

Outcome of Stroke Patients with Cancer and Nonbacterial Thrombotic Endocarditis

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Background and Purpose Nonbacterial thrombotic endocarditis (NBTE) is a cause of stroke in cancer. However, clinical characteristics and outcomes in stroke patients with cancer-associated NBTE are not well known.

Methods We included consecutive patients with stroke and active cancer over a 9-year period who underwent echocardiography. We retrospectively compared clinical characteristics and presence of metastasis between patients with NBTE, those with cryptogenic etiologies, and those with determined etiologies. We also investigated mortality and stroke events during the 6-month follow-up.

Results Among the 245 patients, 20 had NBTE, 96 had cryptogenic etiologies, and 129 had determined etiologies. Metastasis was seen in all 20 patients (100%) with NBTE, 69.8% in patients with cryptogenic etiology, and 48.8% in patients with or determined etiology. During the 6-month follow-up, 127 patients (51.8%) developed stroke and/or died (death in 110 [44.9%] and stroke events in 55 [22.4%]). Patients with NBTE showed significantly higher mortality (80%) and stroke occurrence (50%) than those with cryptogenic etiologies (mortality 54.2%, stroke 25.0%, log-rank $P=0.006$) and determined etiologies (mortality 32.6%, stroke 16.3%, log-rank $P<0.001$). In a multivariate Cox proportional hazard analysis, the presence of NBTE was independently associated with composite outcomes of mortality and stroke events (hazard ratio, 1.941; 95% confidence interval, 1.052 to 3.690).

Conclusions NBTE should be suspected as a potential cause of stroke in patients with metastatic cancer. Patients with NBTE have a high risk of recurrent stroke and mortality. Future studies are necessary to determine strategies to reduce stroke recurrence in patients with NBTE.

Keywords Stroke; Neoplasms; Metastasis; Mortality; Nonbacterial thrombotic endocarditis

Introduction

Cancer may be associated with stroke. In a large cohort study, the 6-month cumulative incidence of ischemic stroke was sig-

nificantly higher in patients with cancer than in matched controls (3.0% vs. 1.62%).¹ Nonbacterial thrombotic endocarditis (NBTE) is characterized by noninfectious vegetation on the cardiac valves.² NBTE is a cause of stroke and most frequently

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develops in patients with systemic cancer.^{3,4}

Most information on NBTE in stroke is derived from case reports or post-mortem studies because of its rarity.⁵⁻⁸ Although patients with acute stroke and active cancer are known to have a substantial short-term risk of recurrent stroke,⁹ the outcomes of stroke patients with cancer-associated NBTE are not well known. In addition, the pathomechanism of NBTE is unknown. However, pathological studies have shown that the vegetation and thrombi retrieved from stroke patients with NBTE have very high platelet fractions.^{10,11} Further, cancer is known to activate platelets, which play an important role in metastasis.¹² These findings suggest a potential association between NBTE and metastasis. Previous case reports and post-mortem studies have shown frequent occurrences of metastasis in patients with NBTE. However, information on the presence of metastasis is insufficient in many cases.¹³⁻¹⁶ Therefore, the association between NBTE and metastasis remains uncertain.

We hypothesized that development of NBTE has a relationship with metastasis. In this study, we investigated association between NBTE and metastasis, and the mortality and occurrence of stroke events for 6 months following an initial stroke in patients with cancer-associated NBTE.

Methods

Study population

This retrospective study used a hospital-based prospective cohort of consecutively enrolled patients with ischemic stroke within 7 days of symptoms onset. Routine evaluations performed were as follows: standard blood tests including D-dimer; brain magnetic resonance imaging (MRI) and/or computed tomography (CT) and cerebral angiography (magnetic resonance angiography, CT angiography, or conventional angiography); Holter monitoring or continuous electrocardiography monitoring during admission in the stroke unit; and transesophageal echocardiography (TEE) and/or transthoracic echocardiography (TTE). TEE was not performed in patients with decreased consciousness, aphasia, impending brain herniation, poor systemic conditions, severe swallowing difficulty, tracheal intubation, or when informed consent could not be obtained.¹⁷

The study hospital is a tertiary university hospital with a dedicated cancer center where patients with cancer routinely undergo extensive evaluations for the presence of metastasis. When cancer or NBTE is diagnosed during admission, patients are referred to oncologists for further evaluation and treatment.

This study included consecutive patients with active cancer who were registered between January 2010 and December 2018

and who underwent echocardiography. Active cancer was defined as cancer that was diagnosed within 6 months, required chemotherapy or surgical treatment within 6 months, or was recurrent, metastatic, or inoperable.¹⁸ Patients with brain malignancy or hematologic malignancy were excluded. The cohort and this study were approved by the Institutional Review Board of the Yonsei University Health System. The need for an informed consent was waived due to the retrospective nature of the study.

Study group

Because the study participants had active cancer, patients were categorized into those with NBTE, those with cryptogenic etiology, and those with determined etiology.¹¹ NBTE was determined based on formal reports by cardiologists who diagnosed vegetation based on echocardiographic examinations. Five patients with NBTE and co-existing atrial fibrillation were classified into the NBTE group. Twenty-one patients with a patent foramen ovale without venous thrombosis and other determinable etiologies were classified into cryptogenic etiology group.

Outcome assessments

All patients were regularly followed up after discharge by neurologists and clinical research assistants in the outpatient clinic using face-to-face interviews or by a telephonic interview using a structured questionnaire.¹⁹ We reviewed the medical records to obtain information on mortality and cause of death. The cause of death was categorized as stroke-related, cancer-related, or others/unknown.²⁰ Information on the occurrence of any new stroke events (cerebral infarction or intracerebral hemorrhage [ICH]) after the initial cerebral infarction was also obtained from medical records. The diagnosis of stroke was based on brain MRI and/or CT results.

Statistical analysis

Variables were expressed as mean±standard deviation, median (interquartile range), or number (percentage), as appropriate. Baseline characteristics among the groups were compared using one-way analysis of variance or the Kruskal-Wallis test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. *Post hoc* analysis was performed using Bonferroni's correction or Dunn's test. Kaplan-Meier estimates and log-rank tests were performed (adjusted by Bonferroni's correction) for mortality, occurrence of stroke, and composite outcomes of mortality and stroke. To determine whether the presence of NBTE was associated with composite events of mortality and stroke, we performed multivariate Cox proportional hazard regression analyses. As all patients with NBTE had metastasis and 90% of patients with NBTE had multiple territory infar-

tions, we constructed two different multivariate regression models to avoid multicollinearity. Model 1 included the presence of NBTE and Model 2 included metastasis and multiple territory infarctions. All statistical analyses were performed using R statistical software version 3.5.1 (<http://www.R-project.org>). A $P < 0.05$ was considered statistically significant.

Results

During the 9-year study period, 289 patients with acute ischemic stroke and active cancer were registered to the cohort. Of those, 245 patients (84.8%) underwent echocardiography and were included in this study (123 patients underwent both TEE and TTE, 25 patients underwent TEE only, and 97 patients underwent TTE only). The mean age of the included patients was 68.7 ± 10.7 years, and 136 patients (55.5%) were men. Compared to patients who underwent echocardiography, those who did not undergo echocardiography were younger, had fewer atrial fibrillation and higher National Institutes of Health Stroke Scale (NIHSS) scores. Cancer types were not different between patients who did or did not undergo echocardiography (Supplementary Table 1).

Comparison between the groups

Of the 245 patients, 20 patients (8.2%) had NBTE, 96 (39.2%) had a cryptogenic etiology, and 129 (52.7%) had determined etiologies. In patients with determined etiologies, those with cardioembolism were 51, those with large artery atherosclerosis were 46, and those with two or more causes were 19 (Supplementary Table 2). Of 150 patients (61.2%) with metastasis, NBTE was diagnosed in 20 patients (13.3%). Compared with patients with determined etiologies, those with NBTE were younger, had more frequent multiple vascular territory involvement, lower platelet counts, lower fibrinogen levels, and higher D-dimer levels (Table 1).

Metastasis, cancer type, and NBTE

All 20 patients with NBTE had metastasis, and NBTE was not detected in patients without metastasis. The presence of metastasis was significantly higher in patients with NBTE (100%) than in those with stroke with a cryptogenic etiology (69.8%; $P = 0.014$ after Bonferroni's correction) or those with a determined etiology (48.8%; $P < 0.001$ after Bonferroni's correction) (Table 1). The cancer type was not significantly different among the three groups (Table 1).

Six-month mortality and stroke events

All patients were followed up for 6 months after the initial

stroke event. During the follow-up, 127 patients (51.8%) developed stroke events and/or died (110 [44.9%] died and 55 [22.4%] patients experienced stroke events). The median survival of patients with NBTE was 44.5 days, and event-free survival of composite outcomes of mortality and stroke was 36 days. During the 6-month follow-up, 90% (18/20) patients with NBTE died or developed stroke, while only 38.8% patients with a determined etiology died or developed stroke (50/129, $P < 0.001$) (Table 2).

Compared to event-free patients, those with events (mortality or stroke) were younger and had lower body mass indices and higher initial NIHSS scores. They also had lower hemoglobin levels, platelet counts, and fibrinogen levels, and higher white blood cell counts and D-dimer levels (Table 3). Metastasis and multiple vascular territory involvements were more common in patients with mortality or stroke events. Cancer type was also different between patients with or without events (Table 3).

In the Kaplan-Meier survival analysis, the 6-month mortality was different among the three groups ($P < 0.001$). Patients with NBTE showed lower 6-month survival probability, lower stroke-free probability, and lower event-free probability than those with cryptogenic or determined etiologies (Figure 1). Mortality, stroke events, and composite outcomes were more common in patients with a cryptogenic etiology than in those with a determined etiology (Figure 1).

Causes of death

During the follow-up, more patients with NBTE died (16/20 [80.0%]) compared to those with a cryptogenic etiology (52/96 [54.2%]) and a determined etiology (32/129 [32.6%]) ($P < 0.001$). Causes of death were cancer-related in 83 (75.5%), stroke-related in 21 (19.1%), and other/unknown in six (5.5%) patients. The cause of death did not significantly differ among the three groups ($P = 0.307$) (Table 2).

Stroke events

During the 6-month follow-up, stroke events occurred in 55/245 (22.4%) of patients; 53 (21.6%) with ischemic stroke and two (0.8%) with ICH. Stroke was diagnosed using diffusion-weighted imaging in 49 patients (89.1%) and by CT in five patients (9.1%). The type of imaging was uncertain in one patient who was diagnosed at another hospital (1.8%). Stroke events occurred most frequently in patients with NBTE (10/20, 50%), followed by those with a cryptogenic etiology (24/96, 25.0%) and those with a determined etiology (21/129, 16.3%) (Table 2). Mortality was more frequent in patients with stroke events than in those without (69.1% [38/55] vs. 37.9% [72/190], $P < 0.001$).

Table 1. Comparison of baseline characteristics according to stroke etiology

Characteristic	NBTE (n=20)	Cryptogenic etiology (n=96)	Determined etiology (n=129)	P
Demographics				
Age (yr)	61.5±8.7	68.1±10.1	70.3±10.9	0.002*†
Male sex	9 (45.0)	43 (44.8)	84 (65.1)	0.006†
Risk factors				
Hypertension	10 (50.0)	57 (59.4)	92 (71.3)	0.062
Diabetes mellitus	5 (25.0)	25 (26.0)	47 (36.4)	0.204
Dyslipidemia	5 (25.0)	13 (13.5)	28 (21.7)	0.228
Atrial fibrillation	5 (25.0)	0 (0)	46 (35.7)	<0.001*†
Current smoker	1 (5.0)	12 (12.5)	17 (13.2)	0.581
Patent foramen ovale	3 (15.0)	21 (21.9)	26 (20.2)	0.782
Body mass index (kg/m ²)	22.3±2.9	22.8±3.5	22.5±3.6	0.676
Medications prior to admission				
Antiplatelets	3 (15.0)	19 (19.8)	39 (30.2)	0.129
Anticoagulants	3 (15.0)	4 (4.2)	15 (11.6)	0.066
Statin	7 (35.0)	18 (18.8)	37 (28.7)	0.138
Medications mainly used after admission				
Antiplatelets	6 (30.0)	56 (58.3)	73 (56.6)	0.048†
Anticoagulants	12 (60.0)	31 (32.3)	49 (38.0)	
Both antiplatelets and anticoagulants	1 (5.0)	2 (2.1)	5 (3.9)	
No medication	1 (5.0)	7 (7.3)	2 (1.6)	
Initial NIHSS score	7 (3–12)	5 (2–10)	5 (1–12)	0.547
Reperfusion therapy	6 (30.0)	12 (12.6)	28 (21.7)	0.095
Multiple territory involvement	18 (90.0)	62 (64.6)	47 (36.4)	<0.001*†
Laboratory findings				
Hemoglobin (g/dL)	11.2±1.6	10.8±2.0	11.7±2.8	0.036†
White blood cells (×10 ⁹ /L)	10.4±5.1	7.8±3.9	8.1±4.2	0.041*
Platelets (×10 ⁹ /L)	133±82	201±113	237±118	<0.001*†
D-dimer (mg/L)	7.4±6.5	4.8±9.0	1.9±2.8	<0.001*†
Fibrinogen (g/L)	2.6±1.6	3.3±1.4	3.5±1.3	0.013†
Metastatic cancer	20 (100.0)	67 (69.8)	63 (48.8)	<0.001*†
Cancer type				
Colorectal	2 (10.0)	11 (11.5)	19 (14.7)	0.118
Gastric/esophageal	3 (15.0)	14 (14.6)	27 (20.9)	
Hepatobiliary	6 (30.0)	20 (20.8)	12 (9.3)	
Pancreas	4 (20.0)	9 (9.4)	9 (7.0)	
Lung	1 (5.0)	21 (21.9)	24 (18.6)	
Bladder/urinary tract	2 (10.0)	3 (3.1)	6 (4.7)	
Female genital organ	1 (5.0)	5 (5.2)	6 (4.7)	
Others	1 (5.0)	13 (13.5)	26 (20.2)	

Values are presented as mean±standard deviation, number (%), or median (interquartile range).

NBTE, nonbacterial thrombotic endocarditis; NIHSS, National Institutes of Health Stroke Scale.

*NBTE vs. Cryptogenic, P<0.05; †NBTE vs. Determined, P<0.05; ‡Cryptogenic vs. Determined, P<0.05.

Table 2. Causes of death and type of stroke event according to stroke etiology

Variable	NBTE (n=20)	Cryptogenic etiology (n=96)	Determined etiology (n=129)	P
Composite outcomes of mortality and stroke	18 (90)	59 (61.5)	50 (38.8)	<0.001 ^{*,†,‡}
Mortality	16 (80)	52 (54.2)	32 (32.6)	<0.001 ^{†,‡}
Causes of death				0.307
Cancer-related	13 (81.2)	43 (82.7)	27 (64.3)	
Stroke-related	2 (12.5)	7 (13.5)	12 (28.6)	
Other/unknown cause	1 (6.3)	2 (3.8)	3 (7.1)	
Any stroke events	10 (50)	24 (25.0)	21 (16.3)	<0.003 [‡]
Stroke type				
Cerebral infarction	10 (100)	23 (95.8)	20 (95.2)	
Intracerebral hemorrhage	0 (0)	1 (4.2)	1 (4.8)	

Values are presented as number (%).

NBTE, nonbacterial thrombotic endocarditis.

*NBTE vs. Cryptogenic, $P<0.05$; †NBTE vs. Determined, $P<0.05$; ‡Cryptogenic vs. Determined, $P<0.05$.

Factors associated with mortality and stroke events

In the multivariate Cox proportional hazard analysis, female sex and a lower body mass index were associated with composite outcomes of mortality and stroke both in Model 1 and Model 2. The composite outcomes were independently associated with the presence of NBTE (hazard ratio [HR], 1.941; 95% confidence interval [CI], 1.052 to 3.690) (Table 4, Model 1). The presence of metastasis (HR, 2.870; 95% CI, 1.648 to 4.996) and the involvement of multiple vascular territories (HR, 2.524; 95% CI, 1.570 to 4.058) were also independently associated with the composite outcomes (Table 4, Model 2).

Discussion

In this study, NBTE was diagnosed in approximately one of 11 stroke patients with active cancer. NBTE was also found exclusively in patients with metastasis. In addition, stroke patients with NBTE had a very high risk of mortality and stroke events during a 6-month follow-up.

The pathomechanism of NBTE remains unknown. Autopsy studies in patients with NBTE have shown that cardiac vegetation is mainly composed of platelets,²¹ and examinations of thrombi retrieved during mechanical thrombectomy in stroke patients with NBTE have indicated very high platelet and low erythrocyte fractions.^{11,22} These studies suggest that platelet-mediated mechanisms play a key role in the development of cancer-associated NBTE. The role of platelets in cancer has been extensively studied; platelets play a crucial role in tumor growth and metastasis.²³

Our study demonstrated that NBTE occurred exclusively in patients with metastasis. Platelets can contribute to tumor in-

vasion and metastasis via several mechanisms. Platelets are essential for the survival of circulating tumor cells,²⁴ and these cells rapidly associate with platelets via their receptors and induce tumor cell-induced platelet aggregation (TCIPA).²⁵ This TCIPA is critical for tumor cell survival as platelets form a physical shield around tumor cells, protecting them from recognition and lysis by natural killer cells and shear-induced damage.^{26,27} These findings suggest that the association of tumor cells with platelets during metastasis may somehow contribute to the development of platelet-rich vegetation in NBTE.

Stroke patients with active cancer have a substantial risk of recurrent stroke. In a retrospective study, ischemic stroke recurred in 16% patients within 6 months of the initial stroke.¹⁵ In the present study cohort, ischemic stroke recurred in 21.6% patients and ICH developed in 0.8% patients. Particularly, 50% patients with NBTE developed stroke within 6 months, significantly higher than those without NBTE. Ninety percent of patients with NBTE had lesions involving multiple vascular territories, which suggests multiple embolization from the heart. Patients with NBTE may be prone to a high risk of multiple thromboembolism because the platelet-rich vegetation (thrombus) is attached to the fast-moving cardiac valves.

This study showed that mortality differed significantly among the three etiology categories of stroke patients with active cancer. During the 6 months of follow-up, 80% patients with NBTE died. However, less than one-third of the patients with a determined etiology died. Patients with a cryptogenic etiology had an intermediate risk of 6-month mortality. The high mortality in patients with NBTE may be associated with metastasis since all patients with NBTE had it. In our previous study, 67.1% stroke patients with metastatic cancer died within 6 months,²⁰ but the 6-month mortality in patients with

Table 3. Comparison of characteristics between patients with and without mortality/stroke events

Characteristic	No events (n=118)	Events (n=127)	P
Demographics			
Age (yr)	68.4±9.9	69.0±11.4	0.664
Male sex	80 (67.8)	56 (44.1)	<0.001
Risk factors			
Hypertension	79 (66.9)	80 (63.0)	0.607
Diabetes mellitus	39 (33.1)	38 (29.9)	0.697
Dyslipidemia	27 (22.9)	19 (15.0)	0.155
Atrial fibrillation	26 (22.0)	25 (19.7)	0.768
Current smoker	20 (16.9)	10 (7.9)	0.049
Body mass index (kg/m ²)	23.2±3.2	22.0±3.8	0.010
Metastatic cancer	42 (35.6)	108 (85.0)	<0.001
Cancer type			0.020
Colorectal	19 (16.1)	13 (10.2)	
Gastric/esophageal	22 (18.6)	22 (17.3)	
Hepatobiliary	13 (11.0)	25 (19.7)	
Pancreas	5 (4.2)	17 (13.4)	
Lung	21 (17.8)	25 (19.7)	
Bladder/urinary tract	8 (6.8)	3 (2.4)	
Female genital organ	5 (4.2)	7 (5.5)	
Others	25 (21.2)	15 (11.8)	
Initial NIHSS score	3 (1–10)	6 (2–11.5)	0.007
Reperfusion therapy	25 (21.2)	21 (16.7)	0.460
Multiple vascular territory involvement	36 (30.5)	91 (71.7)	<0.001
Stroke etiology			
NBTE	2 (10.0)	18 (90.0)	<0.001
Cryptogenic	37 (38.5)	59 (61.5)	
Determined	79 (61.2)	50 (38.8)	
Laboratory findings			
Hemoglobin (g/dL)	11.6±2.1	11.0±2.7	0.033
White blood cells (×10 ⁹ /L)	7.5±3.7	8.9±4.5	0.008
Platelets (×10 ⁹ /L)	243±112	188±116	<0.001
D-dimer (mg/L)	1.1±1.5	5.7±8.3	<0.001
Fibrinogen (g/L)	3.6±1.2	3.2±1.5	0.021

Values are presented as mean±standard deviation, number (%), or median (interquartile range). NIHSS, National Institutes of Health Stroke Scale; NBTE, nonbacterial thrombotic endocarditis.

NBTE was even higher. In the present study, mortality was also higher in patients who developed recurrent stroke; therefore, frequent stroke reoccurrence in patients with NBTE might also increase the risk of death.

In this study, patients with NBTE had higher D-dimer levels and more frequent multiple vascular territory involvement than

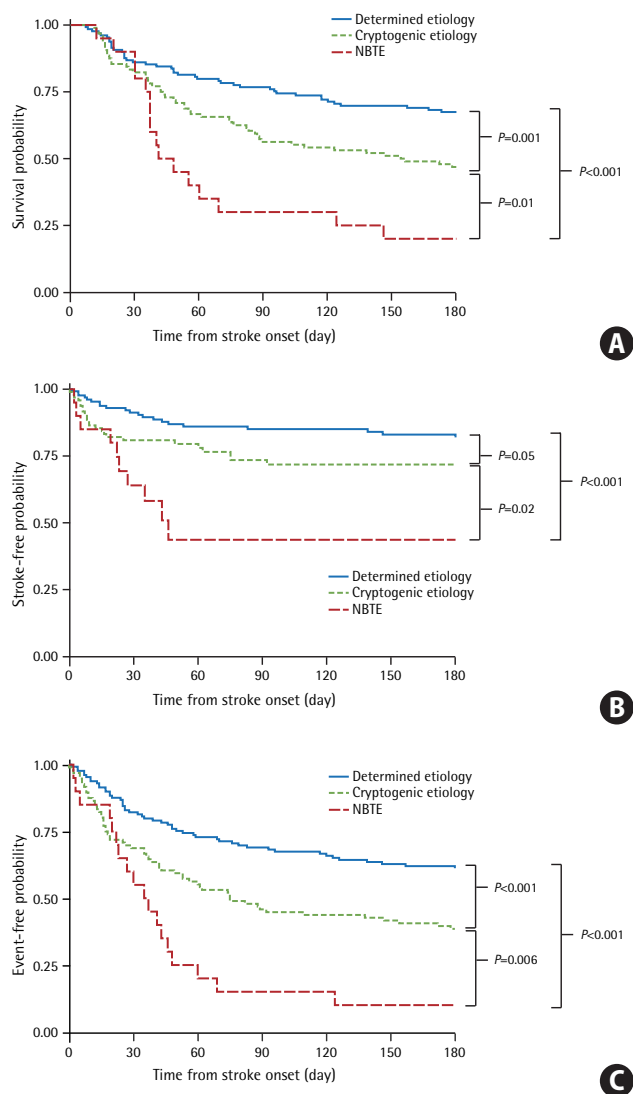


Figure 1. Kaplan-Meier analysis of (A) mortality, (B) stroke events, and (C) composite outcomes of mortality and stroke events during the 6-month follow-up. Bonferroni's correction was performed for intergroup comparisons. NBTE, nonbacterial thrombotic endocarditis.

those of patients with stroke of a determined etiology. These are known characteristics of cancer-related stroke.³ Our findings suggest that some features of cancer-related stroke may be associated with NBTE.^{28,29} Patients with a cryptogenic etiology had intermediate characteristics between those with NBTE and those with a determined etiology. Although NBTE is often not diagnosed despite TEE being performed,³⁰ NBTE has been suggested as the likely cause of cryptogenic stroke in many patients with cancer.²⁹ Therefore, undiagnosed NBTE may have been present in some patients with a cryptogenic etiology.

This study has several limitations. First, although patients were enrolled prospectively, analysis for this study was per-

Table 4. Cox models for 6-month composite outcomes of mortality/stroke events

Variable	Univariate analysis		Multivariate analysis			
	HR (95% CI)	P	Model 1		Model 2	
			HR (95% CI)	P	HR (95% CI)	P
Demographics						
Age (yr)	0.999 (0.982–1.017)	0.931	1.015 (0.996–1.034)	0.137	1.011 (0.992–1.030)	0.269
Male sex	0.471 (0.331–0.669)	<0.001	0.540 (0.347–0.851)	0.007	0.520 (0.333–0.810)	0.004
Risk factors						
Hypertension	0.841 (0.587–1.206)	0.347				
Diabetes mellitus	0.877 (0.600–1.282)	0.498				
Dyslipidemia	0.665 (0.408–1.083)	0.101	0.878 (0.519–1.463)	0.625	0.948 (0.561–1.601)	0.840
Atrial fibrillation	0.902 (0.582–1.396)	0.643				
Current smoker	0.500 (0.262–0.955)	0.036	0.938 (0.429–1.807)	0.862	0.856 (0.418–1.753)	0.670
Body mass index (kg/m ²)	0.927 (0.878–0.979)	0.007	0.926 (0.869–0.980)	0.012	0.929 (0.875–0.986)	0.015
Stroke etiology						
Determined	Reference		Reference			
Cryptogenic	1.976 (1.355–2.882)	<0.001	1.447 (0.938–2.218)	0.090		
NBTE	4.099 (2.371–7.086)	<0.001	1.941 (1.052–3.690)	0.038		
Medications mainly used after admission*						
Antiplatelets	Reference		Reference		Reference	
Anticoagulants	1.810 (1.277–2.567)	0.001	1.353 (0.915–1.999)	0.130	0.958 (0.644–1.427)	0.834
Presence of metastasis	5.332 (3.264–8.708)	<0.001			2.870 (1.648–4.996)	<0.001
Cancer type						
Colorectal	1.113 (0.530–2.339)	0.778	0.694 (0.326–1.565)	0.362	0.796 (0.360–1.761)	0.573
Gastric/esophageal	1.521 (0.789–2.932)	0.210	1.415 (0.675–2.839)	0.342	1.399 (0.682–2.868)	0.359
Hepatobiliary	2.196 (1.157–4.167)	0.016	1.522 (0.745–2.997)	0.236	1.312 (0.649–2.656)	0.450
Pancreas	2.812 (1.402–5.638)	0.004	1.093 (0.513–2.460)	0.826	0.767 (0.339–1.734)	0.523
Lung	1.628 (0.858–3.087)	0.136	1.330 (0.670–2.568)	0.404	1.084 (0.550–2.133)	0.816
Bladder/urinary tract	0.648 (0.188–2.238)	0.493	0.686 (0.201–2.788)	0.576	1.120 (0.293–4.280)	0.869
Female genital organ	2.059 (0.839–5.052)	0.115	1.180 (0.477–3.289)	0.738	1.115 (0.424–2.936)	0.825
Others	Reference		Reference		Reference	
Initial NIHSS score	1.031 (1.004–1.058)	0.024	1.023 (0.994–1.056)	0.140	1.028 (0.998–1.060)	0.071
Reperfusion therapy	0.808 (0.506–1.291)	0.372				
Multiple vascular territory involvement	3.662 (2.482–5.403)	<0.001			2.524 (1.570–4.058)	<0.001
Laboratory findings						
Hemoglobin (g/dL)	0.918 (0.847–0.994)	0.034	0.960 (0.864–1.046)	0.415	1.007 (0.920–1.102)	0.879
White blood cells (×10 ⁹ /L)	1.061 (1.020–1.104)	0.004	1.095 (1.040–1.145)	<0.001	1.094 (1.040–1.151)	0.001
Platelets (×10 ⁹ /L)	0.996 (0.994–0.998)	<0.001	0.997 (0.995–0.999)	0.003	0.997 (0.996–0.999)	0.006
D-dimer (mg/L)	1.078 (1.061–1.095)	<0.001	1.053 (1.028–1.078)	<0.001	1.033 (1.006–1.062)	0.018
Fibrinogen (g/L)	0.998 (0.996–0.999)	0.002	0.999 (0.998–1.001)	0.480	0.999 (0.997–1.001)	0.174

HR, hazard ratio; CI, confidence interval; NBTE, nonbacterial thrombotic endocarditis; NIHSS, National Institutes of Health Stroke Scale.

*Excluded eight patients with both antiplatelet and anticoagulant, 10 patients without antithrombotics.

formed retrospectively at a single center. In addition, as the study hospital has a dedicated cancer center, the frequency of cancer, particularly that of advanced cancer or metastasis,

might be higher than that in other more general hospitals. Second, although most patients (85%) with active cancer underwent echocardiography, TEE (the gold standard for diagnosis

of vegetation^{30,31}) was used in only 60.4%. Although TEE is one of the routine evaluations in our protocol, it was impractical to perform TEE in all patients (it is semi-invasive and requires patient cooperation and informed consent). Vegetation is often invisible on TTE, and even when using TEE, a small vegetation may not be detected. Therefore, the presence of NBTE in this study might have been underestimated. Third, the antithrombotic treatment for stroke prevention in our study population was not controlled. Therefore, the influence of preventive treatment on stroke recurrence is unknown. Finally, our explanation on the role of platelets in metastasis and development of NBTE is speculative.

Conclusions

NBTE should be suspected as a potential mechanism of stroke in patients with metastatic cancer, particularly in those without determinable etiologies. We also showed that patients with NBTE have a very high short-term risk of recurrent stroke and mortality. In addition, mortality was higher in patients who developed recurrent stroke. In this regard, efforts are necessary to reduce the risk of stroke recurrence in these patients. Further studies are necessary to determine optimal preventive treatment in stroke patients with cancer-associated NBTE.

Supplementary materials

Supplementary materials related to this article can be found online at <https://doi.org/10.5853/jos.2020.00619>.

Disclosure

The authors have no financial conflicts of interest.

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Supplementary Table 1. Comparison between patients with and without transesophageal echocardiography

Variable	Without echocardiography (n=44)	With echocardiography (n=245)	P
Demographics			
Age (yr)	64.1±10.5	68.7±10.7	0.010
Male sex	25 (56.8)	136 (55.5)	>0.999
Risk factors			
Hypertension	25 (56.8)	159 (64.9)	0.392
Diabetes mellitus	14 (31.8)	77 (31.4)	>0.999
Dyslipidemia	7 (15.9)	46 (18.8)	0.810
Atrial fibrillation	2 (4.6)	51 (20.8)	0.018
Current smoker	7 (15.9)	46 (18.8)	0.810
Body mass index (kg/m ²)	21.8±3.2	22.6±3.5	0.162
Metastatic cancer	34 (77.3)	150 (61.2)	0.062
Cancer type			0.556
Colorectal	4 (9.1)	32 (13.1)	
Gastric/esophageal	6 (13.6)	44 (18.0)	
Hepatobiliary	4 (9.1)	38 (15.5)	
Pancreas	8 (18.2)	22 (9.0)	
Lung	11 (25.0)	46 (18.8)	
Bladder/urinary tract	2 (4.5)	11 (4.5)	
Female genital organ	1 (2.3)	12 (4.9)	
Others	8 (18.2)	40 (16.3)	
Initial NIHSS score	6.5 (3–15)	5 (2–11)	0.041
Reperfusion therapy	8 (18.2)	46 (18.9)	>0.999
Multiple vascular territory involvement	20 (45.5)	127 (51.8)	0.538
Laboratory findings			
Hemoglobin (g/dL)	11.1±1.8	11.3±2.4	0.557
White blood cells (×10 ⁹ /L)	9.1±5.0	8.2±4.2	0.285
Platelets (×10 ⁹ /L)	219±120	214±117	0.806
D-dimer (mg/L)	5.2±8.0	3.5±6.5	0.201
Fibrinogen (g/L)	3.3±1.4	3.3±1.4	0.870

Values are presented as mean±standard deviation, number (%), or median (interquartile range).
NIHSS, National Institutes of Health Stroke Scale.

Supplementary Table 2. Etiologic mechanisms of stroke in 129 patients with a determined etiology

Mechanism	Etiology
Cardioembolism	51
Atrial fibrillation	31
Patent foramen ovale (with venous thrombosis)	7
Akinetic left ventricular segment	3
Hypokinetic left ventricular segment	3
Valvular heart disease (prosthetic valve replacement)	2
Cardiac thrombus	2
Atrial septal aneurysm	1
Status of inserted pacemaker (sick sinus syndrome)	1
Infective endocarditis	1
Large artery atherosclerosis	46
Small artery disease	10
Other determined etiologies	3
Two or more causes	19
Large artery atherosclerosis+cardioembolism	14
Atrial fibrillation	11
Atrial flutter	1
Prosthetic valve replacement	1
Spontaneous echo contrast	1
Large artery atherosclerosis+small artery disease	3
Cardioembolism+small artery disease	2
Atrial fibrillation	2