# Predictive role of C-reactive protein in stroke recurrence after cardioembolic stroke: the Fukuoka Stroke Registry

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<th>Journal:</th>
<th>BMJ Open</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manuscript ID:</td>
<td>bmjopen-2013-003678</td>
</tr>
<tr>
<td>Article Type:</td>
<td>Research</td>
</tr>
<tr>
<td>Date Submitted by the Author:</td>
<td>29-Jul-2013</td>
</tr>
<tr>
<td>Complete List of Authors:</td>
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<tr>
<td>Primary Subject Heading:</td>
<td>Cardiovascular medicine</td>
</tr>
<tr>
<td>Secondary Subject Heading:</td>
<td>Neurology</td>
</tr>
<tr>
<td>Keywords:</td>
<td>Stroke &lt; NEUROLOGY, STROKE MEDICINE, Thromboembolism &lt; CARDIOLOGY</td>
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</table>
Predictive role of C-reactive protein in stroke recurrence after cardioembolic stroke: the Fukuoka Stroke Registry

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Key words: Aging, Ischemic stroke, C-reactive protein, Recurrence, Cardioembolic stroke

Word count: 3,200 words

Number of reference: 40
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Funding: None

Competing Interest: None declared.
Contributorship statement:

T. Kuwashiro contributed to drafting the manuscript for content, study concept, analysis of data, acquisition of data, and statistical analysis.

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T. Ago contributed to the study concept, analysis of data, and acquisition of data.

J. Kuroda contributed to the study concept, analysis of data, and acquisition of data.

M. Kamouchi contributed to the study concept, study supervision, and obtaining funding.

T. Kitazono contributed to the study concept, study supervision, and obtaining funding.
ABSTRACT

Objectives: We investigated the clinical characteristics of patients with stroke recurrence in the first year after cardioembolic stroke, and determined the predictors associated with recurrence.

Design: A prospective cohort study.

Setting: Multicenter study at the Fukuoka prefecture in Japan.

Participants: We enrolled 2084 consecutive patients who were hospitalized in stroke centers within 7 days of onset from June 2007 to October 2009. The clinical characteristics of patients were assessed on admission, and the clinical course of all patients was followed for 1 year.

Results: Of all patients, 425 (234 males, 76 ± 11 years of age) had cardioembolic stroke and were included in this study. Fifty-one patients (12%) suffered a recurrence during the follow-up period. Age (hazard ratio [HR] 1.04, 95% confidence interval [CI] 1.01 to 1.06, p = 0.014), and level of C-reactive protein (HR 1.11, 95% CI 1.02 to 1.21, p = 0.019) on admission were significantly associated with recurrence in the univariate analyses. Male gender (HR 0.61, 95% CI 0.35 to 1.05, p = 0.076), body mass index (HR 0.94, 95% CI 0.87 to 1.01, p = 0.093), hypertension (HR 0.59, 95% CI 0.33 to 1.06, p = 0.079), diastolic blood pressure (HR 0.99, 95% CI 0.97 to 1.00, p = 0.087), and
hematocrit (HR 0.95, 95% CI 0.91 to 1.00, p = 0.052) were marginally significant in the
univariate Cox analyses. Multivariate Cox proportional hazards analysis showed that
age (HR 1.03, 95% CI 1.00 to 1.06, p = 0.031, per 1-year increase), and C-reactive
protein (HR 1.11, 95% CI 1.02 to 1.21, p = 0.022, per 1-mg/dL increase) were
independent predictors of a recurrence in the first year after cardioembolic stroke.

Conclusions: In patients with cardioembolic ischemic stroke, age and C-reactive
protein are independent risk factors for recurrence in the first year after onset.
ARTICLE SUMMARY

Article focus

1. For the prevention of ischemic stroke recurrence, it seems appropriate to focus on
   the prevention of recurrence within the first year after onset.

2. Preventive measures for recurrence should be appropriately selected on the basis of
   the specific causes of stroke subtypes. In particular, mechanisms responsible for
   brain infarction are significantly different between cardioembolic stroke and
   non-embolic stroke.

3. We focused on cardioembolic stroke and investigated the relationship between
   patient clinical characteristics and stroke recurrence within the first year after stroke
   onset.

Key messages

1. In the present study, the first-year gross recurrence rate of cardioembolic ischemic
   stroke was 12% (51/425).

2. On the results of multivariate Cox regression analysis for stroke recurrence, age (HR
   1.03, 95% CI 1.00 to 1.06, \( p = 0.031 \), per 1-year increase) and C-reactive protein
   (HR 1.11, 95% CI 1.02 to 1.21, \( p = 0.022 \), per 1-mg/dL increase) were independent
predictors of stroke recurrence 1 year after onset.

3. Older patients (≥ 78 years) with higher CRP (≥ 0.19 mg/dL) were at greater risk of stroke recurrence compared with the reference group (age < 78 years, CRP < 0.19 mg/dL) (HR 2.35, 95% CI 1.06 to 5.24, p = 0.036).

Strength and limitations of this study

1. The present study is a multicenter, prospective cohort research in which acute stroke patients are enrolled within 7 days of onset.

2. This is the first study to show that elevation of CRP is strongly associated with stroke recurrence in patients with cardioembolic stroke.

3. The observational design did not allow us to control any therapy used after the onset of the stroke. Moreover, no information on patient compliance with medical treatment was obtained during the follow-up period after discharge from the hospital.
INTRODUCTION

There is considerable evidence on the secondary prevention of ischemic stroke, and methods of treatment for each subtype of stroke have been recommended.[1-3] However, stroke appears to recur in a certain percentage of patients despite appropriate secondary prevention measures.[4] Stroke recurrence is especially high in the first year after stroke onset (8% to 12% of all stroke patients).[5-7] Therefore, for the prevention of ischemic stroke recurrence, it seems appropriate to focus on the prevention of recurrence within the first year after onset.

Although previous studies have shown several independent predictors of stroke recurrence,[8-11] only a few studies have reported risk factors for recurrence according to the subtype of ischemic stroke.[12, 13] The underlying mechanism for stroke onset differs by stroke subtype.[14] In particular, mechanisms responsible for brain infarction are significantly different between cardioembolic stroke and non-embolic stroke.[15] Thus, preventive measures for recurrence should be appropriately selected on the basis of the specific causes of stroke subtypes.

In the present study, we performed a prospective observational study of ischemic stroke to identify the risk factors associated with the recurrence of ischemic stroke in the first year after onset. To determine an appropriate treatment strategy for
each subtype of stroke, we investigated different subtypes of ischemic stroke.

Furthermore, we focused on cardioembolic stroke and investigated the relationship between patient clinical characteristics and stroke recurrence within the first year after stroke onset.
METHODS

Fukuoka Stroke Registry (FSR)

FSR is a multicenter, prospective cohort study in which acute stroke patients are enrolled within 7 days of onset. Patients admitted to one of the seven clinical stroke centers (see appendix) in the Fukuoka Prefecture in Japan have participated in this study since June 2007. The study design was approved by the institutional review boards (IRB) of the ethics committee in all hospitals. IRB approved the study protocols and related materials, such as informed consent, document and study brochures, after careful investigation into the protocols and the matters concerning the ethics of the study to protect the rights, safety and welfare of all participants in compliance with the Declaration of Helsinki. Detailed information of the study, data collection, and harmonization in the FSR have been described previously.[12]

Study Patients

We enrolled 2084 consecutive ischemic stroke patients (1262 males, 822 females, 71 ± 12 years of age) registered in FSR from June 2007 to October 2009. Stroke was defined as the sudden onset of nonconvulsive and focal neurological deficit persisting for >24 hours. All of the patients underwent brain computed tomography
(CT), magnetic resonance imaging (MRI), or both within 24 hours of hospitalization.

The diagnosis and classification of stroke were based on clinical information, and ancillary examinations (such as brain imaging including CT, MRI, cerebral angiography and echocardiography).

Clinical Assessment

We assessed the clinical characteristics and comorbidities of the patients on admission. Body mass index (BMI), waist circumference, systolic and diastolic blood pressure were measured. Values for white blood cells (WBC), hematocrit, total protein, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, blood glucose, hemoglobin A1c (HbA1c), serum creatinine (sCr) and C-reactive protein (CRP), were obtained on admission. We determined the frequency of LDL cholesterol ≥ 140 mg/dL, HDL cholesterol < 40 mg/dL, and triglycerides ≥ 150 mg/dL according to the diagnostic criteria for dyslipidemia.[16] Urine protein and glucose levels were determined with a simplified kit. Estimated glomerular filtration rate (eGFR) was calculated using the equation proposed by the Japanese Society of Nephrology [17]: eGFR (ml/min/1.73 m$^2$) = 194 × sCr$^{-1.094}$ × Age$^{-0.287}$ in males and 194 × sCr$^{-1.094}$ × Age$^{-0.287}$ × 0.739 in females. Chronic kidney disease (CKD) was diagnosed
when the patients had low eGFR (<60 ml/min/1.73 m$^2$) and/or proteinuria on admission.

Risk factors for cardiovascular events were assessed, including hypertension (systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or a history of antihypertensive medication); diabetes mellitus (fasting blood glucose ≥126 mg/dL, positive 75 g oral glucose tolerance test result, or a history of antidiabetic medication or insulin); dyslipidemia (LDL cholesterol ≥ 140 mg/dL, HDL cholesterol < 40 mg/dL, triglycerides ≥ 150 mg/dL or a history of antihypercholesterolemic medication); ischemic heart disease or atrial fibrillation; smoking habit (previous and current); alcohol consumption (including occasional drinking); and previous ischemic stroke.

Furthermore, the ejection fraction (EF) of the acute stroke patients was evaluated using transthoracic echocardiography. We assessed the severity of the neurological deficits of the patients on admission with the National Institutes of Health Stroke Scale (NIHSS) score. The medications (antithrombotic, antihypertensive, and antihypercholesterolemic) prescribed at discharge for vascular risk treatments were also investigated.

**Stroke Classification**

Criteria modified from the TOAST (Trial of ORG 10172 in Acute Stroke)
Treatment classification system [14] were used to determine the subtype of ischemic stroke. According to the results of neuroimaging and neurological examinations, we categorized all ischemic strokes into the following four subtypes: large-artery atherosclerosis, cardioembolism, small-vessel occlusion and others (stroke of other determined etiology and stroke of undetermined etiology). In addition, localization of the culprit lesion in culprit was examined in the anterior or posterior circulation.

**Follow-up Survey**

Detailed information about prognosis, including the recurrence of cerebrovascular events and mortality, was collected at the 3rd, 6th and 12th month after stroke onset. The assessment was conducted through an interview by trained clinical research coordinators who were blinded to the information obtained during hospitalization. The clinical diagnosis of stroke was based on the detailed history, neurological examinations, and ancillary examinations. If needed, we obtained further information on prognosis from the hospital where patients were admitted or from our registration institution after the patients were discharged.

**Statistical Analysis**
Results are presented as the mean ± SD, or median and interquartile range. We used a univariate Cox proportional hazards regression model to identify the individual baseline characteristics that were significant predictors of stroke recurrence. Hazard ratios (HR) and their 95% confidence intervals (CI) were calculated by the Cox model. A multivariate Cox proportional hazards regression model was also used to determine the effect of multiple variables simultaneously on the risk of stroke recurrence. A backward selection procedure was performed using p > 0.10 of the likelihood ratio test for exclusion of variables from the model. The regression model included time to recurrent strokes as the response variables and clinical predictors of recurrence with a univariate p-value < 0.1 as independent covariates. We used the Kaplan-Meier method to evaluate the cumulative stroke recurrence rate after stratifying patients according to the characteristics derived from the multivariate Cox regression model. The log-rank test was used to assess differences between Kaplan-Meier cumulative recurrence rate curves. A p-value < 0.05 was considered to be significant. All statistical analyses were performed using IBM SPSS Statistics, version 19.0 for Windows (SPSS Inc, Chicago, IL).
RESULTS

We detected stroke due to large-artery atherosclerosis in 493 patients, cardioembolism in 425, small-vessel occlusion in 583 and other etiologies (stroke of other or undetermined etiology) in 583 among the 2084 consecutive patients. In the present study, 425 patients (234 males and 191 females, 76 ± 11 years of age) with cardioembolic stroke were followed for 1 year after stroke onset. Thirty-one of these 425 patients died within 1 year, 6 from ischemic stroke, 3 from cerebral hemorrhage, 7 from cardiovascular diseases, 4 from pneumonia, 3 from malignant tumor, 3 from other causes and 5 from unknown causes. We found that 51 patients suffered a recurrence of ischemic stroke during the follow-up period of 1 year. Therefore, the first-year gross recurrence rate of cardioembolic ischemic stroke was 12% (51/425). Two patients had two recurrences in the first year.

A univariate Cox regression analyses was used to evaluate the association between stroke recurrence in all patients, and the clinical characteristics and laboratory data at the time of the initial stroke (table 1). Age (HR 1.04, 95% CI 1.01 to 1.06, p = 0.014), and level of C-reactive protein (HR 1.11, 95% CI 1.02 to 1.21, p = 0.019) on admission were significantly associated with stroke recurrence in the univariate analyses (table 1).
Male gender (HR 0.61, 95% CI 0.35 to 1.05, p = 0.076), BMI (HR 0.94, 95% CI 0.87 to 1.01, p = 0.093), hypertension (HR 0.59, 95% CI 0.33 to 1.06, p = 0.079), diastolic blood pressure (HR 0.99, 95% CI 0.97 to 1.00, p = 0.087), and hematocrit (HR 0.95, 95% CI 0.91 to 1.00, p = 0.052) were marginally significant in the univariate Cox analyses (table 1).

There were no significant differences in the medications prescribed at discharge for the treatment of vascular risk factors (table 2).

The results of multivariate Cox regression analysis for stroke recurrence are shown in table 3. Age (HR 1.03, 95% CI 1.00 to 1.06, p = 0.031, per 1-year increase) and C-reactive protein (HR 1.11, 95% CI 1.02 to 1.21, p = 0.022, per 1-mg/dL increase) were independent predictors of stroke recurrence 1 year after onset.

When patients were divided into four groups for analysis according to the median values of age and CRP, older patients (≥ 78 years) with higher CRP (≥ 0.19 mg/dL) were at greater risk of stroke recurrence compared with the reference group (age < 78 years, CRP < 0.19 mg/dL) (HR 2.35, 95% CI 1.06 to 5.24, p = 0.036, table 4; figure 1). The Kaplan-Meier method was used to estimate the cumulative recurrence rate of stroke in these two groups of patients and the curves were significantly different, as shown in figure 2 (p = 0.027 by the log-rank test).
DISCUSSION

In patients with cardioembolic stroke, we have shown that age and C-reactive protein were independent risk factors for stroke recurrence during the first year of follow-up.

Several epidemiological studies have demonstrated that serum levels of the inflammatory marker CRP are positively associated with the risk of ischemic stroke.[18-20] Many studies showed a significant relationship between elevated CRP and atherosclerosis.[18, 21] Since chronic inflammation directly influences the progression of atherosclerosis, it also enhances the risk of ischemic stroke. Inflammation is an important factor in ischemic stroke, both in the development of atherosclerosis and during the ischemic event. Thus, CRP levels have attracted clinical attention as a predictive marker of ischemic stroke.

However, several studies showed that CRP does not seem to be related to atherosclerosis of large arteries.[22-24] In particular, a few studies reported significant elevations of CRP levels in patients with cardioembolic stroke.[25-27] According to a study of 196 elderly patients with ischemic stroke, mean values of CRP were significantly higher in patients with cardioembolic stroke compared with atherothrombotic large vessel and lacunar stroke in patients who died in the first 30
days.[25] In a study of 648 stroke patients with CRP levels stratified into quartiles, patients with cardioembolic strokes had CRP levels in the higher quartiles, and CRP was an independent predictor of 14-day mortality.[26] A previous case-control study of 199 stroke patients and 202 randomly selected controls showed an independent relationship between elevated blood levels of CRP and cardioembolic stroke.[27]

Although the mechanism underlying this phenomenon is not clear, several possible explanations have been proposed. First, it seems that CRP is commonly elevated in heart disease.[26, 28] Therefore, plasma CRP levels in patients with cardioembolic stroke could be increased because of the presence of heart disease in these patients. CRP is frequently elevated especially in heart diseases such as heart failure and atrial fibrillation.[29] Furthermore, intracardiac clots that often form in these conditions may serve as a source of emboli. Second, the binding of CRP to phospholipids, which are involved in the coagulation cascade, are potentially activated by emboli from the heart.[30] Third, in patients with extensive stroke lesions, levels of CRP have been reported to increase.[31, 32] Of all stroke subtypes, patients with cardioembolic stroke have larger lesions [33] and a worse prognosis.[34]

Additionally, recent studies showed that elevated CRP independently predicted the risk of stroke recurrence and transient ischemic attack in the elderly.[35, 36] In the
acute phase as well as the chronic phase of stroke, the inflammatory cascade is mediated by an increasing concentration of cytokines, adhesion molecules, proteins, macrophages and leukocytes, and the strength of this response is related to early and late clinical outcomes.[19, 37] Thus, further progression of vascular disease could occur because a chronic inflammatory state may persist after the acute phase.

It was uncertain whether age influences the recurrence of ischemic stroke, though aging is one of the most important overall risk factors for stroke. Age was identified as a risk factor for the recurrence of ischemic stroke in some studies,[8, 38] but not in others.[5, 39, 40] In the present study, age was an independent risk factor for recurrence during the first year after cardioembolic stroke onset. The cumulative effects of advancing age on the cardiovascular system and the progressive nature of stroke risk factors over a prolonged period of time substantially increase the risk of ischemic stroke.

The present study has several limitations. The observational design did not allow us to control any therapy used after the onset of the stroke. In addition, a variety of stroke therapies and complications in the acute and chronic phases might affect prognosis. Moreover, no information on patient compliance with medical treatment was obtained during the follow-up period after discharge from the hospital. In addition, a
single measurement of CRP on admission may not accurately reflect the status of the patients during the acute phase. Therefore, further studies with a larger cohort should be conducted in order to resolve these issues.

Even with these limitations, elevated CRP on admission and age were significantly associated with stroke recurrence in patients with cardioembolic stroke. To the best of our knowledge, this is the first study to show that elevation of CRP is strongly associated with stroke recurrence in patients with cardioembolic stroke. In conclusion, age and CRP on admission were found to be independent risk factors for the recurrence of cardioembolic stroke within 1 year of onset.
ACKNOWLEDGMENTS

This study was supported in part by the Japanese Ministry of Education, Culture, Sports, Science and Technology (Coordination, Support and Training Program for Translational Research). The authors are grateful to Associate Professor Hitoshi Inoue in the Research Institute for Information Technology, Kyushu University for his support on the FSR Data Collection System. We also thank all the clinical research coordinators for their help in obtaining informed consent and collecting the clinical data.
APPENDIX

Participating Hospitals in the FSR: Kyushu University Hospital, National Hospital Organization Kyushu Medical Center, National Hospital Organization Fukuoka Higashi Medical Center, Fukuoka Red Cross Hospital, St. Mary’s Hospital, Nippon Steel Yawata Memorial Hospital, Japan Labour Health and Welfare Organization Kyushu Rosai Hospital.

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13) Yoshizuka Hayashi Hospital
REFERENCES


FIGURE LEGENDS

Figure 1

Hazard ratio and 95% CI of four risk groups for stroke recurrence. Four groups were classified by the median value of age and CRP.

Figure 2

Kaplan-Meier estimates of the cumulative recurrence rate of stroke after patients were stratified according to the combination of the median value of age and CRP. A significant difference in recurrence rate was observed between the patients with age ≥ 78 years and CRP ≥ 0.19 mg/dL (solid line) on admission and those with age < 78 years and CRP < 0.19 mg/dL (dotted line, p = 0.027 by log-rank test). Censored cases with death are indicated as (+).
Table 1 Clinical characteristics of the patients and univariate Cox hazard ratios for stroke recurrence

<table>
<thead>
<tr>
<th>Baseline Characteristic or Risk Factor</th>
<th>Recurrence (+)</th>
<th>Recurrence (-)</th>
<th>HR (95%CI)</th>
<th>P</th>
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<tr>
<td>n = 51</td>
<td>n = 374</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Age, y</td>
<td>79.6 ± 10.4</td>
<td>75.5 ± 11.0</td>
<td>1.04 (1.01-1.06)</td>
<td>0.014*</td>
</tr>
<tr>
<td>Male gender</td>
<td>43%</td>
<td>57%</td>
<td>0.61 (0.35-1.05)</td>
<td>0.076</td>
</tr>
<tr>
<td>BMI</td>
<td>21.3 ± 3.2</td>
<td>22.3 ± 3.8</td>
<td>0.94 (0.87-1.01)</td>
<td>0.093</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>79.5 ± 9.5</td>
<td>81.8 ± 10.9</td>
<td>0.98 (0.96-1.01)</td>
<td>0.156</td>
</tr>
<tr>
<td>Smoking</td>
<td>31%</td>
<td>39%</td>
<td>0.73 (0.41-1.33)</td>
<td>0.305</td>
</tr>
<tr>
<td>Drinking</td>
<td>31%</td>
<td>37%</td>
<td>0.78 (0.43-1.41)</td>
<td>0.410</td>
</tr>
<tr>
<td>Hypertension</td>
<td>67%</td>
<td>78%</td>
<td>0.59 (0.33-1.06)</td>
<td>0.079</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>20%</td>
<td>24%</td>
<td>0.78 (0.39-1.56)</td>
<td>0.484</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>28%</td>
<td>37%</td>
<td>0.66 (0.36-1.21)</td>
<td>0.179</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>18%</td>
<td>25%</td>
<td>0.68 (0.33-1.40)</td>
<td>0.294</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>82%</td>
<td>81%</td>
<td>1.14 (0.56-2.34)</td>
<td>0.720</td>
</tr>
<tr>
<td>Previous ischemic stroke</td>
<td>28%</td>
<td>21%</td>
<td>1.35 (0.73-2.50)</td>
<td>0.336</td>
</tr>
<tr>
<td>Findings on Admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP on admission, mm Hg</td>
<td>147 ± 25</td>
<td>154 ± 28</td>
<td>0.99 (0.98-1.00)</td>
<td>0.153</td>
</tr>
<tr>
<td>DBP on admission, mm Hg</td>
<td>79 ± 15</td>
<td>83 ± 18</td>
<td>0.99 (0.97-1.00)</td>
<td>0.087</td>
</tr>
<tr>
<td>Urine protein</td>
<td>39%</td>
<td>37%</td>
<td>1.08 (0.49-2.38)</td>
<td>0.851</td>
</tr>
<tr>
<td>Urine glucose</td>
<td>19%</td>
<td>19%</td>
<td>0.99 (0.38-2.64)</td>
<td>0.990</td>
</tr>
<tr>
<td>eGFR, ml/min/1.73m²</td>
<td>61.0 ± 21.3</td>
<td>63.7 ± 23.2</td>
<td>0.99 (0.98-1.01)</td>
<td>0.995</td>
</tr>
<tr>
<td>eGFR &lt; 60 ml/min/1.73m²</td>
<td>39%</td>
<td>46%</td>
<td>0.80 (0.46-1.41)</td>
<td>0.439</td>
</tr>
<tr>
<td>CKD</td>
<td>51%</td>
<td>52%</td>
<td>0.97 (0.56-1.68)</td>
<td>0.907</td>
</tr>
<tr>
<td>EF &lt; 55%</td>
<td>15%</td>
<td>22%</td>
<td>0.64 (0.29-1.43)</td>
<td>0.278</td>
</tr>
<tr>
<td>NIHSS score on admission</td>
<td>7 (3 to 16)</td>
<td>8 (5 to 16)</td>
<td>1.01 (0.98-1.04)</td>
<td>0.619</td>
</tr>
<tr>
<td>Laboratory Data on Admission</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>WBC, /mm³</td>
<td>6643 ± 2105</td>
<td>7164 ± 2354</td>
<td>1.00 (1.00-1.00)</td>
<td>0.148</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>38.0 ± 6.0</td>
<td>39.6 ± 5.5</td>
<td>0.95 (0.91-1.00)</td>
<td>0.052</td>
</tr>
<tr>
<td>Total protein, g/dL</td>
<td>6.9 ± 0.6</td>
<td>7.0 ± 0.6</td>
<td>0.94 (0.61-1.45)</td>
<td>0.778</td>
</tr>
<tr>
<td>LDL cholesterol ≥ 140 mg/dL</td>
<td>13%</td>
<td>17%</td>
<td>0.73 (0.29-1.87)</td>
<td>0.513</td>
</tr>
<tr>
<td>HDL cholesterol &lt; 40 mg/dL</td>
<td>19%</td>
<td>19%</td>
<td>1.02 (0.49-2.11)</td>
<td>0.962</td>
</tr>
<tr>
<td>LDL-chol / HDL-chol</td>
<td>2.1 ± 0.7</td>
<td>2.2 ± 1.0</td>
<td>0.85 (0.59-1.22)</td>
<td>0.385</td>
</tr>
<tr>
<td>Triglyceride ≥ 150 mg/dL</td>
<td>17%</td>
<td>18%</td>
<td>0.94 (0.44-2.01)</td>
<td>0.869</td>
</tr>
<tr>
<td>Blood glucose, mg/dL</td>
<td>139 ± 49</td>
<td>134 ± 54</td>
<td>1.00 (0.99-1.01)</td>
<td>0.576</td>
</tr>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>CI</td>
<td>P-value</td>
</tr>
<tr>
<td>----------------------</td>
<td>------------</td>
<td>------------</td>
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<td>---------</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>5.5 ± 0.8</td>
<td>5.7 ± 1.40</td>
<td>0.82 (0.58-1.16)</td>
<td>0.260</td>
</tr>
<tr>
<td>sCr, mg/dL</td>
<td>1.03 ± 1.07</td>
<td>1.02 ± 1.05</td>
<td>1.01 (0.78-1.31)</td>
<td>0.934</td>
</tr>
<tr>
<td>CRP, mg/dL</td>
<td>1.44 ± 3.34</td>
<td>0.77 ± 1.74</td>
<td>1.11 (1.02-1.21)</td>
<td>0.019*</td>
</tr>
</tbody>
</table>

**Stroke Location**

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Posterior circulation</td>
<td>20%</td>
<td>19%</td>
<td>1.04 (0.52-2.07)</td>
<td>0.923</td>
</tr>
</tbody>
</table>

BMI, body mass index; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; EF, ejection fraction; HR, hazard ratio; CI, confidence interval.

Data are the mean ± SD for age, BMI, waist circumference, SBP, DBP, eGFR, WBC, Hematocrit, Total protein, LDL-chol / HDL-chol, Blood glucose, HbA1c, sCr and CRP. The median (interquartile range) is shown for NIHSS, and % for the other variables.

*: P < 0.05
Table 2 Medications prescribed at discharge and univariate Cox hazard ratios for stroke recurrence

<table>
<thead>
<tr>
<th>Medication</th>
<th>Recurrence (+)</th>
<th>Recurrence (-)</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiplatelet</td>
<td>16%</td>
<td>21%</td>
<td>0.70 (0.33-1.48)</td>
<td>0.348</td>
</tr>
<tr>
<td>Anticoagulant</td>
<td>88%</td>
<td>90%</td>
<td>0.86 (0.37-2.01)</td>
<td>0.728</td>
</tr>
<tr>
<td>Antihypertensive</td>
<td>53%</td>
<td>61%</td>
<td>0.74 (0.43-1.28)</td>
<td>0.279</td>
</tr>
<tr>
<td>Calcium-channel blocker</td>
<td>21%</td>
<td>21%</td>
<td>1.01 (0.52-1.97)</td>
<td>0.980</td>
</tr>
<tr>
<td>ARB</td>
<td>23%</td>
<td>24%</td>
<td>0.97 (0.51-1.86)</td>
<td>0.932</td>
</tr>
<tr>
<td>β-blocker</td>
<td>14%</td>
<td>22%</td>
<td>0.58 (0.26-1.29)</td>
<td>0.183</td>
</tr>
<tr>
<td>Diuretic</td>
<td>26%</td>
<td>19%</td>
<td>1.40 (0.75-2.63)</td>
<td>0.293</td>
</tr>
<tr>
<td>HMG-CoA reductase inhibitor</td>
<td>16%</td>
<td>21%</td>
<td>0.71 (0.34-1.52)</td>
<td>0.380</td>
</tr>
</tbody>
</table>

ARB, angiotensin receptor blocker;

HMG-CoA reductase inhibitor, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitor.

Data are expressed as %, HR, hazard ratio; CI, confidence interval.
### Table 3 Multivariate Cox hazards ratios for stroke recurrence

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, per 1-year increase</td>
<td>1.03 (1.00—1.06)</td>
<td>0.031*</td>
</tr>
<tr>
<td>C-reactive protein, per 1-mg/dL increase</td>
<td>1.11 (1.02—1.21)</td>
<td>0.022*</td>
</tr>
</tbody>
</table>

HR, hazard ratio; CI, confidence interval.

*: p < 0.05 by multivariate Cox regression analysis using sex and age, as well as the clinical characteristics which showed a significant (p < 0.05) or marginally significant (0.05 ≤ p < 0.1) correlation with stroke recurrence in the univariate analyses.
Table 4 Cox proportional hazards analysis of four risk groups derived from the median value of age and CRP

<table>
<thead>
<tr>
<th>Age ≥ 78 y, CRP &lt; 0.19 mg/dL</th>
<th>R/N</th>
<th>Hazard ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 78 y, CRP ≥ 0.19 mg/dL</td>
<td>18/101</td>
<td>2.35 (1.06—5.24)</td>
<td>0.036*</td>
</tr>
<tr>
<td>Age ≥ 78 y, CRP &lt; 0.19 mg/dL</td>
<td>16/102</td>
<td>2.21 (0.98—5.00)</td>
<td>0.057</td>
</tr>
<tr>
<td>Age &lt; 78 y, CRP ≥ 0.19 mg/dL</td>
<td>8/107</td>
<td>1.41 (0.50—3.97)</td>
<td>0.511</td>
</tr>
<tr>
<td>Age &lt; 78 y, CRP &lt; 0.19 mg/dL</td>
<td>9/115</td>
<td>1.00 (reference)</td>
<td></td>
</tr>
</tbody>
</table>

R, recurrence; N, total number of subjects; HR, hazard ratio; CI, confidence interval.

*: P < 0.05
Figure 1

- Age < 78 y, CRP < 0.19 mg/dL: Hazard ratio: 1.00
- Age ~ 78 y, CRP ≥ 0.19 mg/dL: Hazard ratio: 1.41 (0.50 - 3.91), P value: 0.511
- Age ≥ 78 y, CRP < 0.19 mg/dL: Hazard ratio: 2.21 (0.98 - 5.00), P value: 0.057
- Age ≥ 78 y, CRP ≥ 0.19 mg/dL: Hazard ratio: 2.35 (1.06 - 5.24), P value: 0.036

254x190mm (96 x 96 DPI)
Figure 2

Cumulative risk for recurrence

- Age ≥ 78 y, CRP ≥ 0.19 mg/dL
- Age < 78 y, CRP < 0.19 mg/dL

Months

254x190mm (96 x 96 DPI)
STROBE Statement—Checklist of items that should be included in reports of cohort studies

<table>
<thead>
<tr>
<th>Item No</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| 1       | (a) Indicate the study’s design with a commonly used term in the title or the abstract  
         (b) Provide in the abstract an informative and balanced summary of what was done and what was found |
| 2       | Explain the scientific background and rationale for the investigation being reported |
| 3       | State specific objectives, including any prespecified hypotheses |
| 4       | Present key elements of study design early in the paper |
| 5       | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection |
| 6       | (a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up  
         (b) For matched studies, give matching criteria and number of exposed and unexposed |
| 7       | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable |
| 8*      | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group |
| 9       | Describe any efforts to address potential sources of bias |
| 10      | Explain how the study size was arrived at |
| 11      | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why |
| 12      | (a) Describe all statistical methods, including those used to control for confounding  
         (b) Describe any methods used to examine subgroups and interactions  
         (c) Explain how missing data were addressed  
         (d) If applicable, explain how loss to follow-up was addressed  
         (e) Describe any sensitivity analyses |
| 13*     | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed  
         (b) Give reasons for non-participation at each stage  
         (c) Consider use of a flow diagram |
| 14*     | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders  
         (b) Indicate number of participants with missing data for each variable of interest  
         (c) Summarise follow-up time (eg, average and total amount) |
| 15*     | Report numbers of outcome events or summary measures over time |
| 16      | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included  
         (b) Report category boundaries when continuous variables were categorized  
         (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period |
Other analyses 17 Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses

Discussion

Key results 18 Summarise key results with reference to study objectives

Limitations 19 Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias

Interpretation 20 Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence

Generalisability 21 Discuss the generalisability (external validity) of the study results

Other information

Funding 22 Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Predictive role of C-reactive protein in stroke recurrence after cardioembolic stroke: the Fukuoka Stroke Registry

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<td>Date Submitted by the Author:</td>
<td>13-Sep-2013</td>
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<td>Kuwashiro, Takahiro; Graduate School of Medical Sciences, Kyushu University, Department of Medicine and Clinical Science Sugimori, Hiroshi; Kyushu University, Ago, Tetsuro; Kyushu University, Department of Medicine and Clinical Science Kuroda, Junya; Graduate School of Medical Sciences, Kyushu University, Department of Medicine and Clinical Science Kamouchi, Masahiro; Kyushu University, Kitazono, Takanari; Kyushu University,</td>
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</table>
Predictive role of C-reactive protein in stroke recurrence after cardioembolic stroke: the Fukuoka Stroke Registry

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Junya Kuroda, MD; Masahiro Kamouchi, MD; Takanari Kitazono, MD;
for the FSR Investigators (see appendix)

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Key words: Aging, Ischemic stroke, C-reactive protein, Recurrence, Cardioembolic stroke

Word count: 3,357 words

Number of reference: 43
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ABSTRACT

Objectives: We investigated the clinical characteristics of patients with stroke recurrence in the first year after cardioembolic stroke, and determined the predictors associated with recurrence.

Design: A prospective cohort study.

Setting: Multicenter study at the Fukuoka prefecture in Japan.

Participants: We enrolled 2084 consecutive patients who were hospitalized in stroke centers within 7 days of onset from June 2007 to October 2009. The clinical characteristics of patients were assessed on admission, and the clinical course of all patients was followed for 1 year.

Results: Of all patients, 425 (234 males, 76 ± 11 years of age) had cardioembolic stroke and were included in this study. Fifty-one patients (12%) suffered a recurrence during the follow-up period. Age (hazard ratio [HR] 1.04, 95% confidence interval [CI] 1.01 to 1.06, p = 0.014), and level of C-reactive protein (HR 1.01, 95% CI 1.00 to 1.02, p = 0.018) on admission were significantly associated with recurrence in the univariate analyses. Male gender (HR 0.61, 95% CI 0.35 to 1.05, p = 0.076), body mass index (HR 0.94, 95% CI 0.87 to 1.01, p = 0.093), hypertension (HR 0.59, 95% CI 0.33 to 1.06, p = 0.079), diastolic blood pressure (HR 0.99, 95% CI 0.97 to 1.00, p = 0.087), and
hematocrit (HR 0.95, 95% CI 0.91 to 1.00, p = 0.052) were marginally significant in the
univariate Cox analyses. Multivariate Cox proportional hazards analysis showed that
age (HR 1.03, 95% CI 1.00 to 1.06, p = 0.031, per 1-year increase), and C-reactive
protein (HR 1.01, 95% CI 1.00 to 1.02, p = 0.022, per 1-mg/L increase) were
independent predictors of a recurrence in the first year after cardioembolic stroke.

Conclusions: In patients with cardioembolic ischemic stroke, age and C-reactive
protein are independent risk factors for recurrence in the first year after onset.
ARTICLE SUMMARY

Article focus

1. For the prevention of ischemic stroke recurrence, it seems appropriate to focus on
   the prevention of recurrence within the first year after onset.

2. Preventive measures for recurrence should be appropriately selected on the basis of
   the specific causes of stroke subtypes. In particular, mechanisms responsible for
   brain infarction are significantly different between cardioembolic stroke and
   non-embolic stroke.

3. We focused on cardioembolic stroke and investigated the relationship between
   patient clinical characteristics and stroke recurrence within the first year after stroke
   onset.

Key messages

1. In the present study, the first-year gross recurrence rate of cardioembolic ischemic
   stroke was 12% (51/425).

2. On the results of multivariate Cox regression analysis for stroke recurrence, age (HR
   1.03, 95% CI 1.00 to 1.06, p = 0.031, per 1-year increase) and C-reactive protein
   (HR 1.01, 95% CI 1.00 to 1.02, p = 0.022, per 1-mg/L increase) were independent
predictors of stroke recurrence 1 year after onset.

3. Older patients (≥ 78 years) with higher CRP (≥ 1.9 mg/L) were at greater risk of stroke recurrence compared with the reference group (age < 78 years, CRP < 1.9 mg/L) (HR 2.36, 95% CI 1.06 to 5.25, p = 0.036).

Strength and limitations of this study

1. The present study is a multicenter, prospective cohort research in which acute stroke patients are enrolled within 7 days of onset.

2. This is the first study to show that elevation of CRP is strongly associated with stroke recurrence in patients with cardioembolic stroke.

3. The observational design did not allow us to control any therapy used after the onset of the stroke. Moreover, no information on patient compliance with medical treatment was obtained during the follow-up period after discharge from the hospital.
INTRODUCTION

There is considerable evidence on the secondary prevention of ischemic stroke, and methods of treatment for each subtype of stroke have been recommended.[1-3] However, stroke appears to recur in a certain percentage of patients despite appropriate secondary prevention measures.[4] Stroke recurrence is especially high in the first year after stroke onset (8% to 12% of all stroke patients).[5-7] Therefore, for the prevention of ischemic stroke recurrence, it seems appropriate to focus on the prevention of recurrence within the first year after onset.

Although previous studies have shown several independent predictors of stroke recurrence,[8-11] only a few studies have reported risk factors for recurrence according to the subtype of ischemic stroke.[12, 13] The underlying mechanism for stroke onset differs by stroke subtype.[14] In particular, mechanisms responsible for brain infarction are significantly different between cardioembolic stroke and non-embolic stroke.[15] Indeed, several studies have shown the different plasma levels of inflammatory activation according to stroke subtypes.[16, 17] Thus, preventive measures for recurrence should be appropriately selected on the basis of the specific causes of stroke subtypes.

In the present study, we performed a prospective observational study of
ischemic stroke to identify the risk factors associated with the recurrence of ischemic stroke in the first year after onset. To determine an appropriate treatment strategy for each subtype of stroke, we investigated different subtypes of ischemic stroke. Furthermore, we focused on cardioembolic stroke and investigated the relationship between patient clinical characteristics and stroke recurrence within the first year after stroke onset.
METHODS

Fukuoka Stroke Registry (FSR)

FSR is a multicenter, prospective cohort study in which acute stroke patients are enrolled within 7 days of onset. Patients admitted to one of the seven clinical stroke centers (see appendix) in the Fukuoka Prefecture in Japan have participated in this study since June 2007. The study design was approved by the institutional review boards (IRB) of the ethics committee in all hospitals. IRB approved the study protocols and related materials, such as informed consent, document and study brochures, after careful investigation into the protocols and the matters concerning the ethics of the study to protect the rights, safety and welfare of all participants in compliance with the Declaration of Helsinki. Detailed information of the study, data collection, and harmonization in the FSR have been described previously.[12]

Study Patients

We enrolled 2084 consecutive ischemic stroke patients (1262 males, 822 females, 71 ± 12 years of age) registered in FSR from June 2007 to October 2009.

Stroke was defined as the sudden onset of nonconvulsive and focal neurological deficit persisting for >24 hours. All of the patients underwent brain computed tomography
(CT), magnetic resonance imaging (MRI), or both within 24 hours of hospitalization.

The diagnosis and classification of stroke were based on clinical information, and ancillary examinations (such as brain imaging including CT, MRI, cerebral angiography and echocardiography).

Clinical Assessment

We assessed the clinical characteristics and comorbidities of the patients on admission. Body mass index (BMI), waist circumference, systolic and diastolic blood pressure were measured. Values for white blood cells (WBC), hematocrit, total protein, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, blood glucose, hemoglobin A1c (HbA1c), serum creatinine (sCr) and C-reactive protein (CRP), were obtained on admission. We collected blood samples within 24 hours after admission. We determined the frequency of LDL cholesterol ≥ 140 mg/dL, HDL cholesterol < 40 mg/dL, and triglycerides ≥ 150 mg/dL according to the diagnostic criteria for dyslipidemia.[18] Urine protein and glucose levels were determined with a simplified kit. Estimated glomerular filtration rate (eGFR) was calculated using the equation proposed by the Japanese Society of Nephrology [19]:

\[
eGFR \text{ (ml/min/1.73 m}^2) = 194 \times \text{sCr}^{-1.094} \times \text{Age}^{-0.287} \text{ in males and } 194 \times \text{sCr}^{-1.094} \times 
\]


Age$^{0.287}$ × 0.739 in females. Chronic kidney disease (CKD) was diagnosed when the patients had low eGFR (<60 ml/min/1.73 m$^2$) and/or proteinuria on admission. Risk factors for cardiovascular events were assessed, including hypertension (systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or a history of antihypertensive medication); diabetes mellitus (fasting blood glucose ≥ 126 mg/dL, positive 75 g oral glucose tolerance test result, or a history of antidiabetic medication or insulin); dyslipidemia (LDL cholesterol ≥ 140 mg/dL, HDL cholesterol < 40 mg/dL, triglycerides ≥ 150 mg/dL or a history of antihypercholesterolemic medication); ischemic heart disease or atrial fibrillation; smoking habit (previous and current); alcohol consumption (including occasional drinking); and previous ischemic stroke.

Furthermore, the ejection fraction (EF) of the acute stroke patients was evaluated using transthoracic echocardiography. We assessed the severity of the neurological deficits of the patients on admission with the National Institutes of Health Stroke Scale (NIHSS) score. Moreover, we investigated the frequency of infections such as pneumonia and urinary tract infections in acute phase. The medications (antithrombotic, antihypertensive, and antihypercholesterolemic) prescribed at discharge for vascular risk treatments were also investigated.
Stroke Classification

Criteria modified from the TOAST (Trial of ORG 10172 in Acute Stroke Treatment) classification system [14] were used to determine the subtype of ischemic stroke. According to the results of neuroimaging and neurological examinations, we categorized all ischemic strokes into the following four subtypes: large-artery atherosclerosis, cardioembolism, small-vessel occlusion and others (stroke of other determined etiology and stroke of undetermined etiology). In addition, localization of the culprit lesion in culprit was examined in the anterior or posterior circulation.

Follow-up Survey

Detailed information about prognosis, including the recurrence of cerebrovascular events and mortality, was collected at the 3rd, 6th and 12th month after stroke onset. The assessment was conducted through an interview by trained clinical research coordinators who were blinded to the information obtained during hospitalization. The clinical diagnosis of stroke was based on the detailed history, neurological examinations, and ancillary examinations. If needed, we obtained further information on prognosis from the hospital where patients were admitted or from our registration institution after the patients were discharged.
Statistical Analysis

Results are presented as the mean ± SD, or median and interquartile range. We used a univariate Cox proportional hazards regression model to identify the individual baseline characteristics that were significant predictors of stroke recurrence. Hazard ratios (HR) and their 95% confidence intervals (CI) were calculated by the Cox model. A multivariate Cox proportional hazards regression model was also used to determine the effect of multiple variables simultaneously on the risk of stroke recurrence. A backward selection procedure was performed using p > 0.10 of the likelihood ratio test for exclusion of variables from the model. The regression model included time to recurrent strokes as the response variables and clinical predictors of recurrence with a univariate p-value < 0.1 as independent covariates. We used the Kaplan-Meier method to evaluate the cumulative stroke recurrence rate after stratifying patients according to the characteristics derived from the multivariate Cox regression model. The log-rank test was used to assess differences between Kaplan-Meier cumulative recurrence rate curves. A p-value < 0.05 was considered to be significant. All statistical analyses were performed using IBM SPSS Statistics, version 19.0 for Windows (SPSS Inc, Chicago, IL).
RESULTS

We detected stroke due to large-artery atherosclerosis in 493 patients, cardioembolism in 425, small-vessel occlusion in 583 and other etiologies (stroke of other or undetermined etiology) in 583 among the 2084 consecutive patients. In the present study, 425 patients (234 males and 191 females, 76 ± 11 years of age) with cardioembolic stroke were followed for 1 year after stroke onset. Thirty-one of these 425 patients died within 1 year, 6 from ischemic stroke, 3 from cerebral hemorrhage, 7 from cardiovascular diseases, 4 from pneumonia, 3 from malignant tumor, 3 from other causes and 5 from unknown causes. We found that 51 patients suffered a recurrence of ischemic stroke during the follow-up period of 1 year. Therefore, the first-year gross recurrence rate of cardioembolic ischemic stroke was 12% (51/425). Two patients had two recurrences in the first year.

A univariate Cox regression analyses was used to evaluate the association between stroke recurrence in all patients, and the clinical characteristics and laboratory data at the time of the initial stroke (table 1). Age (HR 1.04, 95% CI 1.01 to 1.06, p = 0.014), and level of C-reactive protein (HR 1.01, 95% CI 1.00 to 1.02, p = 0.018) on admission were significantly associated with stroke recurrence in the univariate analyses (table 1).
Male gender (HR 0.61, 95% CI 0.35 to 1.05, p = 0.076), BMI (HR 0.94, 95% CI 0.87 to 1.01, p = 0.093), hypertension (HR 0.59, 95% CI 0.33 to 1.06, p = 0.079), diastolic blood pressure (HR 0.99, 95% CI 0.97 to 1.00, p = 0.087), and hematocrit (HR 0.95, 95% CI 0.91 to 1.00, p = 0.052) were marginally significant in the univariate Cox analyses (table 1).

There were no significant differences in the medications prescribed at discharge for the treatment of vascular risk factors (table 2).

The results of multivariate Cox regression analysis for stroke recurrence are shown in table 3. Age (HR 1.03, 95% CI 1.00 to 1.06, p = 0.031, per 1-year increase) and C-reactive protein (HR 1.01, 95% CI 1.00 to 1.02, p = 0.022, per 1-mg/L increase) were independent predictors of stroke recurrence 1 year after onset.

When patients were divided into four groups for analysis according to the median values of age and CRP, older patients (≥ 78 years) with higher CRP (≥ 1.9 mg/L) were at greater risk of stroke recurrence compared with the reference group (age < 78 years, CRP < 1.9 mg/L) (HR 2.36, 95% CI 1.06 to 5.25, p = 0.036, table 4; figure 1). The Kaplan-Meier method was used to estimate the cumulative recurrence rate of stroke in these two groups of patients and the curves were significantly different, as shown in figure 2 (p = 0.027 by the log-rank test).
DISCUSSION

In patients with cardioembolic stroke, we have shown that age and C-reactive protein were independent risk factors for stroke recurrence during the first year of follow-up.

Several epidemiological studies have demonstrated that serum levels of the inflammatory marker CRP are positively associated with the risk of ischemic stroke.[20-22] Many studies showed a significant relationship between elevated CRP and atherosclerosis.[20, 23] Since chronic inflammation directly influences the progression of atherosclerosis, it also enhances the risk of ischemic stroke.

Inflammation is an important factor in ischemic stroke, both in the development of atherosclerosis and during the ischemic event. Thus, CRP levels have attracted clinical attention as a predictive marker of ischemic stroke.

However, several studies showed that CRP does not seem to be related to atherosclerosis of large arteries.[24-26] In particular, a few studies reported significant elevations of CRP levels in patients with cardioembolic stroke.[27-29] According to a study of 196 elderly patients with ischemic stroke, mean values of CRP were significantly higher in patients with cardioembolic stroke compared with atherothrombotic large vessel and lacunar stroke in patients who died in the first 30
days.[27] In a study of 648 stroke patients with CRP levels stratified into quartiles, patients with cardioembolic strokes had CRP levels in the higher quartiles, and CRP was an independent predictor of 14-day mortality.[28] A previous case-control study of 199 stroke patients and 202 randomly selected controls showed an independent relationship between elevated blood levels of CRP and cardioembolic stroke.[29]

Although the mechanism underlying this phenomenon is not clear, several possible explanations have been proposed. First, it seems that CRP is commonly elevated in heart disease.[28, 30] Therefore, plasma CRP levels in patients with cardioembolic stroke could be increased because of the presence of heart disease in these patients. CRP is frequently elevated especially in heart diseases such as heart failure and atrial fibrillation.[31] Furthermore, intracardiac clots that often form in these conditions may serve as a source of emboli. In the study of 880 subjects with atrial fibrillation, CRP was positively correlated to stroke risk and related to stroke prognosis.[32] Second, the binding of CRP to phospholipids, which are involved in the coagulation cascade, are potentially activated by emboli from the heart.[33] Third, in patients with extensive stroke lesions, levels of CRP have been reported to increase.[34, 35] Of all stroke subtypes, patients with cardioembolic stroke have larger lesions [36] and a worse prognosis.[37]
Additionally, recent studies showed that elevated CRP independently predicted the risk of stroke recurrence and transient ischemic attack in the elderly.\[38, 39\] In the acute phase as well as the chronic phase of stroke, the inflammatory cascade is mediated by an increasing concentration of cytokines, adhesion molecules, proteins, macrophages and leukocytes, and the strength of this response is related to early and late clinical outcomes.\[21, 40\] Thus, further progression of vascular disease could occur because a chronic inflammatory state may persist after the acute phase.

It was uncertain whether age influences the recurrence of ischemic stroke, though aging is one of the most important overall risk factors for stroke. Age was identified as a risk factor for the recurrence of ischemic stroke in some studies,\[8, 41\] but not in others.\[5, 42, 43\] In the present study, age was an independent risk factor for recurrence during the first year after cardioembolic stroke onset. The cumulative effects of advancing age on the cardiovascular system and the progressive nature of stroke risk factors over a prolonged period of time substantially increase the risk of ischemic stroke.

The present study has several limitations. The observational design did not allow us to control any therapy used after the onset of the stroke. In addition, a variety of stroke therapies and complications in the acute and chronic phases might affect
prognosis. Moreover, no information on patient compliance with medical treatment was obtained during the follow-up period after discharge from the hospital. In particular, effectiveness of the anticoagulant treatment was not examined at the time of recurrence.

In addition, a single measurement of CRP on admission may not accurately reflect the status of the patients during the acute phase. Then, we cannot completely exclude the possibility that CRP values are affected by several factors (e.g., rheumatologic, malignancies and deep venous thrombosis) even if it was collected blood samples during an acute phase. Furthermore, as we did not investigate the classification of the recurrent stroke, the explanation about the relationship between CRP and stroke recurrence may be insufficient. In the present study, the sample size was relatively small and the statistical power may be insufficient to draw conclusions. Therefore, further studies with a larger cohort should be conducted in order to resolve these issues.

Even with these limitations, elevated CRP on admission and age were significantly associated with stroke recurrence in patients with cardioembolic stroke. To the best of our knowledge, this is the first study to show that elevation of CRP is strongly associated with stroke recurrence in patients with cardioembolic stroke. In conclusion, age and CRP on admission were found to be independent risk factors for the recurrence of cardioembolic stroke within 1 year of onset.
ACKNOWLEDGMENTS

This study was supported in part by the Japanese Ministry of Education, Culture, Sports, Science and Technology (Coordination, Support and Training Program for Translational Research). The authors are grateful to Associate Professor Hitoshi Inoue in the Research Institute for Information Technology, Kyushu University for his support on the FSR Data Collection System. We also thank all the clinical research coordinators for their help in obtaining informed consent and collecting the clinical data.

Contributorship

T. Kuwashiro contributed to drafting the manuscript for content, study concept, analysis of data, acquisition of data, and statistical analysis.

H. Sugimori contributed to drafting the manuscript for content, study concept, analysis of data, acquisition of data, and statistical analysis.

T. Ago contributed to the study concept, analysis of data, and acquisition of data.

J. Kuroda contributed to the study concept, analysis of data, and acquisition of data.

M. Kamouchi contributed to the study concept and study supervision.

T. Kitazono contributed to the study concept and study supervision.

Data sharing

No additional data available.
Competing Interest

None

Funding

None
APPENDIX

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REFERENCES


6. **Hankey GJ.** Long-term outcome after ischaemic stroke/transient ischaemic attack.

   *Cerebrovasc Dis* 2003;16 (Suppl 1);14-9.


Committee for Epidemiology and Clinical Management of Atherosclerosis.


FIGURE LEGENDS

Figure 1

Hazard ratio and 95% CI of four risk groups for stroke recurrence. Four groups were classified by the median value of age and CRP.

Figure 2

Kaplan-Meier estimates of the cumulative recurrence rate of stroke after patients were stratified according to the combination of the median value of age and CRP. A significant difference in recurrence rate was observed between the patients with age ≥ 78 years and CRP ≥ 1.9 mg/L (solid line) on admission and those with age < 78 years and CRP < 1.9 mg/L (dotted line, p = 0.027 by log-rank test). Censored cases with death are indicated as (+).
Table 1 Clinical characteristics of the patients and univariate Cox hazard ratios for stroke recurrence

<table>
<thead>
<tr>
<th>Baseline Characteristic or Risk Factor</th>
<th>Recurrence (+) n = 51</th>
<th>Recurrence (-) n = 374</th>
<th>HR (95%CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y</strong></td>
<td>79.6 ± 10.4</td>
<td>75.5 ± 11.0</td>
<td>1.04 (1.01-1.06)</td>
<td>0.014*</td>
</tr>
<tr>
<td>Male gender</td>
<td>43%</td>
<td>57%</td>
<td>0.61 (0.35-1.05)</td>
<td>0.076</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>21.3 ± 3.2</td>
<td>22.3 ± 3.8</td>
<td>0.94 (0.87-1.01)</td>
<td>0.093</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>79.5 ± 9.5</td>
<td>81.8 ± 10.9</td>
<td>0.98 (0.96-1.01)</td>
<td>0.156</td>
</tr>
<tr>
<td>Smoking</td>
<td>31%</td>
<td>39%</td>
<td>0.73 (0.41-1.33)</td>
<td>0.305</td>
</tr>
<tr>
<td>Drinking</td>
<td>31%</td>
<td>37%</td>
<td>0.78 (0.43-1.41)</td>
<td>0.410</td>
</tr>
<tr>
<td>Hypertension</td>
<td>67%</td>
<td>78%</td>
<td>0.59 (0.33-1.06)</td>
<td>0.079</td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td>20%</td>
<td>24%</td>
<td>0.78 (0.39-1.56)</td>
<td>0.484</td>
</tr>
<tr>
<td><strong>Dyslipidemia</strong></td>
<td>28%</td>
<td>37%</td>
<td>0.66 (0.36-1.21)</td>
<td>0.179</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>18%</td>
<td>25%</td>
<td>0.68 (0.33-1.40)</td>
<td>0.294</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>82%</td>
<td>81%</td>
<td>1.14 (0.56-2.34)</td>
<td>0.720</td>
</tr>
<tr>
<td>Previous ischemic stroke</td>
<td>28%</td>
<td>21%</td>
<td>1.35 (0.73-2.50)</td>
<td>0.336</td>
</tr>
<tr>
<td><strong>Findings on Admission</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP on admission, mm Hg</td>
<td>147 ± 25</td>
<td>154 ± 28</td>
<td>0.99 (0.98-1.00)</td>
<td>0.153</td>
</tr>
<tr>
<td>DBP on admission, mm Hg</td>
<td>79 ± 15</td>
<td>83 ± 18</td>
<td>0.99 (0.97-1.00)</td>
<td>0.087</td>
</tr>
<tr>
<td>Urine protein</td>
<td>39%</td>
<td>37%</td>
<td>1.08 (0.49-2.38)</td>
<td>0.851</td>
</tr>
<tr>
<td>Urine glucose</td>
<td>19%</td>
<td>19%</td>
<td>0.99 (0.38-2.64)</td>
<td>0.990</td>
</tr>
<tr>
<td>eGFR, ml/min/1.73m²</td>
<td>61.0 ± 21.3</td>
<td>63.7 ± 23.2</td>
<td>0.99 (0.98-1.01)</td>
<td>0.995</td>
</tr>
<tr>
<td>eGFR &lt; 60 ml/min/1.73m²</td>
<td>39%</td>
<td>46%</td>
<td>0.80 (0.46-1.41)</td>
<td>0.439</td>
</tr>
<tr>
<td>CKD</td>
<td>51%</td>
<td>52%</td>
<td>0.97 (0.56-1.68)</td>
<td>0.907</td>
</tr>
<tr>
<td>EF &lt; 55%</td>
<td>15%</td>
<td>22%</td>
<td>0.64 (0.29-1.43)</td>
<td>0.278</td>
</tr>
<tr>
<td><strong>NIHSS score on admission</strong></td>
<td>7 (3 to 16)</td>
<td>8 (5 to 16)</td>
<td>1.01 (0.98-1.04)</td>
<td>0.619</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>18%</td>
<td>13%</td>
<td>1.40 (0.68-2.88)</td>
<td>0.357</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>14%</td>
<td>11%</td>
<td>1.28 (0.58-2.85)</td>
<td>0.541</td>
</tr>
<tr>
<td><strong>Laboratory Data on Admission</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC, /mm³</td>
<td>6643 ± 2105</td>
<td>7164 ± 2354</td>
<td>1.00 (1.00-1.00)</td>
<td>0.148</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>38.0 ± 6.0</td>
<td>39.6 ± 5.5</td>
<td>0.95 (0.91-1.00)</td>
<td>0.052</td>
</tr>
<tr>
<td>Total protein, g/dL</td>
<td>6.9 ± 0.6</td>
<td>7.0 ± 0.6</td>
<td>0.94 (0.61-1.45)</td>
<td>0.778</td>
</tr>
<tr>
<td>LDL cholesterol ≥ 140 mg/dL</td>
<td>13%</td>
<td>17%</td>
<td>0.73 (0.29-1.87)</td>
<td>0.513</td>
</tr>
<tr>
<td>HDL cholesterol &lt; 40 mg/dL</td>
<td>19%</td>
<td>19%</td>
<td>1.02 (0.49-2.11)</td>
<td>0.962</td>
</tr>
<tr>
<td>LDL-chol / HDL-chol</td>
<td>2.1 ± 0.7</td>
<td>2.2 ± 1.0</td>
<td>0.85 (0.59-1.22)</td>
<td>0.385</td>
</tr>
<tr>
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<tr>
<td>------------------------------</td>
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<td>------------------</td>
<td>-------</td>
</tr>
<tr>
<td>Triglyceride ≥ 150 mg/dL</td>
<td>17%</td>
<td>18%</td>
<td>0.94 (0.44-2.01)</td>
<td>0.869</td>
</tr>
<tr>
<td>Blood glucose, mg/dL</td>
<td>139 ± 49</td>
<td>134 ± 54</td>
<td>1.00 (0.99-1.01)</td>
<td>0.576</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>5.5 ± 0.8</td>
<td>5.7 ± 1.40</td>
<td>0.82 (0.58-1.16)</td>
<td>0.260</td>
</tr>
<tr>
<td>sCr, mg/dL</td>
<td>1.03 ± 1.07</td>
<td>1.02 ± 1.05</td>
<td>1.01 (0.78-1.31)</td>
<td>0.934</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>1.6 (0.6 to 13.0)</td>
<td>1.8 (0.5 to 6.0)</td>
<td>1.01 (1.00-1.02)</td>
<td>0.018*</td>
</tr>
</tbody>
</table>

**Stroke Location**

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Posterior circulation</td>
<td>20%</td>
<td>19%</td>
<td>1.04 (0.52-2.07)</td>
<td>0.923</td>
</tr>
</tbody>
</table>

BMI, body mass index; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; EF, ejection fraction; HR, hazard ratio; CI, confidence interval.

Data are the mean ± SD for age, BMI, waist circumference, SBP, DBP, eGFR, WBC, Hematocrit, Total protein, LDL-chol / HDL-chol, Blood glucose, HbA1c, and sCr. The median (interquartile range) is shown for NIHSS, CRP, and % for the other variables.

*: P < 0.05
Table 2 Medications prescribed at discharge and univariate Cox hazard ratios for stroke recurrence

<table>
<thead>
<tr>
<th></th>
<th>Recurrence (+)</th>
<th>Recurrence (-)</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 51</td>
<td>n = 374</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiplatelet</td>
<td>16%</td>
<td>21%</td>
<td>0.70 (0.33-1.48)</td>
<td>0.348</td>
</tr>
<tr>
<td>Anticoagulant</td>
<td>88%</td>
<td>90%</td>
<td>0.86 (0.37-2.01)</td>
<td>0.728</td>
</tr>
<tr>
<td>Antihypertensive</td>
<td>53%</td>
<td>61%</td>
<td>0.74 (0.43-1.28)</td>
<td>0.279</td>
</tr>
<tr>
<td>Calcium-channel blocker</td>
<td>21%</td>
<td>21%</td>
<td>1.01 (0.52-1.97)</td>
<td>0.980</td>
</tr>
<tr>
<td>ARB</td>
<td>23%</td>
<td>24%</td>
<td>0.97 (0.51-1.86)</td>
<td>0.932</td>
</tr>
<tr>
<td>β-blocker</td>
<td>14%</td>
<td>22%</td>
<td>0.58 (0.26-1.29)</td>
<td>0.183</td>
</tr>
<tr>
<td>Diuretic</td>
<td>26%</td>
<td>19%</td>
<td>1.40 (0.75-2.63)</td>
<td>0.293</td>
</tr>
<tr>
<td>HMG-CoA reductase inhibitor</td>
<td>16%</td>
<td>21%</td>
<td>0.71 (0.34-1.52)</td>
<td>0.380</td>
</tr>
</tbody>
</table>

ARB, angiotensin receptor blocker;
HMG-CoA reductase inhibitor, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitor.

Data are expressed as %, HR, hazard ratio; CI, confidence interval.
### Table 3 Multivariate Cox hazards ratios for stroke recurrence

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, per 1-year increase</td>
<td>1.03 (1.00—1.06)</td>
<td>0.031*</td>
</tr>
<tr>
<td>C-reactive protein, per 1-mg/L increase</td>
<td>1.01 (1.00—1.02)</td>
<td>0.022*</td>
</tr>
</tbody>
</table>

HR, hazard ratio; CI, confidence interval.

*: p < 0.05 by multivariate Cox regression analysis using sex, age, pneumonia and urinary tract infections as well as the clinical characteristics which showed a significant (p < 0.05) or marginally significant (0.05 ≤ p < 0.1) correlation with stroke recurrence in the univariate analyses.
Table 4 Cox proportional hazards analysis of four risk groups derived from the median value of age and CRP

<table>
<thead>
<tr>
<th></th>
<th>R/N</th>
<th>Hazard ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 78 y, CRP &lt; 1.9 mg/L</td>
<td>9/115</td>
<td>1.00 (reference)</td>
<td></td>
</tr>
<tr>
<td>Age &lt; 78 y, CRP ≥ 1.9 mg/L</td>
<td>8/107</td>
<td>1.41 (0.50—3.97)</td>
<td>0.511</td>
</tr>
<tr>
<td>Age ≥ 78 y, CRP &lt; 1.9 mg/L</td>
<td>16/102</td>
<td>2.21 (0.98—5.00)</td>
<td>0.057</td>
</tr>
<tr>
<td>Age ≥ 78 y, CRP ≥ 1.9 mg/L</td>
<td>18/101</td>
<td>2.36 (1.06—5.25)</td>
<td>0.036*</td>
</tr>
</tbody>
</table>

R, recurrence; N, total number of subjects; HR, hazard ratio; CI, confidence interval.

*: P < 0.05
Predictive role of C-reactive protein in stroke recurrence after cardioembolic stroke: the Fukuoka Stroke Registry

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Key words: Aging, Ischemic stroke, C-reactive protein, Recurrence, Cardioembolic stroke

Word count: 3,357 words

Number of reference: 43
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Funding: None

Competing Interest: None declared.
Contributorship statement:

T. Kuwashiro contributed to drafting the manuscript for content, study concept, analysis of data, acquisition of data, and statistical analysis.

H. Sugimori contributed to drafting the manuscript for content, study concept, analysis of data, acquisition of data, and statistical analysis.

T. Ago contributed to the study concept, analysis of data, and acquisition of data.

J. Kuroda contributed to the study concept, analysis of data, and acquisition of data.

M. Kamouchi contributed to the study concept and study supervision.

T. Kitazono contributed to the study concept and study supervision.
ABSTRACT

Objectives: We investigated the clinical characteristics of patients with stroke recurrence in the first year after cardioembolic stroke, and determined the predictors associated with recurrence.

Design: A prospective cohort study.

Setting: Multicenter study at the Fukuoka prefecture in Japan.

Participants: We enrolled 2084 consecutive patients who were hospitalized in stroke centers within 7 days of onset from June 2007 to October 2009. The clinical characteristics of patients were assessed on admission, and the clinical course of all patients was followed for 1 year.

Results: Of all patients, 425 (234 males, 76 ± 11 years of age) had cardioembolic stroke and were included in this study. Fifty-one patients (12%) suffered a recurrence during the follow-up period. Age (hazard ratio [HR] 1.04, 95% confidence interval [CI] 1.01 to 1.06, p = 0.014), and level of C-reactive protein (HR 1.01, 95% CI 1.00 to 1.02, p = 0.018) on admission were significantly associated with recurrence in the univariate analyses. Male gender (HR 0.61, 95% CI 0.35 to 1.05, p = 0.076), body mass index (HR 0.94, 95% CI 0.87 to 1.01, p = 0.093), hypertension (HR 0.59, 95% CI 0.33 to 1.06, p = 0.079), diastolic blood pressure (HR 0.99, 95% CI 0.97 to 1.00, p = 0.087), and
hematocrit (HR 0.95, 95% CI 0.91 to 1.00, p = 0.052) were marginally significant in the
univariate Cox analyses. Multivariate Cox proportional hazards analysis showed that
age (HR 1.03, 95% CI 1.00 to 1.06, p = 0.031, per 1-year increase), and C-reactive
protein (HR 1.01, 95% CI 1.00 to 1.02, p = 0.022, per 1-mg/L increase) were
independent predictors of a recurrence in the first year after cardioembolic stroke.

**Conclusions:** In patients with cardioembolic ischemic stroke, age and C-reactive
protein are independent risk factors for recurrence in the first year after onset.
ARTICLE SUMMARY

Article focus

1. For the prevention of ischemic stroke recurrence, it seems appropriate to focus on the prevention of recurrence within the first year after onset.

2. Preventive measures for recurrence should be appropriately selected on the basis of the specific causes of stroke subtypes. In particular, mechanisms responsible for brain infarction are significantly different between cardioembolic stroke and non-embolic stroke.

3. We focused on cardioembolic stroke and investigated the relationship between patient clinical characteristics and stroke recurrence within the first year after stroke onset.

Key messages

1. In the present study, the first-year gross recurrence rate of cardioembolic ischemic stroke was 12% (51/425).

2. On the results of multivariate Cox regression analysis for stroke recurrence, age (HR 1.03, 95% CI 1.00 to 1.06, p = 0.031, per 1-year increase) and C-reactive protein (HR 1.01, 95% CI 1.00 to 1.02, p = 0.022, per 1-mg/L increase) were independent
predictors of stroke recurrence 1 year after onset.

3. Older patients (≥ 78 years) with higher CRP (≥ 1.9 mg/L) were at greater risk of stroke recurrence compared with the reference group (age < 78 years, CRP < 1.9 mg/L) (HR 2.36, 95% CI 1.06 to 5.25, p = 0.036).

Strength and limitations of this study

1. The present study is a multicenter, prospective cohort research in which acute stroke patients are enrolled within 7 days of onset.

2. This is the first study to show that elevation of CRP is strongly associated with stroke recurrence in patients with cardioembolic stroke.

3. The observational design did not allow us to control any therapy used after the onset of the stroke. Moreover, no information on patient compliance with medical treatment was obtained during the follow-up period after discharge from the hospital.
INTRODUCTION

There is considerable evidence on the secondary prevention of ischemic stroke, and methods of treatment for each subtype of stroke have been recommended.[1-3] However, stroke appears to recur in a certain percentage of patients despite appropriate secondary prevention measures.[4] Stroke recurrence is especially high in the first year after stroke onset (8% to 12% of all stroke patients).[5-7] Therefore, for the prevention of ischemic stroke recurrence, it seems appropriate to focus on the prevention of recurrence within the first year after onset.

Although previous studies have shown several independent predictors of stroke recurrence,[8-11] only a few studies have reported risk factors for recurrence according to the subtype of ischemic stroke.[12, 13] The underlying mechanism for stroke onset differs by stroke subtype.[14] In particular, mechanisms responsible for brain infarction are significantly different between cardioembolic stroke and non-embolic stroke.[15] Indeed, several studies have shown the different plasma levels of inflammatory activation according to stroke subtypes.[16, 17] Thus, preventive measures for recurrence should be appropriately selected on the basis of the specific causes of stroke subtypes.

In the present study, we performed a prospective observational study of
ischemic stroke to identify the risk factors associated with the recurrence of ischemic stroke in the first year after onset. To determine an appropriate treatment strategy for each subtype of stroke, we investigated different subtypes of ischemic stroke. Furthermore, we focused on cardioembolic stroke and investigated the relationship between patient clinical characteristics and stroke recurrence within the first year after stroke onset.
METHODS

Fukuoka Stroke Registry (FSR)

FSR is a multicenter, prospective cohort study in which acute stroke patients are enrolled within 7 days of onset. Patients admitted to one of the seven clinical stroke centers (see appendix) in the Fukuoka Prefecture in Japan have participated in this study since June 2007. The study design was approved by the institutional review boards (IRB) of the ethics committee in all hospitals. IRB approved the study protocols and related materials, such as informed consent, document and study brochures, after careful investigation into the protocols and the matters concerning the ethics of the study to protect the rights, safety and welfare of all participants in compliance with the Declaration of Helsinki. Detailed information of the study, data collection, and harmonization in the FSR have been described previously.[12]

Study Patients

We enrolled 2084 consecutive ischemic stroke patients (1262 males, 822 females, 71 ± 12 years of age) registered in FSR from June 2007 to October 2009. Stroke was defined as the sudden onset of nonconvulsive and focal neurological deficit persisting for >24 hours. All of the patients underwent brain computed tomography
(CT), magnetic resonance imaging (MRI), or both within 24 hours of hospitalization.

The diagnosis and classification of stroke were based on clinical information, and ancillary examinations (such as brain imaging including CT, MRI, cerebral angiography and echocardiography).

**Clinical Assessment**

We assessed the clinical characteristics and comorbidities of the patients on admission. Body mass index (BMI), waist circumference, systolic and diastolic blood pressure were measured. Values for white blood cells (WBC), hematocrit, total protein, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, blood glucose, hemoglobin A1c (HbA1c), serum creatinine (sCr) and C-reactive protein (CRP), were obtained on admission. We collected blood samples within 24 hours after admission. We determined the frequency of LDL cholesterol ≥ 140 mg/dL, HDL cholesterol < 40 mg/dL, and triglycerides ≥ 150 mg/dL according to the diagnostic criteria for dyslipidemia.[18] Urine protein and glucose levels were determined with a simplified kit. Estimated glomerular filtration rate (eGFR) was calculated using the equation proposed by the Japanese Society of Nephrology [19]:

\[
eGFR \text{ (ml/min/1.73 m}^2\text{)} = 194 \times sCr^{-1.094} \times \text{Age}^{-0.287} \text{ in males and } 194 \times sCr^{-1.094} \times \]

\[
(1.153 \times \text{Age})^{-0.203} \text{ in females.}
\]
Age$^{0.287} \times 0.739$ in females. Chronic kidney disease (CKD) was diagnosed when the patients had low eGFR ($<60$ ml/min/1.73 m$^3$) and/or proteinuria on admission. Risk factors for cardiovascular events were assessed, including hypertension (systolic blood pressure $\geq 140$ mmHg, diastolic blood pressure $\geq 90$ mmHg, or a history of antihypertensive medication); diabetes mellitus (fasting blood glucose $\geq 126$ mg/dL, positive 75 g oral glucose tolerance test result, or a history of antidiabetic medication or insulin); dyslipidemia (LDL cholesterol $\geq 140$ mg/dL, HDL cholesterol $< 40$ mg/dL, triglycerides $\geq 150$ mg/dL or a history of antihypercholesterolemic medication); ischemic heart disease or atrial fibrillation; smoking habit (previous and current); alcohol consumption (including occasional drinking); and previous ischemic stroke.

Furthermore, the ejection fraction (EF) of the acute stroke patients was evaluated using transthoracic echocardiography. We assessed the severity of the neurological deficits of the patients on admission with the National Institutes of Health Stroke Scale (NIHSS) score. Moreover, we investigated the frequency of infections such as pneumonia and urinary tract infections in acute phase. The medications (antithrombotic, antihypertensive, and antihypercholesterolemic) prescribed at discharge for vascular risk treatments were also investigated.
Stroke Classification

Criteria modified from the TOAST (Trial of ORG 10172 in Acute Stroke Treatment) classification system [14] were used to determine the subtype of ischemic stroke. According to the results of neuroimaging and neurological examinations, we categorized all ischemic strokes into the following four subtypes: large-artery atherosclerosis, cardioembolism, small-vessel occlusion and others (stroke of other determined etiology and stroke of undetermined etiology). In addition, localization of the culprit lesion in culprit was examined in the anterior or posterior circulation.

Follow-up Survey

Detailed information about prognosis, including the recurrence of cerebrovascular events and mortality, was collected at the 3rd, 6th and 12th month after stroke onset. The assessment was conducted through an interview by trained clinical research coordinators who were blinded to the information obtained during hospitalization. The clinical diagnosis of stroke was based on the detailed history, neurological examinations, and ancillary examinations. If needed, we obtained further information on prognosis from the hospital where patients were admitted or from our registration institution after the patients were discharged.
Statistical Analysis

Results are presented as the mean ± SD, or median and interquartile range. We used a univariate Cox proportional hazards regression model to identify the individual baseline characteristics that were significant predictors of stroke recurrence. Hazard ratios (HR) and their 95% confidence intervals (CI) were calculated by the Cox model. A multivariate Cox proportional hazards regression model was also used to determine the effect of multiple variables simultaneously on the risk of stroke recurrence. A backward selection procedure was performed using p > 0.10 of the likelihood ratio test for exclusion of variables from the model. The regression model included time to recurrent strokes as the response variables and clinical predictors of recurrence with a univariate p-value < 0.1 as independent covariates. We used the Kaplan-Meier method to evaluate the cumulative stroke recurrence rate after stratifying patients according to the characteristics derived from the multivariate Cox regression model. The log-rank test was used to assess differences between Kaplan-Meier cumulative recurrence rate curves. A p-value < 0.05 was considered to be significant. All statistical analyses were performed using IBM SPSS Statistics, version 19.0 for Windows (SPSS Inc, Chicago, IL).
RESULTS

We detected stroke due to large-artery atherosclerosis in 493 patients, cardioembolism in 425, small-vessel occlusion in 583 and other etiologies (stroke of other or undetermined etiology) in 583 among the 2084 consecutive patients. In the present study, 425 patients (234 males and 191 females, 76 ± 11 years of age) with cardioembolic stroke were followed for 1 year after stroke onset. Thirty-one of these 425 patients died within 1 year, 6 from ischemic stroke, 3 from cerebral hemorrhage, 7 from cardiovascular diseases, 4 from pneumonia, 3 from malignant tumor, 3 from other causes and 5 from unknown causes. We found that 51 patients suffered a recurrence of ischemic stroke during the follow-up period of 1 year. Therefore, the first-year gross recurrence rate of cardioembolic ischemic stroke was 12% (51/425). Two patients had two recurrences in the first year.

A univariate Cox regression analyses was used to evaluate the association between stroke recurrence in all patients, and the clinical characteristics and laboratory data at the time of the initial stroke (table 1). Age (HR 1.04, 95% CI 1.01 to 1.06, p = 0.014), and level of C-reactive protein (HR 1.01, 95% CI 1.00 to 1.02, p = 0.018) on admission were significantly associated with stroke recurrence in the univariate analyses (table 1).
Male gender (HR 0.61, 95% CI 0.35 to 1.05, p = 0.076), BMI (HR 0.94, 95% CI 0.87 to 1.01, p = 0.093), hypertension (HR 0.59, 95% CI 0.33 to 1.06, p = 0.079), diastolic blood pressure (HR 0.99, 95% CI 0.97 to 1.00, p = 0.087), and hematocrit (HR 0.95, 95% CI 0.91 to 1.00, p = 0.052) were marginally significant in the univariate Cox analyses (table 1).

There were no significant differences in the medications prescribed at discharge for the treatment of vascular risk factors (table 2).

The results of multivariate Cox regression analysis for stroke recurrence are shown in table 3. Age (HR 1.03, 95% CI 1.00 to 1.06, p = 0.031, per 1-year increase) and C-reactive protein (HR 1.01, 95% CI 1.00 to 1.02, p = 0.022, per 1-mg/L increase) were independent predictors of stroke recurrence 1 year after onset.

When patients were divided into four groups for analysis according to the median values of age and CRP, older patients (≥ 78 years) with higher CRP (≥ 1.9 mg/L) were at greater risk of stroke recurrence compared with the reference group (age < 78 years, CRP < 1.9 mg/L) (HR 2.36, 95% CI 1.06 to 5.25, p = 0.036, table 4; figure 1). The Kaplan-Meier method was used to estimate the cumulative recurrence rate of stroke in these two groups of patients and the curves were significantly different, as shown in figure 2 (p = 0.027 by the log-rank test).
DISCUSSION

In patients with cardioembolic stroke, we have shown that age and C-reactive protein were independent risk factors for stroke recurrence during the first year of follow-up.

Several epidemiological studies have demonstrated that serum levels of the inflammatory marker CRP are positively associated with the risk of ischemic stroke.[20-22] Many studies showed a significant relationship between elevated CRP and atherosclerosis.[20, 23] Since chronic inflammation directly influences the progression of atherosclerosis, it also enhances the risk of ischemic stroke.

Inflammation is an important factor in ischemic stroke, both in the development of atherosclerosis and during the ischemic event. Thus, CRP levels have attracted clinical attention as a predictive marker of ischemic stroke.

However, several studies showed that CRP does not seem to be related to atherosclerosis of large arteries.[24-26] In particular, a few studies reported significant elevations of CRP levels in patients with cardioembolic stroke.[27-29] According to a study of 196 elderly patients with ischemic stroke, mean values of CRP were significantly higher in patients with cardioembolic stroke compared with atherothrombotic large vessel and lacunar stroke in patients who died in the first 30
days.[27] In a study of 648 stroke patients with CRP levels stratified into quartiles, patients with cardioembolic strokes had CRP levels in the higher quartiles, and CRP was an independent predictor of 14-day mortality.[28] A previous case-control study of 199 stroke patients and 202 randomly selected controls showed an independent relationship between elevated blood levels of CRP and cardioembolic stroke.[29]

Although the mechanism underlying this phenomenon is not clear, several possible explanations have been proposed. First, it seems that CRP is commonly elevated in heart disease.[28, 30] Therefore, plasma CRP levels in patients with cardioembolic stroke could be increased because of the presence of heart disease in these patients. CRP is frequently elevated especially in heart diseases such as heart failure and atrial fibrillation.[31] Furthermore, intracardiac clots that often form in these conditions may serve as a source of emboli. In the study of 880 subjects with atrial fibrillation, CRP was positively correlated to stroke risk and related to stroke prognosis.[32] Second, the binding of CRP to phospholipids, which are involved in the coagulation cascade, are potentially activated by emboli from the heart.[33] Third, in patients with extensive stroke lesions, levels of CRP have been reported to increase.[34, 35] Of all stroke subtypes, patients with cardioembolic stroke have larger lesions [36] and a worse prognosis.[37]
Additionally, recent studies showed that elevated CRP independently predicted the risk of stroke recurrence and transient ischemic attack in the elderly.\cite{38, 39} In the acute phase as well as the chronic phase of stroke, the inflammatory cascade is mediated by an increasing concentration of cytokines, adhesion molecules, proteins, macrophages and leukocytes, and the strength of this response is related to early and late clinical outcomes.\cite{21, 40} Thus, further progression of vascular disease could occur because a chronic inflammatory state may persist after the acute phase.

It was uncertain whether age influences the recurrence of ischemic stroke, though aging is one of the most important overall risk factors for stroke. Age was identified as a risk factor for the recurrence of ischemic stroke in some studies,\cite{8, 41} but not in others.\cite{5, 42, 43} In the present study, age was an independent risk factor for recurrence during the first year after cardioembolic stroke onset. The cumulative effects of advancing age on the cardiovascular system and the progressive nature of stroke risk factors over a prolonged period of time substantially increase the risk of ischemic stroke.

The present study has several limitations. The observational design did not allow us to control any therapy used after the onset of the stroke. In addition, a variety of stroke therapies and complications in the acute and chronic phases might affect
prognosis. Moreover, no information on patient compliance with medical treatment was obtained during the follow-up period after discharge from the hospital. In particular, effectiveness of the anticoagulant treatment was not examined at the time of recurrence.

In addition, a single measurement of CRP on admission may not accurately reflect the status of the patients during the acute phase. Then, we cannot completely exclude the possibility that CRP values are affected by several factors (e.g., rheumatologic, malignancies and deep venous thrombosis) even if it was collected blood samples during an acute phase. Furthermore, as we did not investigate the classification of the recurrent stroke, the explanation about the relationship between CRP and stroke recurrence may be insufficient. In the present study, the sample size was relatively small and the statistical power may be insufficient to draw conclusions. Therefore, further studies with a larger cohort should be conducted in order to resolve these issues.

Even with these limitations, elevated CRP on admission and age were significantly associated with stroke recurrence in patients with cardioembolic stroke. To the best of our knowledge, this is the first study to show that elevation of CRP is strongly associated with stroke recurrence in patients with cardioembolic stroke. In conclusion, age and CRP on admission were found to be independent risk factors for the recurrence of cardioembolic stroke within 1 year of onset.
ACKNOWLEDGMENTS

This study was supported in part by the Japanese Ministry of Education, Culture, Sports, Science and Technology (Coordination, Support and Training Program for Translational Research). The authors are grateful to Associate Professor Hitoshi Inoue in the Research Institute for Information Technology, Kyushu University for his support on the FSR Data Collection System. We also thank all the clinical research coordinators for their help in obtaining informed consent and collecting the clinical data.
APPENDIX

Participating Hospitals in the FSR: Kyushu University Hospital, National Hospital Organization Kyushu Medical Center, National Hospital Organization Fukuoka Higashi Medical Center, Fukuoka Red Cross Hospital, St. Mary’s Hospital, Nippon Steel Yawata Memorial Hospital, Japan Labour Health and Welfare Organization Kyushu Rosai Hospital.

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11) Department of Cerebrovascular Disease, Fukuoka Red Cross Hospital

12) Department of Internal Medicine, Seiai Rehabilitation Hospital

13) Yoshizuka Hayashi Hospital
REFERENCES


5. **Hillen T**, Coshall C, Tilling K, *et al.*; South London Stroke Register. Cause of stroke recurrence is multifactorial: patterns, risk factors, and outcomes of stroke...


Committee for Epidemiology and Clinical Management of Atherosclerosis.


FIGURE LEGENDS

Figure 1

Hazard ratio and 95% CI of four risk groups for stroke recurrence. Four groups were classified by the median value of age and CRP.

Figure 2

Kaplan-Meier estimates of the cumulative recurrence rate of stroke after patients were stratified according to the combination of the median value of age and CRP. A significant difference in recurrence rate was observed between the patients with age ≥ 78 years and CRP ≥ 1.9 mg/L (solid line) on admission and those with age < 78 years and CRP < 1.9 mg/L (dotted line, p = 0.027 by log-rank test). Censored cases with death are indicated as (+).
Table 1 Clinical characteristics of the patients and univariate Cox hazard ratios for stroke recurrence

<table>
<thead>
<tr>
<th>Baseline Characteristic or Risk Factor</th>
<th>Recurrence (+) n = 51</th>
<th>Recurrence (-) n = 374</th>
<th>HR (95%CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>79.6 ± 10.4</td>
<td>75.5 ± 11.0</td>
<td>1.04 (1.01-1.06)</td>
<td>0.014*</td>
</tr>
<tr>
<td>Male gender</td>
<td>43%</td>
<td>57%</td>
<td>0.61 (0.35-1.05)</td>
<td>0.076</td>
</tr>
<tr>
<td>BMI</td>
<td>21.3 ± 3.2</td>
<td>22.3 ± 3.8</td>
<td>0.94 (0.87-1.01)</td>
<td>0.093</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>79.5 ± 9.5</td>
<td>81.8 ± 10.9</td>
<td>0.98 (0.96-1.01)</td>
<td>0.156</td>
</tr>
<tr>
<td>Smoking</td>
<td>31%</td>
<td>39%</td>
<td>0.73 (0.41-1.33)</td>
<td>0.305</td>
</tr>
<tr>
<td>Drinking</td>
<td>31%</td>
<td>37%</td>
<td>0.78 (0.43-1.41)</td>
<td>0.410</td>
</tr>
<tr>
<td>Hypertension</td>
<td>67%</td>
<td>78%</td>
<td>0.59 (0.33-1.06)</td>
<td>0.079</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>20%</td>
<td>24%</td>
<td>0.78 (0.39-1.56)</td>
<td>0.484</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>28%</td>
<td>37%</td>
<td>0.66 (0.36-1.21)</td>
<td>0.179</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>18%</td>
<td>25%</td>
<td>0.68 (0.33-1.40)</td>
<td>0.294</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>82%</td>
<td>81%</td>
<td>1.14 (0.56-2.34)</td>
<td>0.720</td>
</tr>
<tr>
<td>Previous ischemic stroke</td>
<td>28%</td>
<td>21%</td>
<td>1.35 (0.73-2.50)</td>
<td>0.336</td>
</tr>
<tr>
<td>Findings on Admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP on admission, mm Hg</td>
<td>147 ± 25</td>
<td>154 ± 28</td>
<td>0.99 (0.98-1.00)</td>
<td>0.153</td>
</tr>
<tr>
<td>DBP on admission, mm Hg</td>
<td>79 ± 15</td>
<td>83 ± 18</td>
<td>0.99 (0.97-1.00)</td>
<td>0.087</td>
</tr>
<tr>
<td>Urine protein</td>
<td>39%</td>
<td>37%</td>
<td>1.08 (0.49-2.38)</td>
<td>0.851</td>
</tr>
<tr>
<td>Urine glucose</td>
<td>19%</td>
<td>19%</td>
<td>0.99 (0.38-2.64)</td>
<td>0.990</td>
</tr>
<tr>
<td>eGFR, ml/min/1.73m²</td>
<td>61.0 ± 21.3</td>
<td>63.7 ± 23.2</td>
<td>0.99 (0.98-1.01)</td>
<td>0.995</td>
</tr>
<tr>
<td>eGFR &lt; 60 ml/min/1.73m²</td>
<td>39%</td>
<td>46%</td>
<td>0.80 (0.46-1.41)</td>
<td>0.439</td>
</tr>
<tr>
<td>CKD</td>
<td>51%</td>
<td>52%</td>
<td>0.97 (0.56-1.68)</td>
<td>0.907</td>
</tr>
<tr>
<td>EF &lt; 55%</td>
<td>15%</td>
<td>22%</td>
<td>0.64 (0.29-1.43)</td>
<td>0.278</td>
</tr>
<tr>
<td>NIHSS score on admission</td>
<td>7 (3 to 16)</td>
<td>8 (5 to 16)</td>
<td>1.01 (0.98-1.04)</td>
<td>0.619</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>18%</td>
<td>13%</td>
<td>1.40 (0.68-2.88)</td>
<td>0.357</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>14%</td>
<td>11%</td>
<td>1.28 (0.58-2.85)</td>
<td>0.541</td>
</tr>
</tbody>
</table>

Laboratory Data on Admission

<table>
<thead>
<tr>
<th></th>
<th>Recurrence (+) n = 51</th>
<th>Recurrence (-) n = 374</th>
<th>HR (95%CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC, /mm³</td>
<td>6643 ± 2105</td>
<td>7164 ± 2354</td>
<td>1.00 (1.00-1.00)</td>
<td>0.148</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>38.0 ± 6.0</td>
<td>39.6 ± 5.5</td>
<td>0.95 (0.91-1.00)</td>
<td>0.052</td>
</tr>
<tr>
<td>Total protein, g/dL</td>
<td>6.9 ± 0.6</td>
<td>7.0 ± 0.6</td>
<td>0.94 (0.61-1.45)</td>
<td>0.778</td>
</tr>
<tr>
<td>LDL cholesterol ≥ 140 mg/dL</td>
<td>13%</td>
<td>17%</td>
<td>0.73 (0.29-1.87)</td>
<td>0.513</td>
</tr>
<tr>
<td>HDL cholesterol &lt; 40 mg/dL</td>
<td>19%</td>
<td>19%</td>
<td>1.02 (0.49-2.11)</td>
<td>0.962</td>
</tr>
<tr>
<td>LDL-chol / HDL-chol</td>
<td>2.1 ± 0.7</td>
<td>2.2 ± 1.0</td>
<td>0.85 (0.59-1.22)</td>
<td>0.385</td>
</tr>
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</tr>
<tr>
<td>Triglyceride ≥ 150 mg/dL</td>
<td>17%</td>
<td>18%</td>
<td>0.94 (0.44-2.01)</td>
<td>0.869</td>
</tr>
<tr>
<td>Blood glucose, mg/dL</td>
<td>139 ± 49</td>
<td>134 ± 54</td>
<td>1.00 (0.99-1.01)</td>
<td>0.576</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>5.5 ± 0.8</td>
<td>5.7 ± 1.40</td>
<td>0.82 (0.58-1.16)</td>
<td>0.260</td>
</tr>
<tr>
<td>sCr, mg/dL</td>
<td>1.03 ± 1.07</td>
<td>1.02 ± 1.05</td>
<td>1.01 (0.78-1.31)</td>
<td>0.934</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>1.6 (0.6 to 13.0)</td>
<td>1.8 (0.5 to 6.0)</td>
<td>1.01 (1.00-1.02)</td>
<td>0.018*</td>
</tr>
</tbody>
</table>

**Stroke Location**

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Posterior circulation</td>
<td>20%</td>
<td>19%</td>
<td>1.04 (0.52-2.07)</td>
<td>0.923</td>
</tr>
</tbody>
</table>

BMI, body mass index; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; EF, ejection fraction; HR, hazard ratio; CI, confidence interval.

Data are the mean ± SD for age, BMI, waist circumference, SBP, DBP, eGFR, WBC, Hematocrit, Total protein, LDL-chol / HDL-chol, Blood glucose, HbA1c, and sCr. The median (interquartile range) is shown for NIHSS, CRP, and % for the other variables.

*: P < 0.05
Table 2 Medications prescribed at discharge and univariate Cox hazard ratios for stroke recurrence

<table>
<thead>
<tr>
<th>Medication</th>
<th>Recurrence (+)</th>
<th>Recurrence (-)</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiplatelet</td>
<td>16% n = 51</td>
<td>21% n = 374</td>
<td>0.70 (0.33-1.48)</td>
<td>0.348</td>
</tr>
<tr>
<td>Anticoagulant</td>
<td>88%</td>
<td>90%</td>
<td>0.86 (0.37-2.01)</td>
<td>0.728</td>
</tr>
<tr>
<td>Antihypertensive</td>
<td>53%</td>
<td>61%</td>
<td>0.74 (0.43-1.28)</td>
<td>0.279</td>
</tr>
<tr>
<td>Calcium-channel blocker</td>
<td>21%</td>
<td>21%</td>
<td>1.01 (0.52-1.97)</td>
<td>0.980</td>
</tr>
<tr>
<td>ARB</td>
<td>23%</td>
<td>24%</td>
<td>0.97 (0.51-1.86)</td>
<td>0.932</td>
</tr>
<tr>
<td>β-blocker</td>
<td>14%</td>
<td>22%</td>
<td>0.58 (0.26-1.29)</td>
<td>0.183</td>
</tr>
<tr>
<td>Diuretic</td>
<td>26%</td>
<td>19%</td>
<td>1.40 (0.75-2.63)</td>
<td>0.293</td>
</tr>
<tr>
<td>HMG-CoA reductase inhibitor</td>
<td>16%</td>
<td>21%</td>
<td>0.71 (0.34-1.52)</td>
<td>0.380</td>
</tr>
</tbody>
</table>

ARB, angiotensin receptor blocker;

HMG-CoA reductase inhibitor, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitor.

Data are expressed as %, HR, hazard ratio; CI, confidence interval.
Table 3 Multivariate Cox hazards ratios for stroke recurrence

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, per 1-year increase</td>
<td>1.03 (1.00—1.06)</td>
<td>0.031*</td>
</tr>
<tr>
<td>C-reactive protein, per 1-mg/L increase</td>
<td>1.01 (1.00—1.02)</td>
<td>0.022*</td>
</tr>
</tbody>
</table>

HR, hazard ratio; CI, confidence interval.

*: p < 0.05 by multivariate Cox regression analysis using sex, age, pneumonia and urinary tract infections as well as the clinical characteristics which showed a significant (p < 0.05) or marginally significant (0.05 ≤ p < 0.1) correlation with stroke recurrence in the univariate analyses.
**Table 4** Cox proportional hazards analysis of four risk groups derived from the median value of age and CRP

<table>
<thead>
<tr>
<th></th>
<th>R/N</th>
<th>Hazard ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 78 y, CRP &lt; 1.9 mg/L</td>
<td>9/115</td>
<td>1.00 (reference)</td>
<td></td>
</tr>
<tr>
<td>Age &lt; 78 y, CRP ≥ 1.9 mg/L</td>
<td>8/107</td>
<td>1.41 (0.50—3.97)</td>
<td>0.511</td>
</tr>
<tr>
<td>Age ≥ 78 y, CRP &lt; 1.9 mg/L</td>
<td>16/102</td>
<td>2.21 (0.98—5.00)</td>
<td>0.057</td>
</tr>
<tr>
<td>Age ≥ 78 y, CRP ≥ 1.9 mg/L</td>
<td>18/101</td>
<td>2.36 (1.06—5.25)</td>
<td>0.036*</td>
</tr>
</tbody>
</table>

R, recurrence; N, total number of subjects; HR, hazard ratio; CI, confidence interval.

*: P < 0.05
Figure 1

<table>
<thead>
<tr>
<th>Age</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 78 y, CRP &lt; 1.9 mg/L</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Age ≥ 78 y, CRP ≥ 1.9 mg/L</td>
<td>1.41 (0.50 - 3.97)</td>
<td>0.511</td>
</tr>
<tr>
<td>Age ≥ 78 y, CRP ≥ 1.9 mg/L</td>
<td>2.21 (0.98 - 5.00)</td>
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</tr>
<tr>
<td>Age ≥ 78 y, CRP ≥ 1.9 mg/L</td>
<td>2.36 (1.06 - 5.25)</td>
<td>0.036</td>
</tr>
</tbody>
</table>

Hazard ratio

119x90mm (300 x 300 DPI)
Figure 2

Cumulative risk for recurrence

- Age ≥ 78 y, CRP ≥ 1.9 mg/L
- Age < 78 y, CRP < 1.9 mg/L

119x90mm (300 x 300 DPI)
<table>
<thead>
<tr>
<th>Item No</th>
<th>Title and abstract</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| 1       | (a) Indicate the study’s design with a commonly used term in the title or the abstract  
|         | (b) Provide in the abstract an informative and balanced summary of what was done and what was found |

**Introduction**

<table>
<thead>
<tr>
<th>Item No</th>
<th>Background/rationale</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Explain the scientific background and rationale for the investigation being reported</td>
<td></td>
</tr>
</tbody>
</table>

**Objectives**

<table>
<thead>
<tr>
<th>Item No</th>
<th>Objectives</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>State specific objectives, including any prespecified hypotheses</td>
<td></td>
</tr>
</tbody>
</table>

**Methods**

<table>
<thead>
<tr>
<th>Item No</th>
<th>Study design</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Present key elements of study design early in the paper</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Item No</th>
<th>Setting</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Item No</th>
<th>Participants</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| 6       | (a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up  
|         | (b) For matched studies, give matching criteria and number of exposed and unexposed |

**Variables**

<table>
<thead>
<tr>
<th>Item No</th>
<th>Variables</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Item No</th>
<th>Data sources/measurement</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>8*</td>
<td>For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group</td>
<td></td>
</tr>
</tbody>
</table>

**Bias**

<table>
<thead>
<tr>
<th>Item No</th>
<th>Bias</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>Describe any efforts to address potential sources of bias</td>
<td></td>
</tr>
</tbody>
</table>

**Study size**

<table>
<thead>
<tr>
<th>Item No</th>
<th>Study size</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Explain how the study size was arrived at</td>
<td></td>
</tr>
</tbody>
</table>

**Quantitative variables**

<table>
<thead>
<tr>
<th>Item No</th>
<th>Quantitative variables</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why</td>
<td></td>
</tr>
</tbody>
</table>

**Statistical methods**

<table>
<thead>
<tr>
<th>Item No</th>
<th>Statistical methods</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| 12      | (a) Describe all statistical methods, including those used to control for confounding  
|         | (b) Describe any methods used to examine subgroups and interactions  
|         | (c) Explain how missing data were addressed  
|         | (d) If applicable, explain how loss to follow-up was addressed  
|         | (e) Describe any sensitivity analyses |

**Results**

<table>
<thead>
<tr>
<th>Item No</th>
<th>Participants</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| 13*     | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed  
|         | (b) Give reasons for non-participation at each stage  
|         | (c) Consider use of a flow diagram |

<table>
<thead>
<tr>
<th>Item No</th>
<th>Descriptive data</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| 14*     | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders  
|         | (b) Indicate number of participants with missing data for each variable of interest  
|         | (c) Summarise follow-up time (eg, average and total amount) |

<table>
<thead>
<tr>
<th>Item No</th>
<th>Outcome data</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>15*</td>
<td>Report numbers of outcome events or summary measures over time</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Item No</th>
<th>Main results</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| 16      | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included  
|         | (b) Report category boundaries when continuous variables were categorized  
|         | (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period |
Other analyses 17 Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses

Discussion

Key results 18 Summarise key results with reference to study objectives

Limitations 19 Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias

Interpretation 20 Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence

Generalisability 21 Discuss the generalisability (external validity) of the study results

Other information

Funding 22 Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.