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ORIGINAL RESEARCH

Predictors of Survival in Patients With Ischemic Stroke and Active Cancer: A Prospective, Multicenter, Observational Study

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BACKGROUND: Limited data exist on the prognostic factors for patients with ischemic stroke and active cancer.

METHODS AND RESULTS: We conducted a prospective, multicenter, observational study in Japan, including patients with acute ischemic stroke and active cancer, to investigate the prognostic factors. We followed up the patients for 1 year after stroke onset. The patients were divided into 2 groups according to cryptogenic stroke and known causes (small-vessel occlusion, large-artery atherosclerosis, cardioembolism, and other determined cause), and survival was compared. The hazard ratios (HRs) and 95% CIs for mortality were calculated using Cox regression models. We identified 135 eligible patients (39% women; median age, 75 years). Of these patients, 51% had distant metastasis. A total of 65 (48%) and 70 (52%) patients had cryptogenic stroke and known causes, respectively. Patients with cryptogenic stroke had significantly shorter survival than those with known causes (HR [95% CI], 3.11 [1.82–5.32]). The multivariable Cox regression analysis revealed that distant metastasis, plasma D-dimer levels, venous thromboembolism (either deep venous thrombosis or pulmonary embolism) complications at stroke onset were independent predictors of mortality after adjusting for potential confounders. Cryptogenic stroke was associated with prognosis in univariable analysis but was not significant in multivariable analysis. The plasma D-dimer levels stratified the prognosis of patients with ischemic stroke and active cancer.

CONCLUSIONS: The prognosis of patients with acute ischemic stroke and active cancer varied considerably depending on stroke mechanism, distant metastasis, and coagulation abnormalities. The present study confirmed that coagulation abnormalities were crucial in determining the prognosis of such patients.

Key Words: active cancer ■ cryptogenic stroke ■ D-dimer ■ distant metastasis ■ ischemic stroke

Patients with cancer are at increased risk of cerebrovascular diseases.[1,2] Stroke is a significant concern for patients with cancer because it can interrupt cancer treatments and worsen survival outcomes.[1–5] Management of cancer and stroke is an important aspect of clinical practice.

Patients with ischemic stroke and active cancer experience poor survival outcomes. Lee et al investigated 268 patients with ischemic stroke and active cancer using data from the OASIS-Cancer (Optimal Anticoagulation Strategy in Stroke Related to Cancer) study and reported a median survival of 109 days.[6]

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CLINICAL PERSPECTIVE

What Is New?

- We conducted a prospective, multicenter, observational study in Japan to determine the prognostic survival factors in patients with acute ischemic stroke and active cancer.
- Distant metastasis, plasma D-dimer levels, venous thromboembolism, (either deep venous thromboembolism or pulmonary embolism) were independent predictors of mortality after adjusting for potential confounders.
- Patients with known stroke causes and mild coagulation abnormalities had a favorable prognosis, whereas those with cryptogenic stroke and severe coagulation abnormalities had a poor outcome.

What Are the Clinical Implications?

- The prognosis of patients with acute ischemic stroke and active cancer varies considerably depending on stroke mechanism, distant metastasis, and coagulation abnormalities.
- Patients who have known stroke causes and mild coagulation abnormalities generally have a favorable prognosis; hence, it is important not to withhold stroke therapy solely because of the presence of active cancer.
- Patients with cryptogenic stroke and severe coagulation abnormalities often experience poor outcomes; therefore, engaging in thorough discussions with the oncologist is crucial to establish an appropriate treatment plan.

Nonstandard Abbreviations and Acronyms

SCAN	Ischemic Stroke in Patients With Cancer and Neoplasia
TOAST	Trial of Org 10172 in Acute Stroke Treatment

Navi et al analyzed 263 patients with ischemic stroke and active cancer and found a median survival of 84 days for 230 patients with complete follow-up.[7] Shin et al investigated 93 patients with cryptogenic stroke and active cancer and showed a median survival of 62 days.[8] Other studies compared ischemic stroke outcomes in patients with and without active cancer, suggesting that patients with ischemic stroke and with active cancer have poorer outcomes than those without ischemic stroke.[9–13] Overall, patients with ischemic stroke and active cancer are known to have poor survival outcomes. However, most of these studies are retrospective,[7–12] and limited data are available about prospective studies.[6,13]

The prognostic indicators of survival are poorly understood in patients with ischemic stroke and active cancer.[14] Previous studies have suggested that distant metastasis, diabetes, plasma D-dimer levels, cryptogenic stroke, and prestroke modified Rankin Scale score were associated with mortality.[8,15–17] Among these factors, cryptogenic stroke is a common ischemic stroke subtype in patients with active cancer.[15,18–20] It is also known that plasma D-dimer levels are high in patients with cancer and with cryptogenic stroke.[18–20] Thus, the fact that both cryptogenic stroke and plasma D-dimer levels predict prognosis may reflect underlying coagulation abnormalities. However, the relationship between cryptogenic stroke and plasma D-dimer levels in predicting cancer-related stroke prognosis has been underexplored.

On the basis of this background, we conducted a prospective, multicenter, observational study of patients with ischemic stroke and with cancer (SCAN [Ischemic Stroke in Patients With Cancer and Neoplasia] study) in Japan. The SCAN study was designed to assess the clinical characteristics of cancer-related strokes. In the present study, we analyzed the survival of patients with acute ischemic stroke and active cancer according to the stroke subtype, using data from the SCAN study.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Standard Protocol Approvals, Registrations, and Patient Consent

This study complied with the Declaration of Helsinki for investigations involving humans and was approved by the Institutional Review Board of Osaka University Hospital (approval number: 15346-10). Written informed consent was obtained from all study patients.

Study Design and Population

The SCAN study is a prospective, multicenter, observational study conducted at 9 hospitals in Japan, between June 2016 and December 2021 (Osaka University Hospital, Osaka General Medical Center, National Cerebral and Cardiovascular Center Hospital, National Hospital Organization Osaka National Hospital, Osaka Rosai Hospital, Kobe City Medical Center General Hospital, National Hospital Organization Osaka Minami Medical Center, Yodogawa Christian Hospital, and Hoshigaoka Medical Center). All hospitals included the SCAN study function as regional stroke centers.

The inclusion criteria for this study were as follows: (1) acute ischemic stroke within 14 days following symptom onset, (2) age ≥20 years, and (3) active cancer at stroke onset. Active cancer was defined as a diagnosis of cancer, either treated in the past 6 months before admission or untreated, or metastatic disease. The SCAN study aimed to enroll ≈250 patients over a 5-year study period, with a 1-year follow-up from the enrollment date to investigate the prognosis of patients with acute ischemic stroke and active cancer.

Clinical Variables

The following baseline variables were obtained from the SCAN study database: age, sex, hypertension, dyslipidemia, diabetes, smoking, atrial fibrillation, past stroke, time from symptom onset to admission, antithrombotic (either antiplatelet or anticoagulant) medication before and after stroke onset, stroke subtype, National Institutes of Health Stroke Scale score, prestroke modified Rankin Scale score, either deep venous thrombosis or pulmonary embolism (DVT/PE) complications at stroke onset, infarct pattern of brain imaging, use of recombinant-tissue plasminogen activator, mechanical thrombectomy, and cancer-related data, including cancer type, distant metastasis, adenocarcinoma, and cancer treatment (cancer surgery, chemotherapy, and radiotherapy). We also collected the recurrent stroke and major bleeding information during the observation period. Stroke recurrence was defined as a new neurologic deficit together with corresponding evidence of acute ischemia or hematoma on brain imaging (computed tomography or magnetic resonance imaging). Major bleeding was defined as clinically overt bleeding that was accompanied by ≈1 of the following: a decrease in hemoglobin levels of at least 2 g/dL or the requirement of a transfusion with at least 2 units of packed red blood cells; symptomatic bleeding requiring immediate treatment that occurred at a critical site, such as intracranial, intraocular, intraspinal, intra-articular, intramuscular with compartment syndrome, pericardial, or retroperitoneal; or bleeding that was fatal.[21] Blood samples were collected immediately after admission before any treatment started, and plasma D-dimer and hs-CRP (high-sensitivity C-reactive protein) levels were quantified.

Subtypes of ischemic stroke were classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria: small-vessel occlusion, large-artery atherosclerosis, cardioembolism, other determined cause, and stroke of undetermined cause.[22] All the patients underwent blood tests, 24-hour electrocardiographic monitoring at least 7 days after admission, carotid ultrasonography, and brain imaging (computed tomography or magnetic resonance imaging). Transthoracic and transesophageal echocardiography was performed as necessary. We determined that patients had a cryptogenic stroke if the cause could not be determined with any degree of confidence.[22] Patients with no apparent cause of ischemic stroke other than malignancies were categorized as having a cryptogenic stroke.

Follow-Up Duration and Outcomes

The observation period was 1 year after the diagnosis of ischemic stroke. All the patients were followed up via telephone or outpatient visits. The incidences of death, stroke recurrence, and major bleeding were investigated.

Statistical Analysis

Descriptive statistics were presented using the median and interquartile range (IQR) for continuous variables and as proportions and counts for categorical variables.

First, we summarized the baseline characteristics of the cohort. Next, we divided the patients into 2 groups based on the cryptogenic stroke and known causes (small-vessel occlusion, large-artery atherosclerosis, cardioembolism, and other determined causes) and verified the survival rates against previously reported findings.[8,15] Values were compared using the Mann-Whitney *U* test for continuous variables and the χ^2 test for categorical variables. Survival rates for all-cause mortality were calculated using the Kaplan-Meier method. Finally, we estimated hazard ratios (HRs) and 95% CIs for mortality using univariable and multivariable Cox proportional hazard models. On the basis of clinical experience, we selected the following variables as potential confounders: age, sex, hypertension, dyslipidemia, diabetes, atrial fibrillation, prestroke modified Rankin Scale score ≤2, National Institutes of Health Stroke Scale score, distant metastasis, cryptogenic stroke, recurrent stroke, major bleeding, past stroke, prestroke antithrombotic use, prestroke cancer treatment status, DVT/PE complications at stroke onset, and plasma D-dimer levels. In the multivariable analysis, we developed 3 models to identify independent predictors of prognosis: the forced entry method for all potential confounders (model 1) and for the variables with $P<0.1$ in the univariable analysis (model 2), and the stepwise selection method to address the possibility of multicollinearity (model 3). Because we were interested in cryptogenic stroke as a prognostic marker for survival, the stroke mechanism was forced to be included in all models, and other factors in model 3 were selected using a stepwise procedure with Akaike information criterion.[23] Recurrent stroke and major bleeding were treated as time-varying variables. Plasma D-dimer levels were divided into quartiles, and the first quartile was used as a reference.

The cumulative incidence of recurrent stroke and major bleeding during the observation period was calculated using the Fine and Gray model,[24] with death as a competing risk. The incidence was compared with the use of antithrombotic medications.

Statistical analysis was performed using the R software (https://cran.r-project.org/). The level of significance was set at $P<0.05$. All tests were 2-tailed.

RESULTS

Study Population and Characteristics of the Patients According to Stroke Subtypes

A total of 135 patients were included in the analysis. Table 1 lists the cancer types of the included patients and whether distant metastasis was present. The most common types of cancers were lung (16%), colorectal (14%), pancreatic (13%), prostate (9%), and gastric (8%) cancers. Distant metastasis was observed in 51% (n=69) of the patients.

Table 2 summarizes the characteristics of the study cohort. Overall, the median (IQR) age was 75 (69–81) years, and 39% of the patients were women. The median (IQR) time from symptom onset to admission was 0 (0–2) days. Antithrombotic medications were used in 30% of the patients before stroke and 82% after ischemic stroke (breakdown of antithrombotic medications after stroke is shown in Table S1). Cryptogenic stroke was the most common stroke subtype (48%), and other determined cause was the least common (7%). The median (IQR) National Institutes of Health Stroke Scale score was 4 (2–10). Ten patients (7%) had DVT/PE at stroke onset. Thrombolysis by recombinant-tissue plasminogen activator and mechanical thrombectomy were performed in 7% and 10% of the patients, respectively. The frequency of the patients undergoing cancer treatment was 76%, and approximately half of them received chemotherapy. The median (IQR) levels of plasma D-dimer and hs-CRP were 3.65 (1.41–11.72) μg/mL and 1.06 (0.18–3.95) mg/dL, respectively.

Table 1. Index of Cancer

Site of cancer	Total (N=135)	Distant metastasis (N=69)
Lung	16 (22)	68 (15)
Colorectal	14 (19)	47 (9)
Pancreas	13 (18)	94 (17)
Prostate	9 (12)	33 (4)
Gastric	8 (11)	45 (5)
Breast	7 (10)	30 (3)
Lip, oral, and pharynx	7 (9)	67 (6)
Esophagus	4 (6)	17 (1)
Bladder	4 (6)	33 (2)
Liver	4 (5)	20 (1)
Gallbladder	3 (4)	75 (3)
Malignant lymphoma	2 (3)	67 (2)
Other*	7 (10)	14 (1)†

Data are presented as percentage (number).

*Includes uterus (n=2), myeloproliferative disorder (n=2), ovarian (n=1), renal (n=1), thyroid (n=1), leukemia (n=1), vulvar (n=1), and soft tissue malignancies (n = 1).

†The percentage of the 7 solid tumors is shown.

Compared with the patients with known causes, those with cryptogenic stroke were more frequent in women, infarcts in multiple vascular territories, DVT/PE complications at stroke onset, and distant metastasis, whereas less frequent in those with hypertension, atrial fibrillation, past stroke, cancer treatment, and antiplatelet medication after stroke. Prestroke functional status was worse in patients with cryptogenic stroke compared with those with known causes (median [IQR] prestroke modified Rankin Scale score, 1 [0–3] versus 0 [0–2]; $P=0.039$). The cryptogenic stoke group had higher plasma D-dimer levels (median [IQR], 10.35 [3.59–22.38] versus 1.76 [0.83–3.73] μg/mL; $P<0.001$) and serum hs-CRP levels (median [IQR], 2.50 [0.44–5.97] versus 0.44 [0.12–2.56] mg/dL; $P<0.001$) compared with the known causes group.

Survival Outcomes and Prognostic Factors

Among the 135 patients included, 133 had completed 1-year follow-up: 2 cases were censored at the end of the follow-up. A total of 62 (46%) patients died during the observation period. The median (IQR) survival time for all patients was 365 (71–365) days. The survival rates (95% CI) at 3 and 12 months were 70% (62%–78%) and 54% (46%–63%), respectively. Figure 1 shows the difference in survival rates between patients with cryptogenic stroke and known causes. Patients with cryptogenic stroke had shorter survival times than those with known causes (median [IQR], 113 [43–365] versus 365 [204–365] days; $P<0.001$; HR [95% CI], 3.11 [1.82–5.32]).

Table 3 summarizes the Cox regression analyses. Univariable analysis revealed that hypertension, atrial fibrillation, cryptogenic stroke, National Institutes of Health Stroke Scale score, DVT/PE complications at stroke onset, distant metastasis, prestroke cancer treatment, recurrent stroke, and plasma D-dimer levels were associated with survival outcomes. Multivariable analysis revealed that DVT/PE complications at stroke onset and distant metastasis were significantly associated with mortality in models 1 and 2. In model 3, which selected variables using a stepwise procedure with Akaike information criterion, DVT/PE complications at stroke onset, distant metastasis, and plasma D-dimer levels were independent predictors of prognosis. Cryptogenic stroke was associated with outcomes in univariable

Table 2. Characteristics of the Patients According to Stroke Subtypes

Variables	Total (N=135)	Cryptogenic stroke (N=65)	Known causes (N=70)	*P* value*
Age, median (IQR), y	75 (69–81)	75 (68–82)	75 (70–80)	0.87
Women	39 (52)	48 (31)	30 (21)	0.035
Hypertension	62 (83)	52 (34)	70 (49)	0.035
Dyslipidemia	34 (46)	31 (20)	37 (26)	0.43
Diabetes	22 (30)	22 (14)	23 (16)	0.85
Smoking	19 (25)	15 (10)	21 (15)	0.37
Atrial fibrillation	22 (30)	5 (3)	37 (26)	<0.001
Past stroke	19 (25)	11 (7)	26 (18)	0.026
Time from symptom onset to admission, median (IQR), d	0 (0–2)	0 (0–2)	0 (0–1)	0.39
Prestroke antithrombotic medication	30 (41)	25 (16)	36 (25)	0.16
Antiplatelets	21 (28)	18 (12)	23 (16)	0.24
Anticoagulants	13 (17)	11 (7)	14 (10)	0.54
Stroke subtypes				
SVO	8 (11)			
LAA	15 (20)			
Cardioembolism	22 (29)			
Other	7 (10)			
Cryptogenic	48 (65)			
NIHSS score, median (IQR)	4 (2–10)	5 (2–10)	3 (2–10)	0.47
Prestroke mRS score, median (IQR)	0 (0–2)	1 (0–3)	0 (0–2)	0.039
Infarcts in multivascular territories	45 (61)	64 (41)	29 (20)	<0.001
DVT/PE complications at stroke onset	7 (10)	14 (9)	1 (1)	0.006
rt-PA	7 (9)	8 (5)	6 (4)	0.65
MT	10 (14)	8 (5)	13 (9)	0.33
Distant metastasis	51 (69)	65 (42)	39 (27)	0.002
Adenocarcinoma†	56 (55)	59 (27)	53 (28)	0.56
Prestroke cancer treatment	76 (103)	67 (43)	86 (60)	0.011
Cancer surgery	28 (38)	17 (11)	39 (27)	0.006
Chemotherapy	47 (64)	52 (33)	44 (31)	0.40
Radiotherapy	11 (15)	9 (6)	13 (9)	0.52
Antithrombotic therapy after stroke onset	82 (111)	85 (55)	80 (56)	0.48
Antiplatelets	32 (43)	17 (11)	45 (32)	<0.001
Anticoagulants	68 (92)	77 (50)	60 (42)	0.11
Recurrent stroke	10 (13)	12 (8)	7 (5)	0.31
Major bleeding	7 (10)	11 (7)	4 (3)	0.15
D-dimer, median (IQR), μg/mL‡	3.65 (1.41–11.72)	10.35 (3.59–22.38)	1.76 (0.83–3.73)	<0.001
Hs-CRP, median (IQR), mg/dL	1.06 (0.18–3.95)	2.50 (0.44–5.97)	0.44 (0.12–2.56)	<0.001

Data are presented as percentage (number) or median (IQR). DVT indicates deep venous thrombosis; hs-CRP, high-sensitivity C-reactive protein; IQR, interquartile range; LAA, large-artery atherosclerosis; mRS, modified Rankin Scale; MT, mechanical thrombectomy; NIHSS, National Institutes of Health Stroke Scale; PE, pulmonary embolism; rt-PA, recombinant-tissue plasminogen activator; and SVO, small-vessel occlusion.

*Comparisons between the patients with cryptogenic stroke and known causes.

†Pathologic findings were not available for 36 patients (19 with cryptogenic stroke and 17 with known causes); therefore, the results were analyzed for 99 patients.

‡Plasma D-dimer levels were not available in 3 patients (1 with cryptogenic stroke and 2 with known causes).

analysis but was not significant in multivariable analysis. These results suggest a strong relationship between cancer progression, the degree of cancer-associated coagulopathy, and prognosis in patients with ischemic stroke and active cancer.

Recurrent Stroke and Major Bleeding During the Observation Period

The cumulative incidences (95% CIs) of recurrent stroke and major bleeding were 10% (5%–15%) and 7% (3%–12%), respectively. Figure 2 shows the cumulative

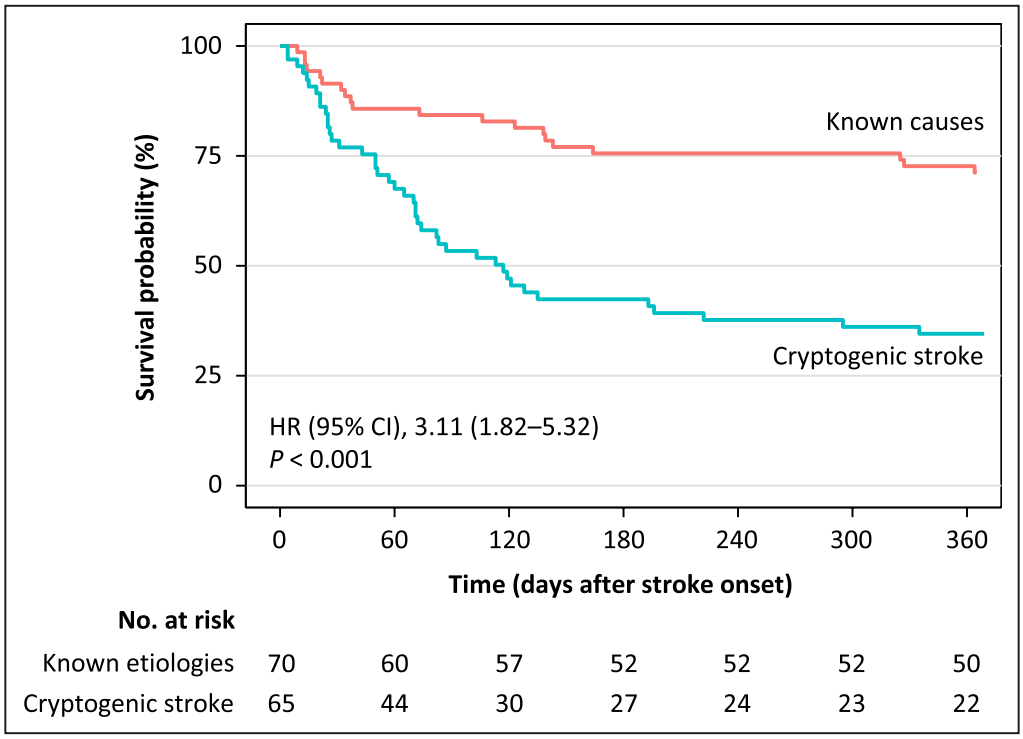

Figure 1. Kaplan-Meier survival curves by stroke mechanism.
HR indicates hazard ratio.

incidence of recurrent stroke between the groups treated with and without antithrombotic medications after stroke. The recurrent stroke was significantly lower in the group with antithrombotic agents than in those without (7% [3%–13%] versus 21% [8%–39%]; *P*=0.04; HR [95% CI], 0.32 [0.11–0.97]). Figure 3 shows the cumulative incidence of major bleeding between the groups. There was no significant difference in major bleeding between the groups treated with and without antithrombotic medications (8% [1%–23%] versus 6% [3%–12%]; *P*=0.86; HR [95% CI], 0.87 [0.18–4.10]).

Survival Estimate Using Distant Metastatic Status, Stroke Subtype, and Plasma D-Dimer Levels

Our analysis revealed that stroke mechanism, coagulation abnormalities, and cancer progression contributed to predicting prognosis in patients with ischemic stroke and active cancer. To investigate the usefulness of plasma D-dimer levels, we examined the relationship between plasma D-dimer levels and survival outcomes, stratified by distant metastasis and stroke subtypes.

Figure 4 shows the distribution of the plasma D-dimer levels according to distant metastasis and cryptogenic stroke status. Plasma D-dimer levels were significantly higher in patients with metastasis than in those without metastasis (Figure 4A; median [IQR], 8.51 [2.20–20.72] versus 1.91 [0.79–6.71] μg/mL; *P*<0.001). As shown in Table 2, patients with cryptogenic stroke had significantly higher plasma D-dimer levels than those with known causes (Figure 4B; median [IQR], 10.35 [3.59–22.38] versus 1.76 [0.83–3.73] μg/mL; *P*<0.001).

Figure 5A shows the survival curves based on distant metastatic status and median plasma D-dimer levels of each group. As shown in Figure 4A, the median plasma D-dimer levels were 1.91 μg/mL for the group without metastasis and 8.51 μg/mL for the group with metastasis; therefore, we divided the patients into 4 groups based on distant metastasis status and median plasma D-dimer levels. The 1-year survival rates were 12% in patients with distant metastasis and high plasma D-dimer levels and 84% in patients without metastasis and low plasma D-dimer levels. Figure 5B shows the survival curves based on stroke subtype and median plasma D-dimer levels of each group. As shown in Figure 4B, the median plasma D-dimer levels were 1.76 μg/mL for the known causes group and 10.35 μg/mL for the cryptogenic stroke group; therefore, we divided the patients into 4 groups based on the stroke subtype and median plasma D-dimer levels. The 1-year survival rates were 20% in patients with cryptogenic stroke and high plasma D-dimer levels and 81% in patients with known stroke causes and low plasma D-dimer levels. These results suggest that

Table 3. HRs for Mortality Using Cox Regression Model (Univariable and Multivariable)

	Univariable	Multivariable		
		Model 1	Model 2	Model 3
Variables	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Age, per 1-y increase	1.00 (0.98–1.02)	1.00 (0.98–1.03)	…	…
Women	0.93 (0.56–1.57)	0.81 (0.40–1.64)	…	…
Hypertension	0.49 (0.30–0.81)†	0.65 (0.30–1.43)	0.61 (0.32–1.16)	0.57 (0.31–1.04)
Dyslipidemia	0.75 (0.44–1.29)	0.68 (0.31–1.49)	…	…
Diabetes	1.29 (0.73–2.28)	1.34 (0.67–2.70)	…	…
Atrial fibrillation	0.45 (0.21–0.94)†	0.62 (0.23–1.70)	0.58 (0.21–1.60)	…
Past stroke	0.46 (0.21–1.01)	0.60 (0.23–1.52)	0.49 (0.19–1.27)	…
Prestroke antithrombotic use	0.67 (0.37–1.19)	0.56 (0.27–1.16)	…	0.55 (0.28–1.06)
Cryptogenic stroke	3.11 (1.82–5.32)‡	0.72 (0.32–1.62)	0.75 (0.35–1.60)	0.87 (0.44–1.68)
NIHSS, per 1-score increase	1.03 (1.00–1.06)†	1.01 (0.96–1.07)	1.01 (0.97–1.06)	…
Prestroke mRS score ≤2	0.72 (0.40–1.23)	0.83 (0.41–1.70)	…	…
DVT/PE complications	4.82 (2.33–9.98)‡	3.16 (1.26–7.95)*	2.63 (1.19–5.82)*	3.16 (1.45–6.85)†
Distant metastasis	5.50 (3.02–10.00)‡	3.22 (1.54–6.74)*	3.19 (1.55–6.57)†	3.24 (1.56–6.73)†
Prestroke cancer treatment	0.50 (0.29–0.86)*	0.51 (0.22–1.18)	0.61 (0.25–1.51)	0.57 (0.25–1.30)
Recurrent stroke	3.31 (1.69–6.48)‡	1.94 (0.52–7.22)	2.43 (0.68–8.65)	1.86 (0.53–6.54)
Major bleeding	2.33 (0.93–5.81)	1.60 (0.27–9.65)	1.14 (0.19–7.05)	…
Plasma D-dimer, quartiles				
<25th	Reference	Reference	Reference	Reference
≥25th and <50th	4.24 (1.39–12.90)*	1.72 (0.44–6.63)	1.81 (0.45–7.24)	2.12 (0.57–7.83)
≥50th and <75th	7.56 (2.59–22.10)‡	3.31 (0.89–12.37)	3.50 (0.96–12.71)	3.55 (1.07–11.75)*
≥75th	11.22 (3.86–32.60)‡	3.16 (0.79–12.58)	3.38 (0.82–13.89)	3.90 (1.17–12.99)*

Model 1, adjusted for all potential confounders with forced entry method. Model 2, adjusted for the variables with $P<0.1$ in the univariable analysis. In model 3, cryptogenic stroke was forced in, and the other factors were selected using a stepwise method with Akaike information criterion. DVT indicates deep venous thrombosis; HR, hazard ratio; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and PE, pulmonary embolism.

*$P<0.05$.

†$P<0.01$.

‡$P<0.001$.

plasma D-dimer levels on admission provide relevant information for predicting the prognosis of patients with ischemic stroke and active cancer.

DISCUSSION

We investigated the prognosis of patients with ischemic stroke and active cancer using data from the SCAN study, a prospective, multicenter, observational study in Japan. Patients with cryptogenic stroke had shorter survival times than those with known causes. Our study confirmed that distant metastasis, plasma D-dimer levels, and DVT/PE complications at stroke onset were independently associated with mortality after adjusting for potential confounders. Furthermore, plasma D-dimer levels stratified the prognosis of patients with distant metastasis and cryptogenic stroke. The current study suggests that there is a strong relationship between the degree of cancer-associated coagulopathy and the prognosis of patients with ischemic stroke and active cancer.

Previous studies have examined the prognosis of patients with ischemic stroke and active cancer. The median survival of these patients, considering all stroke subtypes, ranged from 84 to 109 days.[6,7] In our study, survival time was favorable compared with that in previous reports. The differences in survival among studies could owe to differences in the patients' backgrounds. For example, the proportion of distant metastasis was 66% in the study by Lee et al,[6] 69% in the study by Navi et al,[7] and 51% in our study. In addition, cryptogenic stroke, a predictor of poor outcome in patients with ischemic stroke and active cancer, accounted for 72% in the study by Lee et al,[6] 51% in the study by Navi et al,[7] and 48% in our study. Thus, differences in cancer progression and stroke subtypes may influence patients' survival.

In our cohort, patients with cryptogenic stroke had shorter survival times than those with known causes. This result confirmed the finding from a previous retrospective study by Navi et al[15] There are several possible explanations for this finding. First, patients with cryptogenic stroke and active cancer often have

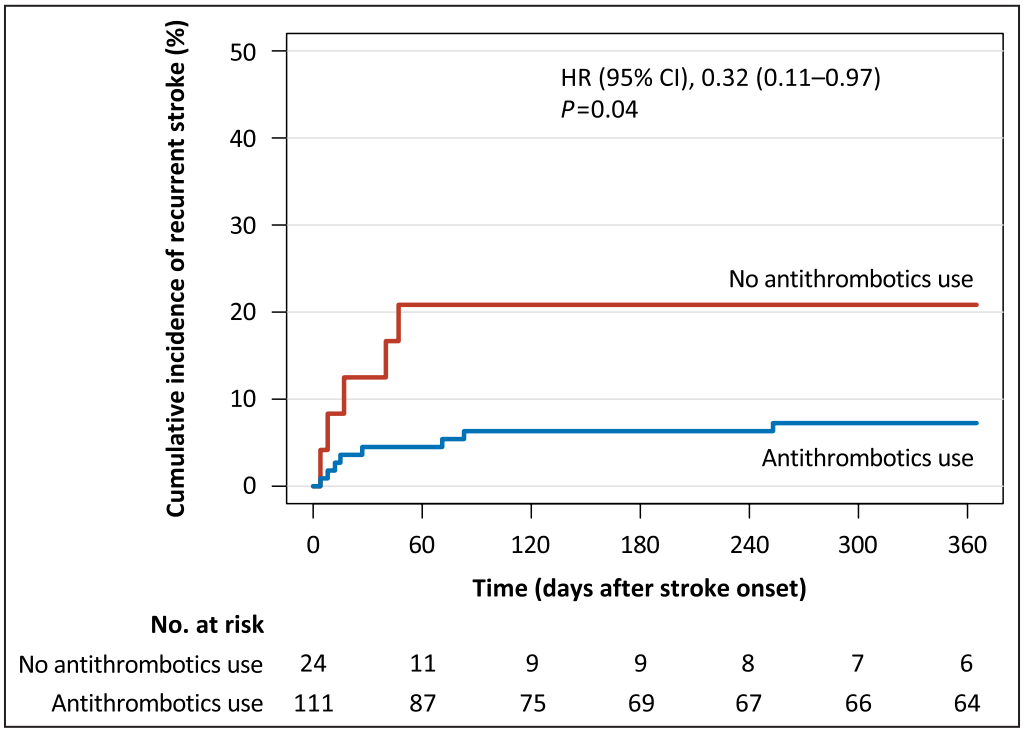

Figure 2. Cumulative incidence of recurrent stroke by antithrombotic agent use.
HR indicates hazard ratio.

cancer-related coagulation abnormalities, resulting in poor outcomes.[25] This is supported by the finding that plasma D-dimer levels were significantly higher in patients with cryptogenic stroke than those with known causes.[18–20] Second, distant metastasis was more common in the cryptogenic stroke group, leading

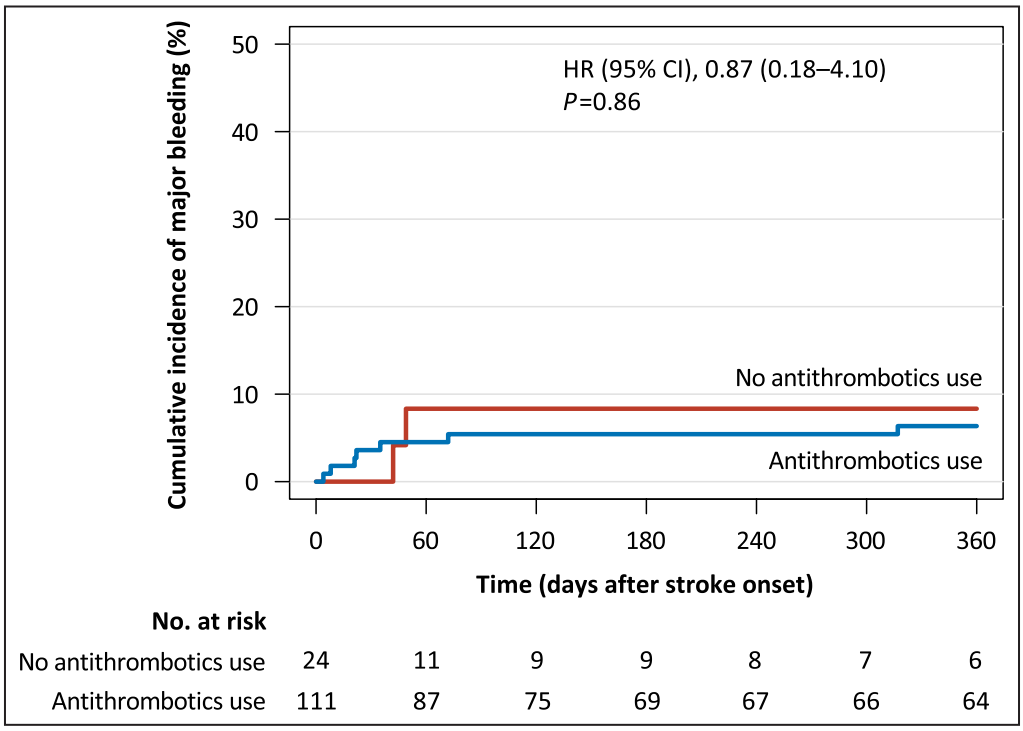

Figure 3. Cumulative incidence of major bleeding by antithrombotic agent use.
HR indicates hazard ratio.

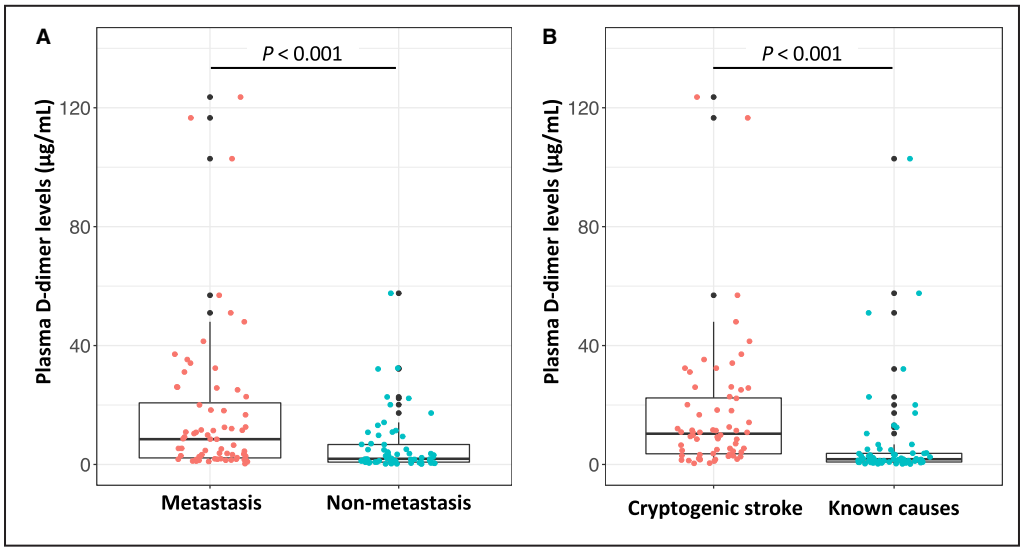

Figure 4. The distribution of plasma D-dimer levels by distant metastasis (A) and stroke subtypes (B).

A, The median plasma D-dimer levels were 8.51 μg/mL (interquartile range, 2.20–20.72 μg/mL) for patients with metastasis and 1.91 (interquartile range, 0.79–6.71 μg/mL) for patients without metastasis. **B**, The median plasma D-dimer levels were 10.35 μg/mL (interquartile range, 3.59–22.38 μg/mL) for patients with cryptogenic stroke and 1.76 (interquartile range, 0.83–3.73 μg/mL) for patients with known causes.

to poor prognosis. These backgrounds are associated with high mortality in patients with cryptogenic stroke and active cancer. The current study also demonstrated that patients with cryptogenic stroke had higher serum hs-CRP levels than those with known causes. Cancer-related chronic inflammation could be associated with cryptogenic stroke and a poor prognosis.[26]

Cryptogenic stroke has been reported as an independent predictor of mortality in patients with ischemic stroke and active cancer.[15] Other studies have shown plasma D-dimer levels to be also associated with poor prognosis.[12,16,17] Plasma D-dimer levels are reportedly high in patients with cryptogenic stroke and active cancer[18–20]; hence, these findings may reflect underlying coagulation abnormalities. The present study examined the prognostic impact of cryptogenic stroke and plasma D-dimer levels using the multivariable model. Cryptogenic stroke was associated with poor prognosis in univariable analysis but was not significant in multivariable analysis. As mentioned earlier, plasma D-dimer levels were higher in patients with cryptogenic stroke than in those with known causes; therefore, the result that cryptogenic stroke was associated with death may be the effect of coagulation abnormalities. Interestingly, among patients with distant metastasis or cryptogenic stroke, those with high plasma D-dimer levels had poorer prognosis than those without. This finding supports the notion that the degree of cancer-associated coagulation abnormalities is related to prognosis. In clinical practice, it would be helpful to use plasma D-dimer levels, in addition to distant metastasis and cryptogenic stoke, to predict the prognosis.

For stroke subtypes, this study classified cryptogenic strokes as patients whose cause could not be confidently identified or had no apparent cause other than malignancy. However, the causative classification for patients with cancer-associated hypercoagulability is debatable. This is attributable to the diversity of cancer-associated stroke phenotypes. For example, if marantic endocarditis, also known as nonbacterial endocarditis, is detected by echocardiography in the population with cancer, it would be classified as cardioembolism.[22] If blood tests confirm disseminated intravascular coagulation, it will be categorized as another determined cause.[22] There are also cases of tumors or air embolisms.[27,28] Meanwhile, even if these causes were not found by screening, they may have gone undetected. If blood tests are incomplete, disseminated intravascular coagulation may not be diagnosed. Therefore, consensus about the causative classification for patients with cancer-associated hypercoagulability will be needed.

Patients with known causes and low D-dimer levels had a better prognosis than those with cryptogenic stroke and severe coagulation abnormalities. This means those with clear traditional stroke causes likely have cancer-independent strokes and have a much better prognosis than those with cancer-related strokes. This is presumably because cancer-associated coagulation abnormalities do not affect morbidity and mortality. In other words, patients with active cancer

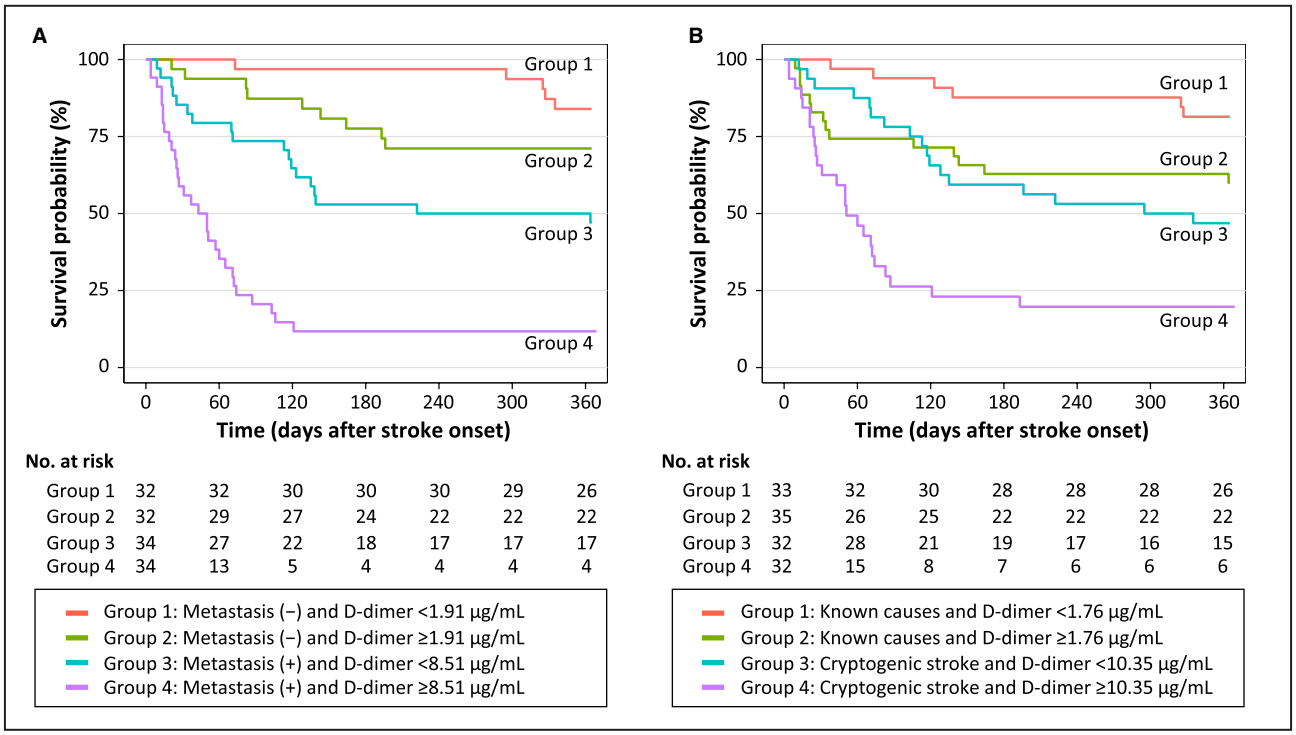

Figure 5. Kaplan-Meier survival curves stratified by distant metastasis (A) and stroke subtype (B) based on quartiles of plasma D-dimer levels.

The survival rates of 132 patients were analyzed because the plasma D-dimer levels on admission were not available for 3 patients. **A**, The median plasma D-dimer levels were 1.91 μg/mL for the group without metastasis and 8.51 μg/mL for the group with metastasis; therefore, patients were divided into 4 groups based on distant metastasis status and median plasma D-dimer levels. **B**, The median plasma D-dimer levels were 1.76 μg/mL for the known causes group and 10.35 μg/mL for the cryptogenic stroke group; therefore, patients were divided into 4 groups based on stroke subtype and median plasma D-dimer levels. Plasma D-dimer levels provide additional prognostic information for patients with distant metastasis and stroke subtype.

just happened to develop an ischemic stroke, and it is unlikely that cancer-associated hypercoagulability is related to the development of strokes. These results can be a message that clinicians should not deny stroke therapy based on a cancer history, where there is no reason to think cancer caused the stroke.

Hemorrhagic complications are among the most significant concerns in the antithrombotic treatment of patients with ischemic stroke and with active cancer.[29] In our analysis, antithrombotic therapy significantly reduced recurrent stroke and did not increase major bleeding. Because the SCAN study was observational, the indication for antithrombotic medications was left to the attending physician's judgment. Therefore, it is likely that antithrombotic treatment was not given to patients at high risk of bleeding. However, our data prove that antithrombotic medications should be given to patients whose physicians determine they can use antithrombotic drugs. Further studies are needed to determine the pros and cons of antithrombotic therapy in patients with stroke and with active cancer.

The strength of this study resides in its prospective and multicenter design. However, this study had several limitations. First, although we tried to enroll as many patients as possible, we could not obtain consent from all the patients to participate in the study. It is possible that consent was not obtained from patients with advanced cancer, and a selection bias could exist. Second, this study did not evaluate whether lowering plasma D-dimer levels with antithrombotic therapy improves prognosis. A recent study has reported that decreasing plasma D-dimer levels with antithrombotic use is associated with prognosis.[17] Third, events, such as stroke recurrence and major bleeding, were collected on the basis of the history provided by the patient or family. Thus, the events may have been underestimated if they were not reported by the participants. Last, this study was limited to Japanese patients, so our findings may not generalize to other populations with stroke.

In conclusion, this study analyzed the survival of patients with ischemic stroke and active cancer, using data from the SCAN study. The prognosis of patients with ischemic stroke and with active cancer varies considerably depending on distant metastasis, venous thromboembolism complications, and coagulation

abnormalities. On the basis of this information, clinicians can decide how to treat patients with ischemic stroke and active cancer.

ARTICLE INFORMATION

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Disclosures

Dr Gon reports lecturer fees from Eisai, Kyowa Kirin, and Pfizer unrelated to this study. Dr Sakaguchi reports lecturer fees from Bayer, Chugai, CSL Behring, Daiichi Sankyo, Eisai, Kyowa Kirin, Ono, Otsuka, Takeda, and UCB Japan unrelated to this study. Dr Yamagami reports grants from Bristol-Myers Squibb and lecturer fees from Bayer, Bristol-Myers Squibb, Daiichi Sankyo, Medtronic, Otsuka, and Stryker unrelated to this study. Dr Todo reports lecturer fees from Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, Daiichi Sankyo, Kyowa Kirin, Medtronic, Otsuka, Pfizer, Stryker, and Takeda unrelated to this study. The remaining authors have no disclosures to report.

Supplemental Material

Data S1
Table S1

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SUPPLEMENTAL MATERIAL

Data S1. The SCAN Study Investigators:

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Yodogawa Christian Hospital – Y. Abe

Hoshigaoka Medical Center – A. Nakanaga, S. Sugiura, and T. Takahashi

Table S1. Breakdown of stroke mechanisms and antithrombotic medication after stroke.

	SVO	LAA	CES	Others	Cryptogenic
Antiplatelets	11	14	1	10	7
Aspirin	6	4	1	3	4
Cilostazol	2	0	0	2	0
Clopidogrel	3	2	0	1	1
Aspirin + cilostazol	0	0	0	2	1
Aspirin + clopidogrel	1	8	0	1	1
Cilostazol + clopidogrel	0	0	0	1	0
Anticoagulants	3	12	18	20	39
Apixaban	0	0	2	0	0
Rivaroxaban	0	0	1	1	1
Edoxaban	0	0	1	0	0
Dabigatran	0	0	0	0	3
Warfarin	0	0	1	0	0
Heparin	0	5	7	17	26
Rivaroxaban + heparin	0	0	2	0	0
Edoxaban + heparin	0	0	1	0	0
Warfarin + heparin	0	0	0	0	3
Argatroban	3	6	4	3	4
Warfarin + argatroban	0	1	0	0	0
Argatroban + heparin	0	0	0	1	1

SVO, small vessel occlusion; LAA, large artery atherosclerosis; CES, cardioembolism.