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

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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: Multicentre study at the Fukuoka prefecture in Japan.

Participants: We enroled 2084 consecutive patients who were hospitalised in stroke centres 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 men, 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 (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 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 haematocrit (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 ischaemic stroke, age and C reactive protein are independent risk factors for recurrence in the first year after onset.

Strengths and limitations of this study

- The present study is a multicentre, prospective cohort research in which acute stroke patients are enroled within 7 days of onset.
- This is the first study to show that elevation of C reactive protein is strongly associated with stroke recurrence in patients with cardioembolic stroke.
- 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 ischaemic 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 (8–12% of all stroke patients).[5–7] Therefore, for the prevention of ischaemic 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 ischaemic 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 ischaemic stroke to identify the risk factors associated with the recurrence of ischaemic stroke in the first year after onset. To determine an

appropriate treatment strategy for each subtype of stroke, we investigated different subtypes of ischaemic 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

Fukuoka Stroke Registry (FSR) is a multicentre, prospective cohort study in which acute stroke patients are enroled within 7 days of onset. Patients admitted to one of the seven clinical stroke centres (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 harmonisation in the FSR have been described previously.[12]

Study patients

We enroled 2084 consecutive ischaemic stroke patients (1262 men, 822 women, 71±12 years of age) registered in FSR from June 2007 to October 2009. Stroke was defined as the sudden onset of non-convulsive and focal neurological deficit persisting for >24 h. All of the patients underwent brain CT, MRI or both within 24 h of hospitalisation. 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, haematocrit, total protein, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, blood glucose, haemoglobin A1c, serum creatinine (sCr) and C reactive protein (CRP), were obtained on admission. We collected blood samples within 24 h 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 dyslipidaemia.[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 (mL/min/1.73 m^2)=194×$sCr^{-1.094}$×$Age^{-0.287}$ in men and 194×$sCr^{-1.094}$×$Age^{-0.287}$×0.739 in women. Chronic kidney disease 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 mm Hg, diastolic blood pressure ≥90 mm Hg 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); dyslipidaemia (LDL cholesterol ≥140 mg/dL, HDL cholesterol <40 mg/dL, triglycerides ≥150 mg/dL or a history of antihypercholesterolaemic medication); ischaemic heart disease or atrial fibrillation; smoking habit (previous and current); alcohol consumption (including occasional drinking) and previous ischaemic stroke. Furthermore, the ejection fraction 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 score. Moreover, we investigated the frequency of infections such as pneumonia and urinary tract infections in acute phase. The medications (antithrombotic, antihypertensive and antihypercholesterolaemic) 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 ischaemic stroke. According to the results of neuroimaging and neurological examinations, we categorised all ischaemic strokes into the following four subtypes: large-artery atherosclerosis, cardioembolism, small-vessel occlusion and others (stroke of other determined aetiology and stroke of undetermined aetiology). In addition, localisation 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 co-ordinators who were blinded to the information obtained during hospitalisation. 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 IQR. We used a univariate Cox proportional hazards regression model to identify the individual baseline characteristics that were significant predictors of stroke recurrence. HR and their 95% 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, V.19.0 for Windows (SPSS Inc, Chicago, Illinois, USA).

RESULTS

We detected stroke due to large-artery atherosclerosis in 493 patients, cardioembolism in 425, small-vessel occlusion in 583 and other aetiologies (stroke of other or

Table 1 Clinical characteristics of the patients and univariate Cox HRs for stroke recurrence

	Recurrence (+) n=51	Recurrence (–) n=374	HR (95% CI)	p Value
Baseline characteristic or risk factor				
Age (year)	79.6±10.4	75.5±11.0	1.04 (1.01 to 1.06)	0.014*
Male gender	43%	57%	0.61 (0.35 to 1.05)	0.076
BMI	21.3±3.2	22.3±3.8	0.94 (0.87 to 1.01)	0.093
Waist circumference (cm)	79.5±9.5	81.8±10.9	0.98 (0.96 to 1.01)	0.156
Smoking	31%	39%	0.73 (0.41 to 1.33)	0.305
Drinking	31%	37%	0.78 (0.43 to 1.41)	0.410
Hypertension	67%	78%	0.59 (0.33 to 1.06)	0.079
Diabetes mellitus	20%	24%	0.78 (0.39 to 1.56)	0.484
Dyslipidaemia	28%	37%	0.66 (0.36 to 1.21)	0.179
Ischaemic heart disease	18%	25%	0.68 (0.33 to 1.40)	0.294
Atrial fibrillation	82%	81%	1.14 (0.56 to 2.34)	0.720
Previous ischaemic stroke	28%	21%	1.35 (0.73 to 2.50)	0.336
Findings on admission				
SBP on admission (mm Hg)	147±25	154±28	0.99 (0.98 to 1.00)	0.153
DBP on admission (mm Hg)	79±15	83±18	0.99 (0.97 to 1.00)	0.087
Urine protein	39%	37%	1.08 (0.49 to 2.38)	0.851
Urine glucose	19%	19%	0.99 (0.38 to 2.64)	0.990
eGFR (mL/min/1.73 m^2)	61.0±21.3	63.7±23.2	0.99 (0.98 to 1.01)	0.995
eGFR <60 mL/min/1.73 m^2	39%	46%	0.80 (0.46 to 1.41)	0.439
CKD	51%	52%	0.97 (0.56 to 1.68)	0.907
EF <55%	15%	22%	0.64 (0.29 to 1.43)	0.278
NIHSS score on admission	7 (3–16)	8 (5–16)	1.01 (0.98 to 1.04)	0.619
Pneumonia	18%	13%	1.40 (0.68 to 2.88)	0.357
Urinary tract infection	14%	11%	1.28 (0.58 to 2.85)	0.541
Laboratory data on admission				
WBC, /mm^3	6643±2105	7164±2354	1.00 (1.00 to 1.00)	0.148
Haematocrit, %	38.0±6.0	39.6±5.5	0.95 (0.91 to 1.00)	0.052
Total protein, g/dL	6.9±0.6	7.0±0.6	0.94 (0.61 to 1.45)	0.778
LDL cholesterol ≥140 mg/dL	13%	17%	0.73 (0.29 to 1.87)	0.513
HDL cholesterol <40 mg/dL	19%	19%	1.02 (0.49 to 2.11)	0.962
LDL-cholesterol/HDL-cholesterol	2.1±0.7	2.2±1.0	0.85 (0.59 to 1.22)	0.385
Triglyceride ≥150 mg/dL	17%	18%	0.94 (0.44 to 2.01)	0.869
Blood glucose, mg/dL	139±49	134±54	1.00 (0.99 to 1.01)	0.576
HbA1c, %	5.5±0.8	5.7±1.40	0.82 (0.58 to 1.16)	0.260
sCr, mg/dL	1.03±1.07	1.02±1.05	1.01 (0.78 to 1.31)	0.934
CRP, mg/L	1.6 (0.6–13.0)	1.8 (0.5–6.0)	1.01 (1.00 to 1.02)	0.018*
Stroke location				
Posterior circulation	20%	19%	1.04 (0.52 to 2.07)	0.923

*p<0.05.
Data are the mean±SD for age, BMI, waist circumference, SBP, DBP, eGFR, WCC, haematocrit, total protein, LDL-cholesterol/HDL-cholesterol, blood glucose, HbA1c and sCr. The median (IQR) is shown for NIHSS, CRP and per cent for the other variables.
ARB, angiotensin receptor blocker; BMI, body mass index; CKD, chronic kidney disease; CRP, C reactive protein; DBP, diastolic blood pressure; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HbAlc, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure; sCr, serum creatinine; WCC, white cell count.

Table 2 Medications prescribed at discharge and univariate Cox FRs for stroke recurrence

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

Data are expressed as %.
ARB, angiotensin receptor blocker; HMG-CoA reductase inhibitor, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitor.

undetermined aetiology) in 583 among the 2084 consecutive patients. In the present study, 425 patients (234 men and 191 women, 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 ischaemic stroke, 3 from cerebral haemorrhage, 7 from cardiovascular diseases, 4 from pneumonia, 3 from malignant tumour, 3 from other causes and 5 from unknown causes. We found that 51 patients suffered a recurrence of ischaemic stroke during the follow-up period of 1 year. Therefore, the first-year gross recurrence rate of cardioembolic ischaemic 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 CRP (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 haematocrit (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 for the treatment of vascular risk factors at discharge (table 2).

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

Table 3 Multivariate Cox HRs for stroke recurrence

	HR (95% CI)	p Value
Age, per 1-year increase	1.03 (1.00 to 1.06)	0.031*
C reactive protein, per 1 mg/L increase	1.01 (1.00 to 1.02)	0.022*

*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

	R/N	HR (95% CI)	p Value
Age <78 year, CRP <1.9 mg/L	9/115	1.00 (reference)	
Age <78 year, CRP ≥1.9 mg/L	8/107	1.41 (0.50 to 3.97)	0.511
Age ≥78 year, CRP <1.9 mg/L	16/102	2.21 (0.98 to 5.00)	0.057
Age ≥78 year, CRP ≥1.9 mg/L	18/101	2.36 (1.06 to 5.25)	0.036*

*p<0.05.
CRP, C reactive protein; N, total number of patients; R, recurrence.

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 patients 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 ischaemic 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 leucocytes, 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 ischaemic stroke, though ageing is one of the most important overall risk factors for stroke. Age was identified as a risk factor for the recurrence of ischaemic 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 ischaemic 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

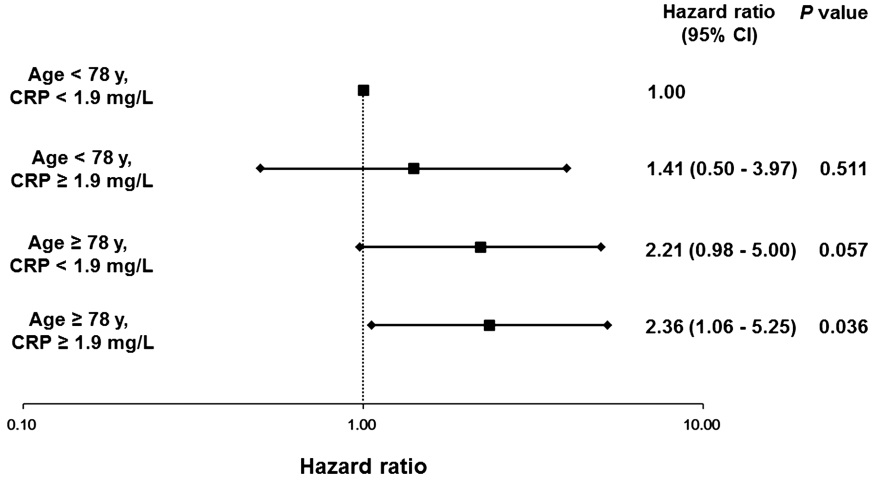

Figure 1 HR and 95% CI of four risk groups for stroke recurrence. Four groups were classified by the median value of age and C reactive protein.

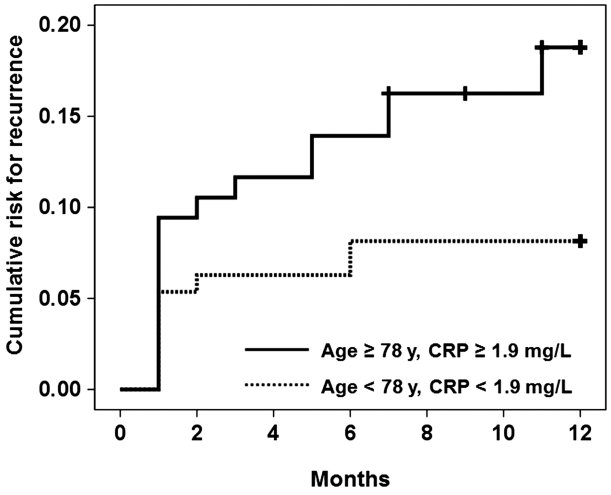

Figure 2 Kaplan-Meier estimates of the cumulative recurrence rate of stroke after patients were stratified according to the combination of the median value of age and C reactive protein (CRP). A significant difference in recurrence rate was observed between the patients with age ≥78 years and CRP ≥1.9 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 (+).

status of the patients during the acute phase. Thus, we could not exclude the possibility that CRP values were affected by several factors (eg, rheumatological, malignancies and deep vein thrombosis) even though we made every effort to avoid this by collecting blood samples only 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.

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Contributors TKu and HS contributed to the drafting of the manuscript for content, study concept, analysis, acquisition and statistical analysis of the data. TA and JK contributed to the study concept, analysis and acquisition of the data. MK and TKi contributed to the study concept and study supervision.

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Patient consent Obtained.

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APPENDIX

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