In the 56 SAH patients with DCI, we assessed infarct load semiquantitatively by the number of regions involved in DCI. The median number of regions was 2 (interquartile range, 1–4.5).

On univariate analyses, infarct load was associated with poorer mRS, IADL, MoCA, and MMSE. After adjustments for age, admission WFNS grade and mode of aneurysm treatment, infarct load remained significantly associated with mRS (odds ratio, 0.2; 95% CI, 0.1–0.4; \( P=0.002 \)), MoCA (odds ratio, −1.1; 95% CI, −2.0 to −0.3; \( P=0.011 \)), and MMSE (odds ratio, −1.6; 95% CI, −2.6 to −0.6; \( P=0.002 \)). There was a trend of association with IADL (odds ratio, −0.7; 95% CI, −1.4 to 0.1; \( P=0.070 \)).

Infarct Load at Different Cerebral Artery Territories
We further explored the effect of infarct load at different deep and cortical cerebral artery territories. After adjustments for age, admission WFNS grade and mode of aneurysm treatment, MCA cortical infarct load and MCA perforator infarct load were significantly associated with MoCA, MMSE, and mRS (Table 2). Other cerebral artery territories were not significantly associated with the 3-month outcomes.

Discussion
In our analysis, we first established that both perforator location and MCA cortical location of DCI were related to cognitive and functional outcomes independent of age, admission WFNS, and mode of aneurysm treatment. Further on, we showed that a semiquantitative method to score DCI load was feasible and significantly associated with cognitive and functional outcomes. We finally explored the effect of DCI loads in different deep and cortical regions according to cerebral artery territories and showed that MCA cortical infarct and perforator infarct loads were independently associated with cognitive outcomes and mRS.

Rabinstein et al11 suggested that single cortical infarct and multiple subcortical infarcts were common patterns of DCI, whereas Naidech et al10 suggested a description of single versus multiple, cortical versus deep versus combined. Both the articles suggested that multiple infarcts were associated with poor outcome. A quantitative assessment of DCI was attempted by Rosenberg et al.15 They performed a volumetric assessment of DCI in patients with SAH who were dependent or bedbound and showed that infarct volume was associated with outcome. These 3 studies, however, did not further assess the infarct load according to vascular territories. Previous studies had showed that cerebral infarction present at CT 1 year after SAH and mode of aneurysm treatment were related to cognitive performance.27–31 Many of these studies used single-slice CT at 1 year, which would probably miss small DCI. They used many specific neuropsychological tests, such as copy and delayed production of Rey figure and modified Stroop test, for assessments. The raw scores were compared and no standardized conversion was done. The construct was not aimed to give an overall impression of cognitive function. In our study, we used MoCA and MMSE to assess the overall cognitive function. MoCA and MMSE had been shown to correlate with functional outcomes and cognitive domain deficits in patients with SAH.4,18

We showed the DCI loads in the MCA territories were associated with MoCA, MMSE, and mRS at 3 months. The

Table 2. Infarct Loads of Different Cerebral Artery Territories and 3-Month Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Cortical MCA Infarct Load</th>
<th>Perforator MCA Infarct Load</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified Rankin Scale</td>
<td>0.3 (0.1 to 0.5), ( P=0.003 )</td>
<td>0.7 (0.2 to 1.3), ( P=0.012 )</td>
</tr>
<tr>
<td>Instrumental ADL</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Montreal Cognitive Assessment</td>
<td>−1.6 (12.9 to −0.3), ( P=0.015 )</td>
<td>−4.1 (−8.0 to −0.1), ( P=0.045 )</td>
</tr>
<tr>
<td>Mini-Mental State Examination</td>
<td>−2.3 (−3.8 to −0.8), ( P=0.004 )</td>
<td>−4.9 (−9.4 to −0.3), ( P=0.036 )</td>
</tr>
</tbody>
</table>

Data are in odds ratio (95% confidence interval), \( P \) value. ADL indicates activity of daily living; MCA, middle cerebral artery; and n.s., not statistically significant.
absence of correlation with other regions such as ACA did not mean that DCI at these regions were asymptomatic. These DCI might have a more significant impact on a specific aspect of cognitive function, which could only be detected by a comprehensive neuropsychology battery. Disruption of white matter track, especially from perforator infarcts, might be an important mechanism of cognitive dysfunction and functional connectivity should be considered in future studies for better understanding.32

There were limitations of this study. The sample size did not allow patient subgroup analyses. The presence and the absence of DCI may be affected by the clinical management of delayed cerebral ischemia and vasospasm. We did not find difference in summative cognitive scores (MMSE and MoCA) between left- and right-sided DCI, in which different patterns of cognitive domain deficits were likely.33 These different patterns of cognitive domain deficits might not be detected by summative cognitive scores. Hypodense lesions on CT at 4 to 6 weeks post treatment may not accurately detect all DCI. We assessed 5-mm CT slices for pc-ASPECTS when compared with finer reconstructed slices, which might be less sensitive. Moreover, CT diagnosis of DCI is less sensitive than magnetic resonance imaging.34,35 Causes of DCI cannot be diagnosed in plain CT; CT angiography and perfusion can be helpful to assess the relationship with major vessel vasospasm.36,37 We have not compared our DCI load assessment using number of regions to volumetric assessment.

Conclusions
MCA cortical infarct and perforator infarct loads were independently associated with MoCA, MMSE, and mRS. These 2 parameters may be potential markers for severity of delayed cerebral ischemia and can prognosticate cognitive outcomes.

Sources of Funding
This study was funded by Chinese University of Hong Kong Research Fund.

Disclosures
None.

References


Location, Infarct Load, and 3-Month Outcomes of Delayed Cerebral Infarction After Aneurysmal Subarachnoid Hemorrhage

George Kwok Chu Wong, Ryan Chi Hang Nung, Jacqueline Ching Man Sitt, Vincent Chung Tong Mok, Adrian Wong, Faith Lok Yan Ho, Wai Sang Poon, Defeng Wang, Jill Abrigo and Deyond Yun Woon Siu

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