Extent of white matter lesions is related to acute subcortical infarcts and predicts further stroke risk in patients with first ever ischaemic stroke

J H Fu, C Z Lu, Z Hong, Q Dong, Y Luo, K S Wong

Objective: To investigate whether the extent of white matter lesions (WML) on fluid attenuated inversion recovery (FLAIR) MRI sequences is an independent risk factor for recurrent stroke, and to document the pattern of acute cerebral infarcts using diffusion weighted imaging (DWI) in patients with different severities of WML.

Methods: In a prospective cohort study, 228 consecutive stroke patients were studied between 1999 and 2001 in a community hospital. The severity of WML was graded as 0 (no WML), 1 (mild), 2 (moderate), or 3 (severe) according to the FLAIR appearances. DWI was used to document the location and size of the infarct.

Results: 31 patients had grade 0 WML, 69 had grade 1, 59 had grade 2, and 69 had grade 3. Age was independently associated with WML on logistic regression analysis (p = 0.0001). Acute cerebral infarcts in deep white matter were correlated with increasing severity of WML. On a median follow up of 23.0 months, life table analysis showed that recurrent stroke was related to the severity of WML (recurrence rate 7.8% in grade 0, 9.3% in grade 1, 17.7% in grade 2, 43.7% in grade 3; p = 0.0001). Survival was reduced in patients with severe WML (p = 0.0068). A Cox proportional hazards model showed WML to be predictive of recurrent stroke (p = 0.000, hazard ratio = 4.177 (95% confidence interval, 2.038 to 8.564)) and also for survival (p = 0.040, hazard ratio = 2.021 (1.032 to 3.960)).

Conclusions: Patients with severe leukoaraiosis have increased risk of deep subcortical stroke and a higher risk of recurrent stroke.
MRI acquisition

All MRI examinations of the brain were done within three days of symptom onset with a 1.5 T scanner (GE Signa Horizon), using a head coil with quadrature detection. The brain imaging protocol involved the following:

- T1 and T2 weighted spin echo axial images (T1: time of repetition (TR)/time of echo (TE), 320/14 ms; T2: TR/TE, 2200/100 ms; matrix 256 x 256 x 160);
- Sagittal T1 weighted images;
- FLAIR axial images (TR/TE, 8002/126 ms; inversion time (TI) = 2000 ms; matrix 256 x 256 x 160);
- Axial isotropic diffusion weighted (DWI) SE echo planar imaging (EPI) sequence (TR/TE, 9999/101 ms; b = 0, 1000; matrix 128 x 128); all axial images had 5 mm slice thickness with 0.5 mm slice gap.

WML were considered present if visible as hyperintense lesions on the FLAIR MRI sequence, without prominent hypointensity on T1 weighted scans. They were rated on a 0 to 3 scale: grade 0, no lesion (including symmetrical, well defined caps or bands); grade 1, focal lesions; grade 2, beginning confluence of lesions; grade 3, diffuse involvement of the entire region, with or without involvement of U fibres. DWI was used to evaluate the location and size of the new indexed cerebral infarcts. The location of new infarcts was classified into frontal lobe, parietal lobe, temporal lobe, occipital lobe, basal ganglia, deep white matter (including centrum semiovale and periventricular), cerebellum, brain stem, and multiple foci (infarcts that involved more than one of the above areas). The size of new cerebral infarcts was classified into lacunar infarcts (defined where the diameter of the lesion was no more than 15 mm on DWI) and non-lacunar infarcts. The MRIs were read without knowledge of the clinical data.

Group division and follow up

All patients were followed by regular clinic visits or by telephone calls. The end point events consisted of recurrent stroke or death. Stroke recurrence was defined as a new

### Table 1  Clinical characteristics of patients with different severity of white matter lesions

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-WML (n = 31)</th>
<th>Mild WML (n = 69)</th>
<th>Moderate WML (n = 59)</th>
<th>Severe WML (n = 69)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (n)</td>
<td>21 (67.7%)</td>
<td>38 (55.1%)</td>
<td>33 (55.9%)</td>
<td>38 (55.1%)</td>
<td>0.818</td>
</tr>
<tr>
<td>Age (y)</td>
<td>50.5 (5.2)</td>
<td>66.3 (6.7)</td>
<td>71.0 (5.9)</td>
<td>75.9 (7.1)</td>
<td>0.0001†</td>
</tr>
<tr>
<td>Hypertension (n)</td>
<td>13 (41.9%)</td>
<td>34 (49.3%)</td>
<td>41 (69.5%)</td>
<td>57 (82.6%)</td>
<td>0.0001†</td>
</tr>
<tr>
<td>Duration of hypertension (y)</td>
<td>2.7 (4.8)</td>
<td>5.4 (8.1)</td>
<td>10.3 (11.2)</td>
<td>13.7 (11.2)</td>
<td>0.0001†</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>136.3 (26.9)</td>
<td>146.9 (32.3)</td>
<td>162.9 (33.8)</td>
<td>175.2 (30.7)</td>
<td>0.0001†</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>83.1 (13.9)</td>
<td>87.0 (14.9)</td>
<td>92.3 (16.2)</td>
<td>97.3 (15.6)</td>
<td>0.0001†</td>
</tr>
<tr>
<td>Diabetes mellitus (n)</td>
<td>3 (9.7%)</td>
<td>15 (21.7%)</td>
<td>17 (28.8%)</td>
<td>15 (21.7%)</td>
<td>0.226</td>
</tr>
<tr>
<td>Ischaemic heart disease (n)</td>
<td>1 (3.2%)</td>
<td>5 (7.2%)</td>
<td>10 (17.2%)</td>
<td>18 (26.1%)</td>
<td>0.004†</td>
</tr>
<tr>
<td>Atrial fibrillation (n)</td>
<td>3 (9.7%)</td>
<td>6 (8.7%)</td>
<td>6 (10.3%)</td>
<td>6 (8.7%)</td>
<td>0.967</td>
</tr>
<tr>
<td>Smoking (n)</td>
<td>10 (32.3%)</td>
<td>18 (26.1%)</td>
<td>13 (22.0%)</td>
<td>21 (30.4%)</td>
<td>0.659</td>
</tr>
<tr>
<td>Alcohol consumption (n)</td>
<td>6 (19.4%)</td>
<td>13 (18.8%)</td>
<td>11 (18.6%)</td>
<td>17 (24.6%)</td>
<td>0.805</td>
</tr>
</tbody>
</table>

Values are mean (SD) or n (%).

* Wilcoxon signed rank test, p value <0.05.
† One way analysis of variance.

DBP, diastolic blood pressure; SBP, systolic blood pressure; WML, white matter lesion; y, years.

### Table 2  The location and size of new infarcts on diffusion weighted imaging of magnetic resonance images in the four groups

<table>
<thead>
<tr>
<th>Infarct</th>
<th>Non-WML (n = 31)</th>
<th>Mild WML (n = 69)</th>
<th>Moderate WML (n = 59)</th>
<th>Severe WML (n = 69)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>New infarcts on DWI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontal lobe</td>
<td>4 (12.9%)</td>
<td>4 (5.8%)</td>
<td>3 (8.5%)</td>
<td>3 (4.3%)</td>
<td></td>
</tr>
<tr>
<td>Parietal lobe</td>
<td>2 (6.5%)</td>
<td>2 (2.9%)</td>
<td>3 (5.1%)</td>
<td>3 (4.3%)</td>
<td></td>
</tr>
<tr>
<td>Temporal lobe</td>
<td>3 (9.7%)</td>
<td>1 (1.4%)</td>
<td>0 (0%)</td>
<td>2 (2.9%)</td>
<td></td>
</tr>
<tr>
<td>Occipital lobe</td>
<td>2 (6.5%)</td>
<td>1 (1.4%)</td>
<td>1 (1.7%)</td>
<td>3 (4.3%)</td>
<td></td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>1 (3.2%)</td>
<td>9 (13.0%)</td>
<td>6 (10.2%)</td>
<td>7 (10.1%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Deep WM</td>
<td>2 (6.5%)</td>
<td>12 (17.4%)</td>
<td>12 (20.3%)</td>
<td>29 (42.0%)</td>
<td></td>
</tr>
<tr>
<td>Cerebellum</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (1.7%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Brain stem</td>
<td>1 (3.2%)</td>
<td>6 (8.7%)</td>
<td>5 (8.5%)</td>
<td>3 (4.3%)</td>
<td></td>
</tr>
<tr>
<td>Multi-foci</td>
<td>16 (51.6%)</td>
<td>34 (49.3%)</td>
<td>26 (44.1%)</td>
<td>19 (27.5%)</td>
<td></td>
</tr>
<tr>
<td>Size</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.82</td>
</tr>
<tr>
<td>Li</td>
<td>3 (10.7%)</td>
<td>11 (15.9%)</td>
<td>10 (16.9%)</td>
<td>11 (15.9%)</td>
<td></td>
</tr>
<tr>
<td>Non-Li</td>
<td>28 (89.3%)</td>
<td>58 (84.1%)</td>
<td>49 (83.1%)</td>
<td>58 (84.1%)</td>
<td></td>
</tr>
</tbody>
</table>

*p<0.05, non-WML v severe WML
†p=0.05, mild v severe WML
L, lacunar infarct; WM, white matter; WML, white matter lesion.
neurological deficit or an exacerbation of a previous deficit lasting more than 24 hours, according to Burn et al.21 Cause of death was defined as the first stroke, recurrent stroke, and other reasons.

Statistical analyses
Statistical analysis software (SAS) 6.12 was used for the statistical analysis. A univariate analysis was carried out with \( t \) tests for continuous variables and the \( \chi^2 \) test for categorical variables. The associations between the potential risk factors and the severity of WML were analysed by multiple logistic regression. The prognostic impact of WML on the risk of stroke recurrence and death was assessed with Kaplan–Meier event-free survival analyses (including a log-rank test to compare groups) and Cox proportional hazards regression modelling. A level of \( p<0.05 \) was considered statistically significant.

RESULTS
There were 31 patients with grade 0 WML, 69 with grade 1, 59 with grade 2, and 69 with grade 3 at the initial evaluation. The median follow up time was 23.0 months (range 0.9 to 37.1). During the follow up period, 11 cases (4.8%) dropped out, including one in grade 0 WML, five in grade 1, four in grade 2, and one in grade 3. At the end of the study, we had complete data on 217 patients for analysis.

Table 2 shows the location and size of the acute infarcts in the four groups. The extent of WML was strongly associated with the location of new lesions on DWI. Acute cerebral infarcts occurred more often in the deep white matter with increasing severity of WML. Follow up data were obtained by clinic visits in 85 patients (37.3%), and by telephone interview in 132 patients (57.9%). The median follow up time was 23.0 months (range 0.9 to 37.1). During the follow up period, 11 cases (4.8%) dropped out, including one in grade 0 WML, five in grade 1, four in grade 2, and one in grade 3. At the end of the study, we had complete data on 217 patients for analysis.

Life table analysis shows the recurrent stroke rate in the four groups (Fig 1). Recurrent stroke occurred in 29 patients (13.4%) including two in grade 0 WML (one with ischaemic stroke, the other with cerebral haemorrhage); three in grade 1 (one with ischaemic stroke, two with cerebral haemorrhage); eight in grade 2 (six with ischaemic stroke, two with cerebral haemorrhage), and 16 in grade 3 (15 with ischaemic stroke, one with cerebral haemorrhage). The one, two, and three year cumulative rates of recurrent stroke were 3.2%, 7.8%, and 7.8% in grade 0 WML; 3.2%, 3.2%, 9.3% in grade 1: 9.4%, 17.7%, 17.7% in grade 2; and 15.9%, 30.2%, 43.7% in grade 3. The recurrent stroke rate was significantly higher in patients with severe WML than in those with mild or no WML (log-rank test, \( p = 0.001 \)).

Assessment of the risk of recurrent stroke was repeated using Cox regression analysis. After the factors relating to the recurrent stroke listed in table 3 were taken into account, the extent of WML remained a significant predictor for recurrent stroke (\( p = 0.000; \) hazard ratio = 4.177 (95% confidence interval, 2.038 to 8.564)).

Table 3 shows the survival rate curves of the four groups at the end of the study. Twenty five patients (11.5%) died during the follow up period: two in grade 0 (one from the first stroke, the other from a recurrent stroke); three in grade 1 (two from the first stroke, one from a recurrent stroke); six in grade 2 (four from the first stroke, one from a recurrent stroke, and one from other causes); and 14 in grade 3 (nine from the first stroke, three from a recurrent stroke, and two from other causes). The one year, two year, and three year cumulative rates of survival were 96.8%, 92.2%, and 92.2%, respectively, in grade 0 WML; 96.8%, 96.8%, and 92.0% in grade 1; 91.7%, 91.7%, and 83.7% in grade 2; and 87.5%, 91.7%, and 91.7% in grade 3.
78.8%, and 75.6% in grade 3. The survival rate was significantly lower in patients with severe WML than in those with no or mild WML (log-rank test, p = 0.0068).

Assessment of the survival rate was repeated using Cox regression analysis. After the factors relating to the survival rate listed in table 3 were taken into account, the extent of WML remained a significant predictor of survival (p = 0.040, hazard ratio = 2.021 (95% CI, 1.032 to 3.960)). Other predictors of survival are shown in table 3.

**DISCUSSION**

The two major findings of this prospective study of stroke patients were that acute deep white matter infarcts, as shown on DWI, and further strokes are both related to the severity of WML. DWI can distinguish acute infarct from old ischaemia and is thus ideal for showing the exact location of infarcts in patients with severe WML, which CT cannot do. Our data showed that the more severe the WML, the more likely it is that an acute infarct is located in the deep white matter. This result support the hypothesis that severe WML may in part be a sequel of multiple acute infarcts of the deep white matter.

The strength of our study includes the use of advanced magnetic resonance imaging such as FLAIR and DWI. FLAIR is reported to be more sensitive for detecting periventricular lesions than T2 sequences, and can effectively differentiate small ischaemic lesions from dilated perivascular spaces in the deep white matter. To the best of our knowledge, this study is the first to determine the impact of WML on the prognosis of patients with first ever ischaemic stroke using functional MRI techniques. We also found that the extent of WML in the index stroke was a strong predictor of recurrent stroke and of increased mortality. The three year cumulative incidence of recurrent stroke (43.7%) in the patients with severe WML was more than four times as great as in the patients with mild WML (9.3%) or with no WML (7.8%). Life table analysis showed the survival rate in the severe WML group was lower than in the mild WML or no WML groups.

The results of our study are in agreement with previous reports that assessed WML on CT but not on MRI. In the Dutch TIA trial, the risk of stroke was 15% in 337 patients with WML, compared with 8.0% in 2680 patients without WML. In the north American symptomatic carotid endarterectomy trial (NASCET), the three year risk of stroke for medically treated patients was 37.2% in 69 patients with widespread WML, compared with 27.3% in 173 patients with limited WML and 20.2% in 1073 patients with no WML. An American study of 221 patients with ischaemic stroke indicated that severe WML predicted increased morbidity and mortality over patients with mild or no WML. In a Japanese study of 215 patients with lacunar infarcts, the 95 patients with WML had a significantly increased risk of recurrent stroke or death.

Our study has certain weaknesses that needed to be acknowledged. First, this was a hospital based study which may not be representative of stroke patients in the community. However, it is difficult to use sophisticated neuroimaging technique such as functional MRI in the community setting. Second, cognitive function was not assessed in our cohort. Recent studies have indicated that WML may be associated with cognitive impairment, although this has not been fully established. The inclusion of cognition assessment will further clarify the clinical significance of WML. Finally, we did not include stroke severity in our study. Stroke severity is likely to be important in predicting death and recurrent events.

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**REFERENCES**


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