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Title

Clinical features and prognostic factors in patients with cancer-associated multiple ischemic stroke: A retrospective observational study

Authors

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Running head:

Prognostic factors of the cancer-associated multiple ischemic stroke

Keywords: Cancer-associated ischemic stroke, Multiple cerebral infarctions, Cancer, Stroke, Hypoalbuminemia, Trousseau syndrome.

Highlights

- Cancer-mediated hypercoagulability sometimes develops multiple ischemic strokes that involve various cerebrovascular territories (multiple CAIS).
- In our study, multiple CAIS occurred in elderly patients with advanced cancer, mostly independent in daily living with relatively high KPS scores, but their survival was ~1–2 months.
- Hypoalbuminemia at the onset of multiple CAIS was significantly associated with short survival.

Abstract

Objectives: To investigate the patient demographics, survival after diagnosis, and prognostic factors among patients with multiple-territory cerebral infarctions due to cancer-associated ischemic stroke (multiple CAIS).

Materials and Methods: We performed a retrospective review of the medical records from a 10-year period of consecutive patients with multiple CAIS, defined as 1) newly developed multiple cerebral infarctions involving two or more cerebrovascular territories, 2) association with active cancer diagnosed or treated <6 months before or after stroke, and 3) exclusion of obvious etiologies other than cancer-associated coagulopathy in routine screening. We extracted demographic features, stroke severity and characteristics, cancer characteristics, comorbidities, and laboratory data. Univariable Cox proportional hazards regression was used to idenify the prognostic factors.

Results: The median age was 74 years (interquartile range, 68.3–80.5), and the median survival after diagnosis was 44.5 (27.3–76.8) days in 26 patients with complete follow-up. The median National Institutes of Health Stroke Scale was 5.5 (2.0–9.0). Twenty (76.9%) patients had received a cancer diagnosis prior to the diagnosis of multiple CAIS, and most patients (25 patients, 96.2%) had stage IV cancer. Univariate analysis

showed that high serum albumin (hazard ratio, 0.31; 95% confidence interval, 0.11–0.88) was significantly associated with prolonged survival, whereas stroke severity and comorbidities were not associated with survival.

Conclusion: Multiple CAIS predominantly occurred in elderly patients with advanced cancer, and their survival was short. Serum albumin levels were significantly associated with prognosis, indicating the poor general condition associated with cancers may affect prognosis.

1. Introduction

Cancer causes coagulation abnormalities in arterial and venous systems [1,2]. A highly active cancer is an established risk factor of ischemic stroke [3], and patients with cancer sometimes receive additional burden due to cancer-associated ischemic stroke (CAIS) [4,5]. Multiple cerebral infarctions involving various cerebrovascular territories in cryptogenic CAIS, referred to as "multiple CAIS" in this report, are of particular clinical interest since they lead to poor prognosis, with a median survival of at most a few months [6–8].

Although multiple CAIS has a poor prognosis, there is no guideline for appropriate treatment and patient care, particularly in the acute stage of stroke [9], which is partly because it is difficult to predict the prognosis of each patient and identify prognostic factors after multiple CAIS occurs. Although pioneering research has explored some prognostic factors of CAIS [7], these factors have not been identified for multiple CAIS. The study aim was to investigate the demography, survival after diagnosis, and prognostic factors of multiple CAIS by performing a retrospective review of medical records from a 10-year period. Treatment strategies and patient care are discussed on the basis of the results.

2. Patients and Methods

2.1 Study Design and Setting

This was a retrospective cohort study of patients with active cancer diagnosed with multiple ischemic strokes of various cerebrovascular territories in inpatient and outpatient settings at Aizawa Hospital, which is a private hospital located in the central region of Matsumoto City in the middle of the Japanese mainland. The city has a population of ~240,000, and the hospital has 460 beds and discharges approximately 12,000 inpatients a year. The outpatient departments have been accepting ~220,000 patients a year, including ~30,000 patients per year in the Emergency Department.

2.2 Participants

We retrospectively reviewed the medical records of all consecutive patients from November 2009 through November 2019. We first selected patients with suspected multiple CAIS who had the following keywords in their medical records: cancer, malignancy, ischemic stroke, or Trousseau syndrome. Among these patients, those who met the following three criteria were identified as multiple CAIS patients: 1) newly developed multiple cerebral infarctions involving two or more cerebrovascular territories (out of two bilateral anterior plus one posterior circulation territories)

confirmed by magnetic resonance imaging (MRI) [6]; 2) association with active cancer defined as cancer diagnosed or treated within 6 months before or after stroke or cancer with metastatic disease; 3) exclusion of obvious etiologies other than cancer-associated coagulopathy in routine MRI, magnetic resonance angiography, and trans-thoracic echocardiography screening. Patients who met these criteria were included in the present study and data until death were extracted from the medical records. Death statistics were obtained from the medical records, which were updated regularly, and out-of-hospital information, including records from other hospitals, nursing facilities, and obituaries from the bereaved families. Patients with no confirmation of death were censored at the date of last follow-up.

2.3 Variables

Clinical data collected at the time of multiple CAIS diagnosis included the demographic features (age, sex, and survival days after diagnosis), stroke characteristics (number of vascular territories with lesions, National Institutes of Health Stroke Scale [NIHSS], and the modified Rankin Scale [mRS]), cancer characteristics (previously known or diagnosed after stroke, any treatment for cancer, stage, Karnofsy Performance Scale [KPS], tumor type, and histological type), history of the thrombotic disease (deep

vein thrombosis [DVT] of the lower extremities and antithrombotic medication), comorbidities (hypertension, dyslipidemia, chronic kidney disease, and diabetes), and laboratory data (white blood cell count, hemoglobin level, platelet count, serum albumin level, and D-dimer level) at the diagnosis of multiple CAIS.

2.4 Statistical Analysis

The descriptive statistics are presented as the median and interquartile range (IQR) for continuous data, or counts and proportions for categorical data. To identify prognostic factors, we performed univariable analyses using the Cox proportional hazards regression model. In univariate analysis, we subjected all patients, including censored cases. We reported the hazard ratio (HR) along with the 95% confidence interval (CI) and *P*-value. All statistical analyses were performed in R software (version 3.6.2) with RStudio (version 1.2.5033) for the macOS.

2.5 Ethical Statement

This study was approved by the ethics committee of Aizawa Hospital for research on human subjects and conducted according to the Declaration of Helsinki.

3. Results

3.1 Participants

Out of the 244 patients suspected of having ischemic strokes with cancer, we identified 46 patients who met the criteria for multiple CAIS (Figure 1). Of these 46 patients, 17 were excluded due to missing data. Finally, 29 patients were included in the study analysis. Of these, 26 had data extractable until death and the remaining three patients were censored at the time of transfer to another hospital.

3.2 Demographic and Clinical Characteristics

The baseline characteristics of the 26 patients with multiple CAIS having complete follow-up data are presented in Table 1, and the Kaplan–Meier curves for survival for all 29 patients including censored patients are shown in Figure 2. In 26 patients with complete follow-up, patients tended to be of advanced age (median age, 74 [IQR, 68.3–80.5 years]), and their survival time was short (median, 44.5 [IQR, 27.3–76.8 days] in 26 patients with complete follow-up). Most patients (80.8%) had lesions in three vascular territories. Stroke severity ranged from mild to moderate on the NIHSS (median, 5.5 [IQR, 2.0–9.0]), whereas the disability was moderate to moderately severe on the mRS (median, 4.0 [IQR, 2.0–4.0]). Venous ultrasound of the lower extremities was performed in 18

patients, with DVT identified in 9 (50.0%) patients. One patient received anticoagulant medications (edoxaban 30 mg daily for DVT diagnosed 2 months earlier), and no patient had received antiplatelet medications. Most patients (84.6%) received acute-phase antithrombotic treatment, but some did not because of the high bleeding risk of cancer (Table 2). Chronic antithrombotic treatment was usually given (61.5%), but not in cases of early death. Hypertension (42.3%) was the most common comorbidity (Table 1). Laboratory testing demonstrated a predominance of hypoalbuminemia (median, 3.4 g/dL [IQR, 3.2–3.9 g/dL]) with hypohemoglobinemia (median, 11.8 g/dL [IQR, 9.8–12.9 g/dL]). D-dimer levels were markedly raised (median, 21.1 mg/dL [IQR, 7.8–29.9 mg/dL]).

3.3 Cancer Characteristics

Twenty (76.9%) patients were diagnosed with cancer prior to the stroke, and the 17 patients had received cancer therapy. The KPS was generally distributed in 60–90% so that cancer symptoms before multiple CAIS required almost no hospital care. Eight (30.8%) patients received treatment for cancer after multiple CAIS, and two patients were newly diagnosed with cancer after multiple CAIS and treatment were initiated (Table 2). Most patients (96.2%) had stage IV cancer (Table 1). Gastrointestinal cancers

(pancreatic, colon, bile duct, gastric, and papilla of duodenum cancer) were relatively common (73.0%), and the three most frequent cancers were also gastrointestinal (Table 3). The histological type was dominated by adenocarcinoma (53.8%).

3.4 Prognostic Factor Analyses

Univariate analysis subjected all 29 patients, including 3 censored cases, using the Cox proportional hazards model (Figure 3) showed that higher serum albumin (HR, 0.31 [95% CI, 0.11–0.88]) was significantly associated with prolonged survival. None of the comorbidities associated with stroke nor the clinical severity of the stroke were associated with prognosis.

4. Discussion

4.1 Prognosis

The prognosis of multiple CAIS is poor. A previous study of CAIS, including non-multiple infarction, reported a median survival of 4.5 months [7]. Owing to its poor prognosis, CAIS signals a high risk of near-term mortality in patients with cancer [10]. In a separate study of multiple CAIS that was similar in scope to our study, the median

survival time was only 33 days [8]. In our study, the median survival time was 44.5 days in patients with complete follow-up, which corroborates the findings of previous studies and further emphasizes the poor prognosis of patients with multiple CAIS. It should be noted that less than one-third of patients received anti-cancer treatments after multiple CAIS diagnoses. Terminating or not starting cancer treatment should be considered to provide a bias toward shorter survival in the case series in this study. KPS scores before the onset of multiple CAIS are relatively high, and most patients do not require care, suggesting that multiple CAIS is associated with rapid cancer progression.

4.2 Types of Underlying Cancer

In our study, the most frequent cancer type in patients with multiple CAIS was gastrointestinal cancer, which accounted for 73% of patients. However, some previous reports have found that lung and gynecologic cancers were more common in patients with CAIS, with proportions of 5–30% and 6–21%, respectively, whereas gastrointestinal diseases were relatively less frequent at approximately 6–11% [7,11]. As noted in the limitations section, these differences may be due to bias from our single-center study, reflecting the unique role of hospitals in the community. On the other hand, our histological findings regarding cancer type were consistent with previous

findings demonstrating adenocarcinoma as the predominant cancer type [12,13]. In general, adenocarcinoma tends to cause coagulation abnormalities due to mucin production, which activates coagulation factors or reacts with secretin on the surface of platelets or the vascular endothelium [1,13,14]. Patients with adenocarcinoma also tend to be at higher risk of recurrent ischemic stroke compared to other cancer patients [10].

4.3 Comorbidities of Stroke and Thrombotic Background

In our study, patients tended to have fewer classical comorbidities of stroke. According to the latest data from the Japanese stroke registry (Annual report 2021, Japan Stroke Data Bank), hypertension, dyslipidemia, renal disease, and diabetes mellitus are present in 70.1%, 37.9%, 8.1%, and 26.0% of patients with ischemic stroke, respectively. All of these comorbidities tended to be less common among patients included in our study. Consistent with our results, previous studies have reported that CAIS is associated with decreased prevalence of comorbidity of hypertension, diabetes, and dyslipidemia compared with non-cancer-related cerebral infarction [15-17]. In CAIS patients, the cryptic subtype is associated with lower prevalence of hypertension and diabetes mellitus compared to CAIS with the conventional etiology [18]. This contrast highlights the difference between etiologies of multiple CAIS due to cancer-related coagulopathy and

typical stroke due to cardiovascular risks such as atherosclerotic changes [19], which is further supported by the results of our study. We should also consider potential biases due to the limitation of a retrospective study for a complete assessment of patient background.

While only one patient was receiving anticoagulants, DVT was present in half of patients at the time of multiple CAIS diagnosis, suggesting that multiple CAIS tends to be the first clinically apparent manifestation of cancer-induced coagulation abnormalities, whereas concealed DVT may be present before a diagnosis of multiple CAIS.

4.4 Prognostic Factors

To our knowledge, this is the first study to investigate the prognostic factors associated with multiple CAIS. Higher serum albumin levels were significantly associated with prolonged survival in our study. Hypoalbuminemia, on the other hand, has previously been reported to be commonly observed in patients with cancer and CAIS [15,20]. It is now understood that hypoalbuminemia in patients with cancer is predominantly due to the chronic inflammation of cancer [21–23], with other factors, such

as reduced food intake, increased microvascular permeability and albumin degradation, are also thought to contribute [20]. Previous studies have shown that hypoalbuminemia is associated with decreased 5-year survival following ischemic stroke [24], but more importantly, hypoalbuminemia has been recognized as a significant factor associated with poor prognosis in cancer patients [20]. Indeed, albumin is commonly included in the risk scores related to cancer (e.g., the GPS [25], modified GPS [25], PNI [26], COUNT [27], CAR [28], and other scoring systems). Thus, our results confirm the utility of serum albumin levels in predicting the survival of patients with terminal cancer, including patients with multiple CAIS.

Unexpectedly, the clinical stroke severity (NIHSS or mRS scores) was not associated with shorter survival in multiple CAIS in our study. Previous studies have reported an association between clinical stroke severity and survival among patients with CAIS or ischemic stroke [7, 29–31]. These differences in the contribution of stroke to the prognosis of CAIS may be related to the cancer stage. A previous study of CAIS [7] reported that 47% of the study population had metastatic cancer (stage IV), which differs greatly from the 96.2% observed in our study. The strong effect of hypoalbuminemia in our study indicates advanced cancer has a greater impact on prognosis than stroke severity.

On the other hand, cancer stage was not associated with prognosis in our study. This inconsistency may be attributable to the homogeneity of our multiple CAIS population in which 96.2% of the patients had stage IV cancer. Accordingly, it may be more appropriate to use other clinical markers of cancer progression rather than cancer stage when predicting the prognosis of patients with multiple CAIS.

D-dimer was not associated with shorter survival in multiple CAIS. Recently, CAIS has been regarded as a distinctive subset of embolic stroke of undetermined source (ESUS) [3]. In ESUS, high D-dimer levels are a poor prognostic factor [32,33], with high D-dimer levels associated with cancer comorbidity [32–34]. Together with previous reports, our results indicate serum D-dimer levels have no utility in risk stratification in multiple CAIS patients but may have utility in identifying patients with CAIS as a cause of ESUS, a poor prognostic subgroup.

Although our study suggested a strong association of cancer progression with poor prognostic factors in multiple CAIS, no study has directly compared the prognosis with non-cancer associated multiple-territory cerebral infarctions. It has been reported that the mortality rate for 5 patients with multiple stroke of two or more territories was 25% at a median follow-up of 13 months (IQR 9 to 21 months) [35], a remarkably favorable

course compared to that of the patient series in the present study. Further studies are warranted to clarify the effect of cancer association on the prognosis.

4.5 Treatment Strategies for Multiple CAIS

No previous study has evaluated the usefulness of anticoagulation therapy in patients with CAIS or multiple CAIS. Although treatment strategies were beyond the scope of our study, our results show that choosing a proper treatment strategy will be difficult. Given that most patients with multiple CAIS had advanced cancer and a survival time of ~1–2 months, which would be even shorter in hypoalbuminemia, intensive treatment for strokes may be less effective for improving survival. Even if the treatment of ischemic stroke is estimated to be a high priority, a better risk–benefit balance of anticoagulation therapy should be sought, which might prevent the recurrence of infarction, although there is a risk of cancer-related bleeding. More clinical evidence is needed to enable better selection of the treatment strategy for patients with multiple CAIS.

4.6 Limitations

The present study had limitations that should be considered when assessing our results. Since this was a single-center, retrospective study, there was the potential for selection bias by clustering patients who shared a specific background related to prognosis. A high proportion of patients treated at our hospital have gastrointestinal cancer compared to other cancers, particularly ovarian cancer. Accurate acquisition of patient background could be incomplete owing to the limitations of a retrospective study. This may underestimate the presence of comorbidities and DVT. The relatively small proportion of classic stroke-related comorbidities, such as hypertension and diabetes mellitus, may be related to these study limitations. Second, the number of included patients was small, and the sample size was not calculated prior to the study, which weakened the power to detect prognostic factors. Finally, there are limitations in identifying etiologies as our study design did not strictly rule out etiologies of cerebral infarction other than cancer-induced coagulation abnormalities.

5. Conclusion

Multiple CAIS is a serious condition that occurs mostly in patients with advanced cancer who are independent in daily living with relatively high KPS scores. The underlying poor general condition of patients due to cancers, as reflected by

hypoalbuminemia, may be more related to the prognosis of these patients than to stroke severity. The risk–benefit profile of anticoagulant therapy should be carefully considered in multiple CAIS.

Authors' Contributions

Jun Tanimura, Tomokiyo Yamamoto, and Takao Hashimoto contributed to the study conception and design, interpretation of data, and manuscript writing. Jun Tanimura and Takao Hashimoto contributed to data collection and analysis. All authors reviewed and edited the manuscript and approved the final version for submission.

Competing Interests

None of the authors have any potential conflicts of interest associated with this research.

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Table 1. Baseline characteristics of patients with multiple CAIS.

	All patients (n = 26)
Demographic data	
Age (year)	74 (68.3–80.5)
Female	16 (61.5%)
Survival after diagnosis (day)	44.5 (27.3–76.8)
Characteristics of stroke	
Vascular territories with lesions	
- 2	5 (19.2%)
- 3	21 (80.8%)
National Institutes of Health Stroke Scale (NIHSS)	5.5 (2.0–9.0)
modified Rankin Scale (mRS)	4.0 (2.0–4.0)
Characteristics of cancer	
Previously diagnosed	20 (76.9%)
- Any treatment for cancer	17/20 (85.0%)
Stage	
- III	1 (3.8%)
- IV	25 (96.2%)
Karnofsy Performance Scale (%)	90 (60–90)
History of thrombotic disease	
Deep vein thrombosis *	9/18 (50.0%)
Antiplatelet medication	0 (0%)
Anticoagulant medication	1 (3.8%)
Comorbidity	
Hypertension	11 (42.3%)
Dyslipidemia	6 (23.0%)
Chronic kidney disease	2 (7.7%)
Diabetes	1 (3.8%)
Laboratory finding	
White blood cell ($\times 10^2/\mu L$)	67.2 (60.0–96.4)
Hemoglobin (g/dL)	11.8 (9.8–12.9)
Platelet ($\times 10^4/\mu L$)	15.1 (10.6–19.3)
Albumin (g/dL)	3.4 (3.2–3.9)
D-dimer (mg/dL)	21.1 (7.8–29.9)

* Only 18 patients who were performed venous ultrasound of the lower extremities were analyzed. Continuous variables are presented as the median (interquartile range).

Categorical data are presented as counts (proportions). CAIS: cancer-associated ischemic stroke.

Table 2. Treatment of stroke and cancer in patients with multiple CAIS.

	All patients (n=26)
Anti-thrombotic treatment	
Before multiple CAIS	1 (3.8%)
- DOAC	1 (3.8%)
Acute phase of multiple CAIS	22 (84.6%)
- Heparin (intravenous)	22 (84.6%)
Chronic phase of multiple CAIS	16 (61.5%)
- Heparin (subcutaneous)	1 (3.8%)
- Warfarin	9 (34.6%)
- DOAC	5 (19.2%)
- Aspirin	1 (3.8%)
Cancer treatment	
Before multiple CAIS *	17/20 (85.0%)
- Surgery	3/20 (15.0%)
- Chemotherapy	7/20 (35.0%)
- Surgery + Chemotherapy	6/20 (30.0%)
- TACE	1/20 (5.0%)
After multiple CAIS	8 (30.8%)
- Chemotherapy	7 (26.9%)
- Hyperthermia therapy	1 (3.8%)
- New introduction of cancer treatment	2/8 (25.0%)

* Only 20 patients who had previously been diagnosed with cancer were analyzed. CAIS: cancer-associated ischemic stroke, DOAC: direct oral anticoagulant, TACE: transcatheter arterial chemoembolization.

Table 3. Characteristics of the cancer.

	All patients (n = 26)
Cancer type	
Pancreas	5 (19.3%)
Colon	5 (19.3%)
Bile	5 (19.3%)
Lung	3 (11.5%)
Gastric	2 (7.7%)
Breast	2 (7.7%)
Hepatocellular	1 (3.8%)
Papilla of duodenum	1 (3.8%)
Ovarian	1 (3.8%)
Unknown origin	1 (3.8%)
Histological type	
Adenocarcinoma	14 (53.8%)
Squamous cell carcinoma	1 (3.8%)
Large cell neuroendocrine carcinoma	1 (3.8%)
Adenosquamous carcinoma	1 (3.8%)
not assessed	9 (34.6%)

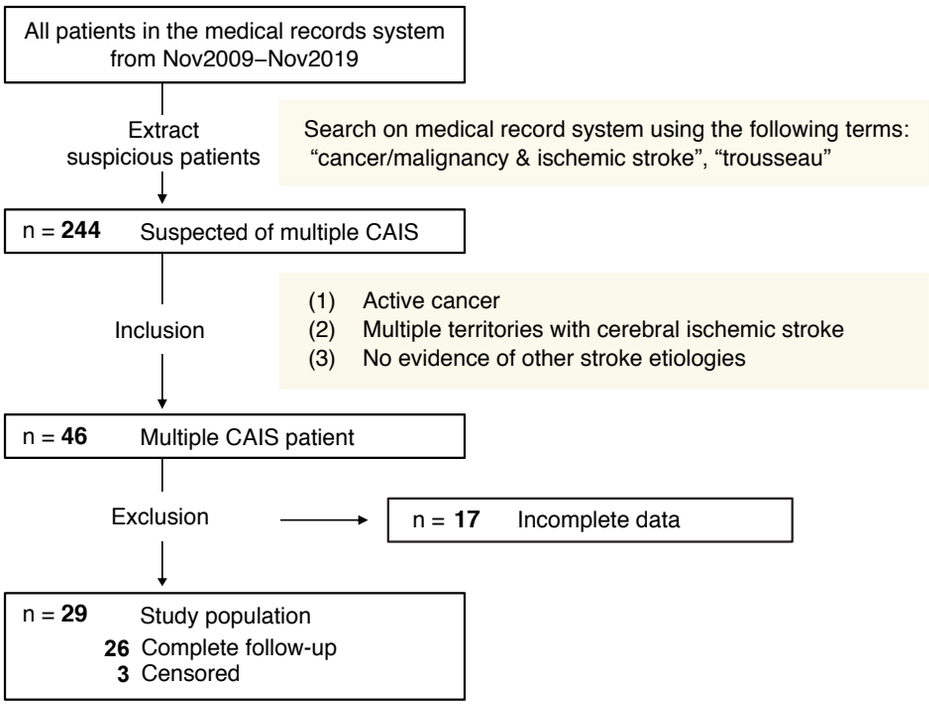
Number of patients are presented as counts (proportions).

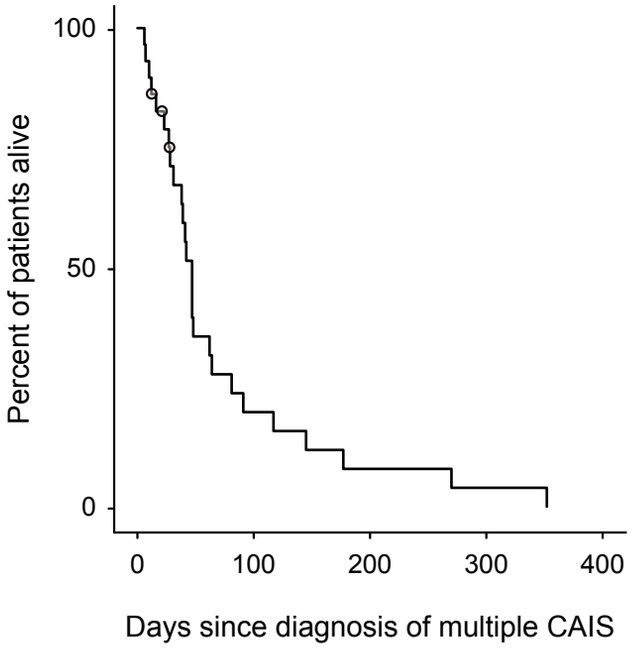
Figure Legends

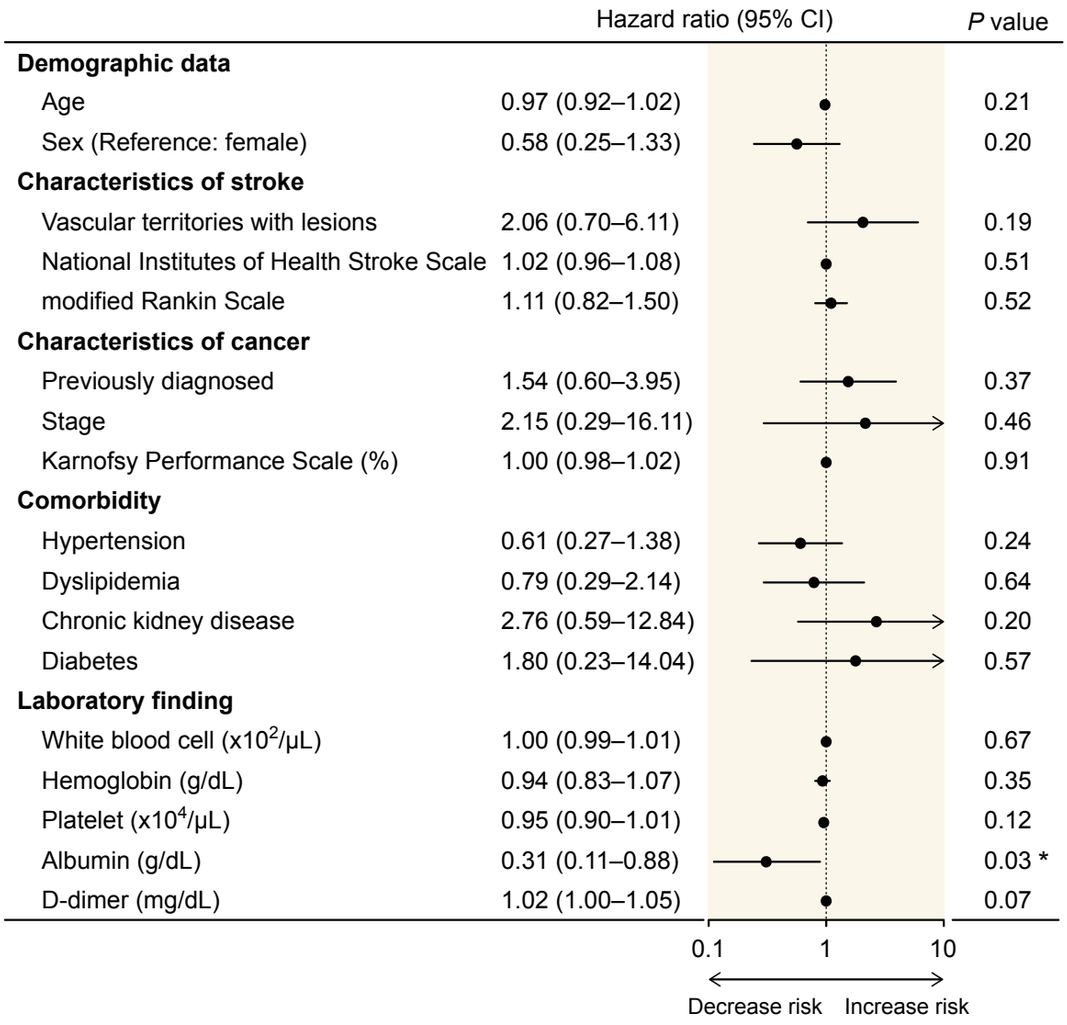
Figure 1. Flow diagram showing the patient extraction, inclusion, and exclusion of medical records. CAIS: cancer-associated ischemic stroke.

Figure 2. Kaplan-Meier curves of 29 patients with multiple CAIS. Circles indicate three censored cases. CAIS, cancer-associated ischemic stroke.

Figure 3. Forest plot of hazard ratios calculated by univariable Cox proportional hazards regression model. Univariate analysis was subjected to all 29 patients, including three censored cases. Dots and bars represent hazard ratios and 95% confidence intervals, and arrows represent that the confidence interval spread further than the limit (0.1–10). * *P* values < 0.05. CI: Confidence interval.


All patients in the medical records system from Nov2009–Nov2019
Extract suspicious patients
Search on medical record system using the following terms: "cancer/malignancy & ischemic stroke", "trousseau"
n = 244 Suspected of multiple CAIS
Inclusion
(1) Active cancer
(2) Multiple territories with cerebral ischemic stroke
(3) No evidence of other stroke etiologies
n = 46 Multiple CAIS patient
Exclusion
n = 17 Incomplete data
n = 29 Study population
26 Complete follow-up
3 Censored


100
50
0
Percent of patients alive
0
100
200
300
400
Days since diagnosis of multiple CAIS


Hazard ratio (95% CI)
P value
Demographic data
Age
0.97 (0.92–1.02)
0.21
Sex (Reference: female)
0.58 (0.25–1.33)
0.20
Characteristics of stroke
Vascular territories with lesions
2.06 (0.70–6.11)
0.19
National Institutes of Health Stroke Scale
1.02 (0.96–1.08)
0.51
modified Rankin Scale
1.11 (0.82–1.50)
0.52
Characteristics of cancer
Previously diagnosed
1.54 (0.60–3.95)
0.37
Stage
2.15 (0.29–16.11)
0.46
Karnofsy Performance Scale (%)
1.00 (0.98–1.02)
0.91
Comorbidity
Hypertension
0.61 (0.27–1.38)
0.24
Dyslipidemia
0.79 (0.29–2.14)
0.64
Chronic kidney disease
2.76 (0.59–12.84)
0.20
Diabetes
1.80 (0.23–14.04)
0.57
Laboratory finding
White blood cell (x10^2/μL)
1.00 (0.99–1.01)
0.67
Hemoglobin (g/dL)
0.94 (0.83–1.07)
0.35
Platelet (x10^4/μL)
0.95 (0.90–1.01)
0.12
Albumin (g/dL)
0.31 (0.11–0.88)
0.03 *
D-dimer (mg/dL)
1.02 (1.00–1.05)
0.07
0.1
1
10
Decrease risk
Increase risk