Cerebral Small Vessel Disease and Kidney Function Predict Long-Term Survival in Patients With Acute Stroke

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Background and Purpose—Cerebral small vessel disease reflected by white matter lesions (WMLs) in MRI and kidney function reflected by estimated glomerular filtration rate (eGFR) is closely associated in patients without stroke. We studied whether eGFR and WMLs predict long-term survival in patients with acute stroke.

Methods—After exclusion of patients with low eGFR (N=5 [1.3%]; <30 mL/min/1.73 m²), consecutive patients with acute stroke (N=378) subjected to MRI and serum creatinine determination were included in the study and prospectively followed-up up to 12 years.

Results—Of the patients, 71.2% had died during the follow-up, 152 (40.2%) had moderate (eGFR 60 mL/min/1.73 m² or only mild to moderate WMLs, or both, was associated with improved survival compared with all other combinations.

Conclusions—Cerebral small vessel disease is closely associated with kidney function in patients with acute stroke. Cerebral small vessel disease and kidney function are closely associated predictors of poor poststroke survival. (Stroke. 2010;41:1914-1920.)

Key Words: cerebral # glomerular # small vessel disease # stroke # survival

Chronic kidney disease and cardiovascular disease are independent risk factors for poor cardiovascular outcome in the general population. Impaired renal function, whether determined by creatinine level, creatinine clearance, urea level, or estimated glomerular filtration rate (eGFR), is a predictor of stroke mortality in patients hospitalized for acute stroke. The association of cerebral white matter lesions (WMLs) as seen on MRI, microvascular disease, and kidney function has been demonstrated previously in cross-sectional studies in patients without a history of stroke and in patients with several stages of renal impairment. However, data on patients with acute stroke are lacking. Cognitive decline, a common phenomenon in the elderly, is closely associated with both WMLs and kidney function as determined by eGFR. WMLs are a marker of cerebral small vessel disease. Severe WMLs are an important predictor of cardiovascular and noncardiovascular survival in older people without a history of stroke. Increased frequency and extent of WMLs also occur in patients with ischemic stroke. In addition, severe WMLs predict long-term survival in patients with acute stroke. Previous studies addressing the effect of renal function on survival of patients with acute stroke did not report data on WMLs.

The intimate association of glomerular and cerebral small vessel disease has been subject to considerable debate. We hypothesized that kidney function as estimated by eGFR, potentially reflecting glomerular small vessel disease and cerebral small vessel disease as determined by MRI, might be associated with each other and could be used to predict long-term survival in patients hospitalized for acute stroke.
Methods

Patients
The Helsinki Stroke Aging Memory (SAM) cohort comprised a consecutive series of all Finnish (white) patients with suspected stroke admitted to Helsinki University Central Hospital (n = 1622) between December 1, 1993, and March 30, 1995, as described in detail previously.23-24 According to predetermined exclusion criteria, patients without ischemic stroke (n = 175), with intracerebral hemorrhage (n = 229), or with subarachnoid hemorrhage (n = 69) were excluded. Of the 1149 patients with ischemic stroke, we further excluded those aged <55 years (n = 258) or >85 years (n = 88), those not living in Helsinki (n = 158), and those not speaking the Finnish language (n = 3). A total of 642 patients fulfilled the inclusion criteria and were invited to a follow-up visit 3 months later. Of these, 71 died (11.1%) before the 3-month follow-up, 82 refused (12.8%), and 3 were lost (0.5%) due to undefined causes. Four hundred eighty-six of the living patients were included in the cohort.25 Of these, 383 (78.9%) had data on both serum creatinine level and MRI. Of these, patients with low eGFR (N = 5 [1.3%]; <30 mL/min/1.73 m²) were excluded from the analysis and the final cohort consisted of 378 patients. This final study population did not differ in demographic and medical parameters from the original cohort. A detailed medical and neurological history was taken and stroke subtypes were defined.24 Atrial fibrillation (AF) was defined by clinical criteria and medical parameters from the original cohort. A detailed medical assessment of the present follow-up study.27 Of the patients, 108 (28.6%) had mild, 68 (18.0%) had moderate, and 202 (53.7%) had severe WMLs. All the analyses were between moderate and mild WML categories, these categories were combined.

Determination of eGFR
Renal function on admission was calculated using the abbreviated equation of the Modification Diet for Renal Disease,30 which estimates eGFR: eGFR (mL/min/1.73 m²) = 186.3 × serum creatinine (exp[−1.154]) × age (exp[0.203]) × (0.742 if female). All the patients in our cohort were of white origin and therefore no correction had to be made for black race. eGFR was classified on the basis of internationally accepted classification.31 Patients with low (Stages 4 and 5) eGFR (N = 5 [1.3%]; <30 mL/min/1.73 m²) and very low survival rate were excluded from the analysis. Patients were divided into those with normal or mildly impaired (N = 226 [59.8%]; Stages 1 to 2; eGFR ≥60 mL/min/1.73 m²) eGFR and those with low to moderate (N = 152 [40.0%]; Stage 3; eGFR <60 mL/min/1.73 m²) eGFR.

Survival
Long-term survival data and causes of death at September 21, 2006, were obtained from Statistics Finland. The mean (±SD) follow-up time was 7.5 ± 4.0 years with a range between 0.3 and 12.8 years. Of the 378 patients with MRI data, 269 (71.2%) had died during the follow-up and data on survival were obtained in all the cases. Of all the dead subjects, the cause of death could not be verified for 8 cases (2.1%) with a death certificate. The outcome events were death from any cause and specific causes of death.

Statistical Analysis
SPSS/WIN (Version 12.0; SPSS Inc) software was used. The χ² test was used to test dichotomous variables and Student t test for independent samples to test continuous variables. Binary logistic regression analysis was used to study the association of different degrees of eGFR and WMLs. Kaplan–Meier log-rank test was used to analyze the effect of different factors on survival (sex, hypertension, diabetes mellitus, AF, HF, MI, PAD, smoking, modified Rankin score, WML degree, and eGFR). The cumulative hazard function was also used and according to these analyses, the proportional hazards assumption was met for each parameter included in further models. Three models were constructed, the first using covariates known to associate both with eGFR and WMLs (Model 1: age, sex, and stroke severity as assessed by modified Rankin score), another with classic factors associated with stroke (Model 2: age, sex, stroke severity, hypertension, diabetes mellitus, AF, HF, MI, PAD, smoking, and serum cholesterol), and the third using covariates proven to predict survival in univariate analyses with Kaplan–Meier log-rank test (Model 3: age, sex, modified Rankin score, AF, HF, PAD). All 4 different combinations of eGFR and WML were also tested in the models: (1) eGFR <60 mL/min/1.73 m² + mild to moderate WMLs; (2) eGFR <60 mL/min/1.73 m² + severe WMLs; (3) eGFR ≥60 mL/min/l.73 m² + mild to moderate WMLs; and (4) eGFR ≥60 mL/min/1.73 m² + severe WMLs. All the analyses were also performed including patients with first-ever stroke only (78.8%). Because the results were similar in both analyses, all the stroke cases were included in the study. Statistical significance was set at P < 0.05 and borderline significance was considered at P < 0.10.

Results

Patient Characteristics
Patients with eGFR <60 mL/min/1.73 m² (N = 152 [40.2%]) were older (P < 0.0001), were more often females (P < 0.0001), had more seldom history of MI (P = 0.013), had higher serum creatinine level on admission (P < 0.0001), and had more often severe WMLs (P = 0.003) compared with those with
Table 1. Demographics and Clinical and Laboratory Characteristics of 378 Patients With Acute Stroke

<table>
<thead>
<tr>
<th>Variable</th>
<th>All (N=378)</th>
<th>eGFR &lt;60 mL/min/1.73 m² (N=152)</th>
<th>eGFR ≥60 mL/min/1.73 m² (N=226)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD)</td>
<td>70.7 (7.6)</td>
<td>73.8 (6.4)</td>
<td>68.8 (7.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female sex, no. (%)</td>
<td>197 (52.1)</td>
<td>97 (63.8)</td>
<td>100 (44.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypertension, no. (%)</td>
<td>184 (48.7)</td>
<td>79 (52.0)</td>
<td>105 (46.5)</td>
<td>0.293</td>
</tr>
<tr>
<td>DM, no. (%)</td>
<td>91 (24.1)</td>
<td>30 (19.7)</td>
<td>61 (27.0)</td>
<td>0.106</td>
</tr>
<tr>
<td>AF, no. (%)</td>
<td>75 (19.8)</td>
<td>36 (23.7)</td>
<td>39 (17.3)</td>
<td>0.130</td>
</tr>
<tr>
<td>HF, no. (%)</td>
<td>80 (21.2)</td>
<td>38 (25.0)</td>
<td>42 (18.7)</td>
<td>0.140</td>
</tr>
<tr>
<td>ML, no. (%)</td>
<td>70 (18.5)</td>
<td>19 (12.5)</td>
<td>51 (22.6)</td>
<td>0.013</td>
</tr>
<tr>
<td>PAD, no. (%)</td>
<td>43 (11.4)</td>
<td>16 (10.5)</td>
<td>27 (11.9)</td>
<td>0.670</td>
</tr>
<tr>
<td>Smoking, no. (%)</td>
<td>185 (48.9)</td>
<td>66 (43.4)</td>
<td>119 (52.7)</td>
<td>0.071</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L (SD)</td>
<td>5.6 (1.2)</td>
<td>5.6 (1.3)</td>
<td>5.6 (1.1)</td>
<td>0.889</td>
</tr>
<tr>
<td>Creatinine on admission, μmol/L (SD)</td>
<td>90.5 (24.2)</td>
<td>106.6 (22.6)</td>
<td>79.7 (18.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Poor modified Rankin score, no. (%)</td>
<td>137 (36.2)</td>
<td>61 (40.1)</td>
<td>76 (33.6)</td>
<td>0.197</td>
</tr>
<tr>
<td>Severe WML</td>
<td>203 (53.7)</td>
<td>96 (63.2)</td>
<td>107 (47.3)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

*Stroke Aging Memory (SAM) cohort according to eGFR. Poor modified Rankin score (ie, Rankin score 3–5), cerebral WMLs.

Dichotomous variables: χ² test; continuous variables: Student t test for independent samples.

DM indicates diabetes mellitus.

eGFR ≥60 mL/min/1.73 m² (N=226 [59.8%]; Table 1). eGFR values were normally distributed. To test whether WMLs are indeed associated with eGFR, further analyses were adjusted with age and sex. According to logistic regression analysis adjusted with age and sex, eGFR <60 mL/min/1.73 m² was associated with severe degree of WMLs (relative risk 2.77, 95% CI 1.10 to 6.98, P=0.030).

Factors Affecting Long-Term Survival

In Kaplan–Meier univariate analysis, history of AF (P<0.0001), HF (P<0.0001), PAD (P=0.004), and poor modified Rankin score (P<0.0001) were associated with poor survival, whereas sex (P=0.840), hypertension (P=0.824), diabetes (P=0.230), MI (P=0.182), and smoking (P=0.099) were not associated with survival.

Poor survival was predicted by eGFR <60 mL/min/1.73 m² (6.3, 95% CI 4.9 to 7.7 versus 9.0, 95% CI 7.9 to 10.0 years, P<0.0001; Figure A) and by severe WMLs (6.0, 95% CI 4.8 to 7.4 versus 9.3, 95% CI 8.0 to 10.6 years, P<0.0001; Figure B). Strikingly, these survival curves were almost superimposable.

In further analyses testing all the 4 possible combinations of eGFR and WML stages, presence of both eGFR ≥60 mL/min/1.73 m² and mild to moderate WMLs was associated with favorable outcome (11.3, 95% CI 9.6 to 13.1 years) compared with all other combinations of eGFR and WMLs (P<0.0001 to 0.004; Figure C).

To account for multiple factors, Cox regression survival analysis was performed. In analysis adjusted with age, sex, and stroke severity (Model 1), eGFR <60 mL/min/1.73 m² (hazard ratio [HR]1.30, 95% CI 1.00 to 1.67, P=0.047) and severe WMLs with a borderline significance (HR 1.27, 95%CI 0.99 to 1.63, P=0.067) were associated with impaired survival (Table 2). Inclusion of both of these predictors in the model resulted in lack of significant association with survival indicating a possible interaction of eGFR with WML stage (Table 2). To account for a possible residual confounding effect of associated comorbidities, in further analysis adjusted with classical risk factors (age, sex, stroke severity, hypertension, diabetes, AF, HF, MI, PAD, smoking, and serum cholesterol; Model 2), eGFR <60 mL/min/1.73 m² (HR 1.37, 95% CI 1.04 to 1.79, P=0.025) and severe WMLs (HR 1.34, 95% CI 1.03 to 1.74, P=0.028) remained associated with impaired survival (Table 2). Inclusion of both of these predictors in the model resulted in lack of significant association with survival as shown previously. In a third model (Model 3), the analyses were repeated adjusting with significant predictors from previous Kaplan–Meier univariate analyses (age, sex, stroke severity, AF, HF, PAD). In these analyses, eGFR <60 mL/min/1.73 m² (HR 1.30, 95% CI 1.00 to 1.68, P=0.047) and severe WMLs (HR 1.32, 95% CI 1.02 to 1.71, P=0.033) were associated with impaired survival, whereas inclusion of both of these predictors in the model resulted in lack of significant association with survival (Table 2).

When analyzing all the 4 possible combinations of eGFR and WMLs with adjusted Cox regression survival analysis, presence of both eGFR ≥60 mL/min/1.73 m² and mild to moderate WMLs was associated with favorable outcome in long-term follow-up compared with all other groups (Table 3). Different adjusted models (Models 1, 2, and 3; see “Statistical Analyses”) resulted in similar results.

Discussion

In the present study, for the first time to our knowledge, we demonstrated that cerebral small vessel disease is connected to kidney function as estimated by eGFR in patients hospitalized for acute stroke. Whether this association is due to coexisting glomerular small vessel disease remains to be elucidated in future studies. In addition, we demonstrated that...
small vessel disease and kidney function are closely associated predictors of poor poststroke survival.

We speculate that cerebral small vessel disease and glomerular small vessel disease might have a common soil of pathogenesis and therefore be closely connected with each other not only due to anatomic and vasoregulatory similarities. First, cerebral small vessel disease is reflected by WMLs and WMLs are directly related with risk of recurrent strokes and poor survival mostly due to cardiovascular causes. Second, the association of WMLs and glomerular small vessel disease has been demonstrated in several different stages of kidney disease involving predialysis patients and patients with end-stage kidney disease. Third, metabolic alterations and disturbances in cerebral blood flow have been demonstrated to be associated with degree of renal function. Our results are in accordance with these findings because in the present study, severe white matter lesions were more frequent (63.2% versus 47.3%) in patients with low to moderate eGFR compared with those with eGFR ≥60 mL/min/1.73 m². The association of low eGFR and severe WMLs was also demonstrated after adjusting for age and sex, the factors previously known to associate with renal function and WMLs, also labeled as age-related white matter changes. According to survival analysis, the survival curves for eGFR and WMLs were almost superimposable in line with the HRs for low eGFR and WMLs suggesting a possible associated cause of the small vessel disease in the brain and kidney, not unlikely.

Previous findings on the association of calculated creatinine clearance, creatinine level, high urea or ratio of urea to creatinine, and eGFR with long-term survival in patients hospitalized for acute stroke are in line with our findings. Using the same cohort, we have previously demonstrated the effect of WMLs and cognitive status on long-term survival after acute stroke. Interestingly, cognitive function, kidney function, and WMLs have been shown to be closely associated with each other, most probably due to coexisting cerebral and glomerular small vessel disease. The intimate association of cerebral and glomerular small vessel disease is supported by the coexistence of lipohyalinosis and...

Figure. Univariate analysis of the effect of eGFR (mL/min/1.73 m²) and cerebral WMLs as determined by MRI on stroke survival in Stroke Aging Memory Cohort in patients hospitalized for acute stroke. The effect of eGFR (A); WMLs (B); and different combinations of both (C; end point: all-cause death); Kaplan-Meier log-rank test.
Table 2. Cox Regression Analysis on the Association of eGFR and Severe Cerebral WMLs as Determined by MRI With Poor Long-Term Survival in 378 Patients With Acute Stroke in the SAM Cohort

<table>
<thead>
<tr>
<th>Variable</th>
<th>eGFR Model</th>
<th>WML Model</th>
<th>eGFR + WML Model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR 95% CI</td>
<td>HR 95% CI</td>
<td>HR 95% CI</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Model 1 (adjusted with age, sex, poor modified Rankin score)</td>
</tr>
<tr>
<td>eGFR &lt; 60 mL/min/1.73 m²</td>
<td>1.30</td>
<td>1.00–1.67</td>
<td>0.047</td>
</tr>
<tr>
<td>Severe WML</td>
<td>Not included</td>
<td>1.00–1.63</td>
<td>0.067</td>
</tr>
<tr>
<td></td>
<td>Model 2 (adjusted with age, sex, poor modified Rankin score, hypertension, diabetes, AF, HF, MI, PAD, smoking, serum cholesterol)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR &lt; 60 mL/min/1.73 m²</td>
<td>1.37</td>
<td>1.04–1.79</td>
<td>0.025</td>
</tr>
<tr>
<td>Severe WML</td>
<td>Not included</td>
<td>1.03–1.74</td>
<td>0.028</td>
</tr>
<tr>
<td></td>
<td>Model 3 (adjusted with age, sex, poor modified Rankin score, AF, HF, PAD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR &lt; 60 mL/min/1.73 m²</td>
<td>1.30</td>
<td>1.00–1.68</td>
<td>0.047</td>
</tr>
<tr>
<td>Severe WML</td>
<td>Not included</td>
<td>1.02–1.71</td>
<td>0.033</td>
</tr>
</tbody>
</table>

Poor modified Rankin score (ie, Rankin score 3–5). Reference eGFR ≥60 mL/min/1.73 m² or mild–moderate WMLs. Cox proportional hazards regression model.

Table 3. Cox Regression Analysis on the Association of Different Combinations of eGFR and cerebral WMLs as Determined by MRI With Poor Long-Term Survival in 378 Patients With Acute Stroke in the SAM Cohort

<table>
<thead>
<tr>
<th>Reference Group</th>
<th>12-Year Overall Mortality Relative to Reference Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>eGFR ≥60 mL/min/1.73 m² + WMLMM</td>
</tr>
<tr>
<td></td>
<td>HR 95% CI</td>
</tr>
<tr>
<td>eGFR ≥60 mL/min/1.73 m² + WMLMM</td>
<td>1.63</td>
</tr>
<tr>
<td>eGFR ≥60 mL/min/1.73 m² + WMLs</td>
<td>0.68</td>
</tr>
<tr>
<td>eGFR &lt;60 mL/min/1.73 m² + WMLMM</td>
<td>0.62</td>
</tr>
<tr>
<td>eGFR &lt;60 mL/min/1.73 m² + WMLs</td>
<td>0.65</td>
</tr>
</tbody>
</table>

WMLMM indicates mild–moderate cerebral WMLs; WMLs, severe WMLs. Cox proportional hazards regression model with age, sex, and poor modified Rankin score as covariates.
with vascular disease independent of glomerular filtration rate. Due to the homogenous population, the present results may not be applicable to other populations.

We demonstrated that kidney function is closely associated with cerebral small vessel disease in patients hospitalized for acute stroke. Furthermore, we demonstrated that kidney function and cerebral small vessel disease are closely associated predictors of poor poststroke survival.

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Disclosures
None.

References

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