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ORIGINAL RESEARCH

Von Willebrand Factor Antigen Levels Predict Poor Outcomes in Patients With Stroke and Cancer: Findings From the Multicenter, Prospective, Observational SCAN Study

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BACKGROUND: Patients with acute ischemic stroke and active cancer have more severe neurological symptoms, elevated risks of stroke recurrence, and death compared with the general population. We examined whether von Willebrand factor (vWF) antigen levels at stroke onset were associated with the poor outcomes of patients with stroke and cancer.

METHODS AND RESULTS: Using data from 90 patients with acute ischemic stroke and active cancer who were registered in the SCAN (Ischemic Stroke in Patients With Cancer and Neoplasia) study, a prospective multicenter, observational study in Japan, we divided patients into 2 groups according to their median vWF antigen levels (high, n=46; or low, n=44). The high-vWF group had a significantly higher initial National Institutes of Health Stroke Scale score (median, 7 [interquartile range, 3–11.25] versus 3 [interquartile range, 1–8.5]; $P<0.05$) and a significantly higher incidence of cryptogenic stroke (32 [70%] versus 16 [36%]; $P<0.01$) and venous thromboembolism (7 [15%] versus 0 [0%]; $P<0.01$), as well as multiple lesions (28 [62%] versus 12 [27%]; $P<0.001$), than the low-vWF group. We observed no significant difference in the rate of stroke recurrence within 1 year between the groups. However, increased vWF levels were an independent predictor of death within 1 year of stroke onset, after adjusting for potential confounders (odds ratio, 6.77 [95% CI, 1.49–30.78]; $P<0.05$).

CONCLUSIONS: Elevated vWF antigen levels were associated with adverse outcomes in patients with cancer-associated stroke and may represent a useful biomarker to guide future therapeutic interventions.

Key Words: active cancer ■ cancer-associated stroke ■ ischemic stroke ■ von Willebrand factor antigen levels

Patients with cancer have an elevated risk of stroke compared with the general population.[1] In addition, patients with stroke and cancer have higher rates of recurrent thromboembolism and death than those without cancer.[2] The procoagulant mechanisms underlying stroke in patients with cancer (cancer-associated stroke) are complex and multifaceted. However, histological analyses of thrombi in individuals

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CLINICAL PERSPECTIVE

What Is New?

- Elevated von Willebrand factor antigen levels were associated with severe neurological symptoms in patients with stroke and cancer.
- Moreover, high von Willebrand factor antigen levels were an independent predictor of death within 1 year after adjusting for potential confounders (odds ratio, 6.77 [95% CI, 1.49–30.78]; $P<0.05$).

What Are the Clinical Implications?

- Von Willebrand factor antigen levels may be a useful biomarker to identify patients with a poor prognosis and guide future therapeutic interventions.

Nonstandard Abbreviations and Acronyms

SCAN	Ischemic Stroke in Patients With Cancer and Neoplasia
vWF	von Willebrand factor

with cancer-associated stroke revealed that they were enriched in platelets,[3,4] suggesting that platelets play an important role in the pathophysiology of cancer-associated stroke.

Von Willebrand factor (vWF) is a large multimeric glycoprotein produced in endothelial cells and megakaryocytes. vWF mediates platelet adhesion and aggregation at sites of vascular injury by binding to the collagen and platelet receptors.[5] In addition to its role in thrombosis and hemostasis, vWF contributes to cancer progression and metastasis by promoting proinflammatory signaling, angiogenesis, and vascular permeability.[6]

In the general population, the association between elevated vWF levels and stroke severity,[7] stroke recurrence,[8] poststroke morbidity,[9] and poststroke death[10] has frequently been reported. However, the role of vWF levels in cancer-associated stroke remains unclear.

We thus analyzed the association between vWF antigen levels and clinical outcomes in patients with ischemic stroke and active cancer by conducting a multicenter prospective observational study.[11] The first aim of this study was to evaluate whether vWF antigen levels at stroke onset were associated with stroke severity in patients with cancer-associated stroke. The second aim was to examine if vWF antigen levels were linked to stroke recurrence within 1 year after cancer-associated stroke. The third aim was to investigate if vWF antigen levels could independently predict death within 1 year after cancer-associated stroke onset.

METHODS

The data that support the findings of this study are available from the corresponding author upon 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.

Participants

The SCAN (Ischemic Stroke in Patients with Cancer and Neoplasia) study was a prospective, multicenter, observational study designed to examine the clinical characteristics of cancer-associated stroke. The SCAN study included 135 patients with acute ischemic stroke and active cancer who were hospitalized within 14 days after a stroke between July 2016 and December 2020 from 9 stroke centers in Japan. Active cancer was defined as a diagnosis of cancer, either treated in the past 6 months before admission or untreated, or metastatic disease.[11,12] The main patient baseline characteristics were published previously.[11] All the patients were followed up for 1 year after their stroke to investigate the prognosis of patients with acute stroke and active cancer. This study complied with the Declaration of Helsinki and was approved by the institutional review board of each participating hospital. Of the 135 patients with acute ischemic stroke and active cancer enrolled in the SCAN study, 45 patients were excluded on the basis of missing vWF antigen level data.

Blood Samples

Blood samples were obtained immediately after patient admission and before any treatment was initiated. vWF antigen levels were measured by latex agglutination on the STA clot analyzer (STA Liatest vWF, Roche Diagnostics K.K., Tokyo, Japan). Samples within the 50% to 155% range were considered to have normal vWF antigen levels. hs-CRP (high-sensitivity C-reactive protein) concentrations were measured using a latex agglutination immunoassay. D-dimer levels were measured using a latex turbidimetric immunoassay.

Stroke and Outcomes

Initial neurological deficits were assessed using the National Institutes of Health Stroke Scale score on admission. All primary and subsequent strokes were

confirmed using magnetic resonance imaging or computed tomography scans. Functional outcomes were assessed using the modified Rankin Scale score at 1 year after the stroke. Stroke was classified into 5 subtypes on the basis of pathogenesis using the Trial of Org 10172 in Acute Stroke Treatment classification.[13] Vascular neurologists determined the treatment strategy for acute stroke and selected the antithrombotic medication for secondary prevention, which were independent of the vWF antigen values.

Cancer Stage

Cancers were coded according to the *International Classification of Diseases for Oncology, Third Edition* (*ICD-O-3*). The TNM staging system was used to determine cancer stage. Cancer stage was recorded at stroke onset. Stages III and IV were defined as advanced stages.

Statistical Analysis

All data were presented as counts and percentage or medians with interquartile range (IQR). Categorical variables were compared using the chi-squared test, whereas continuous variables were compared using the Wilcoxon test. The Spearman rank test was used to study correlations between continuous variables. Survival and stroke recurrence rates were evaluated using the Kaplan–Meier method. In the analysis of stroke recurrence, death was treated as a competing risk using the Fine and Gray regression model. Logistic regression analyses were performed to determine if vWF antigen levels could independently predict clinical outcomes. We tested 4 models. Model 1 included age and sex. Model 2 included the variables in model 1 plus cancer stage. Model 3 included the variables in model 2 plus National Institutes of Health Stroke Scale score at admission. Model 4 included the variables in model 3 plus D-dimer and hs-CRP levels. *P* values <0.05 were regarded as a measure of statistical significance. Statistical analyses were performed using JMP 16.1.0 software (SAS institute Inc., Cary, NC) and R software (https://cran.r-project.org).

RESULTS

Study Populations

A total of 90 patients were evaluated in this analysis. The median age was 75.5 years (interquartile range [IQR], 70–82) and 33 (37%) were women. Patients were divided into 2 groups according to their median vWF antigen levels (low-vWF group: 61%–244%, n=44; and high-vWF group: 246%–555%, n=46; Figure 1A).

The baseline patient characteristics are summarized in Table 1. There were no significant differences in the background, past medical history, cancer status, or cancer sites between the 2 groups. More than half of the patients in each group had advanced cancer. The patients in the low-vWF group had significantly higher rates of cancer surgery before onset of stroke than those in the high-vWF group (Table 1).

Clinical Differences in Cancer-Associated Stroke According to vWF Antigen Levels

We then examined the clinical feature of stroke in the patients with cancer (Table 2). At admission, the patients in the high-vWF group had significantly higher National Institutes of Health Stroke Scale scores (median, 3 [IQR, 1–8.5] versus 7 [IQR, 3–11.25]; $P<0.05$), hs-CRP levels (median, 0.6 [IQR, 0.1–2.8] versus 2.5 [IQR, 1.1–5.2]; $P<0.01$), D-dimer levels (median, 1.9 [IQR, 1.1–4.9] versus 11.4 [IQR, 3.4–25.9]; $P<0.001$), incidence of cryptogenic stroke (16 [36%] versus 32 [70%]; $P<0.01$), and multiple lesions (12 [27%] versus 28 [62%]; $P<0.001$) compared with those in the low-vWF group (Table 2). However, the high-vWF group had significantly lower platelet counts (median, 22.8 [IQR, 17.6–29.1] versus 16.0 [IQR, 8.2–25.0]; $P<0.001$; Table 2). Moreover, we found significant positive associations between vWF antigen levels and National Institutes of Health Stroke Scale scores ($\rho=0.276$, $P<0.01$), D-dimer levels ($\rho=0.481$, $P<0.0001$) and hs-CRP levels ($\rho=0.287$, $P<0.01$) (Figure 1B through 1D). The high-vWF group also had a significantly higher incidence of systemic venous thromboembolism (7 [15%] versus 0 [0%]; $P<0.001$) as a complication at admission (Table 2). Meanwhile, no differences in the rates of intravenous tissue-type plasminogen activator treatment and endovascular therapy were found between the 2 groups (Table 2). We did, however, find that patients in the low-vWF group used significantly higher amounts of antiplatelet medication for secondary stroke prevention than those in the high-vWF group (21 [48%] versus 5 [11%]; $P<0.0001$; Table 2). By contrast, the number of patients in the high-vWF group receiving anticoagulant therapy was higher than that in the low-vWF group (36 [78%] versus 27 [62%]), although this did not reach statistical significance ($P=0.079$) (Table 2).

Prognostic Value of vWF Antigen Levels in Cancer-Associated Stroke

Next, we assessed the rate of stroke recurrence within 1 year after the stroke. We found that 3 patients (7%) in the low-vWF group and 4 patients (9%) in the high-vWF group experienced stroke recurrence. However, we observed no significant difference in the rates of stroke recurrence within 1 year between the 2 groups (low-vWF group: 6.8% [95% CI, 1.7–16.9]; high-vWF group: 8.7% [95% CI, 2.7–19.1]; $P=0.73$; Figure 2A). In addition, all strokes recurred within 100 days after the initial stroke in both groups.

We then compared functional outcomes at 1 year after the initial stroke. We found that the high-vWF group

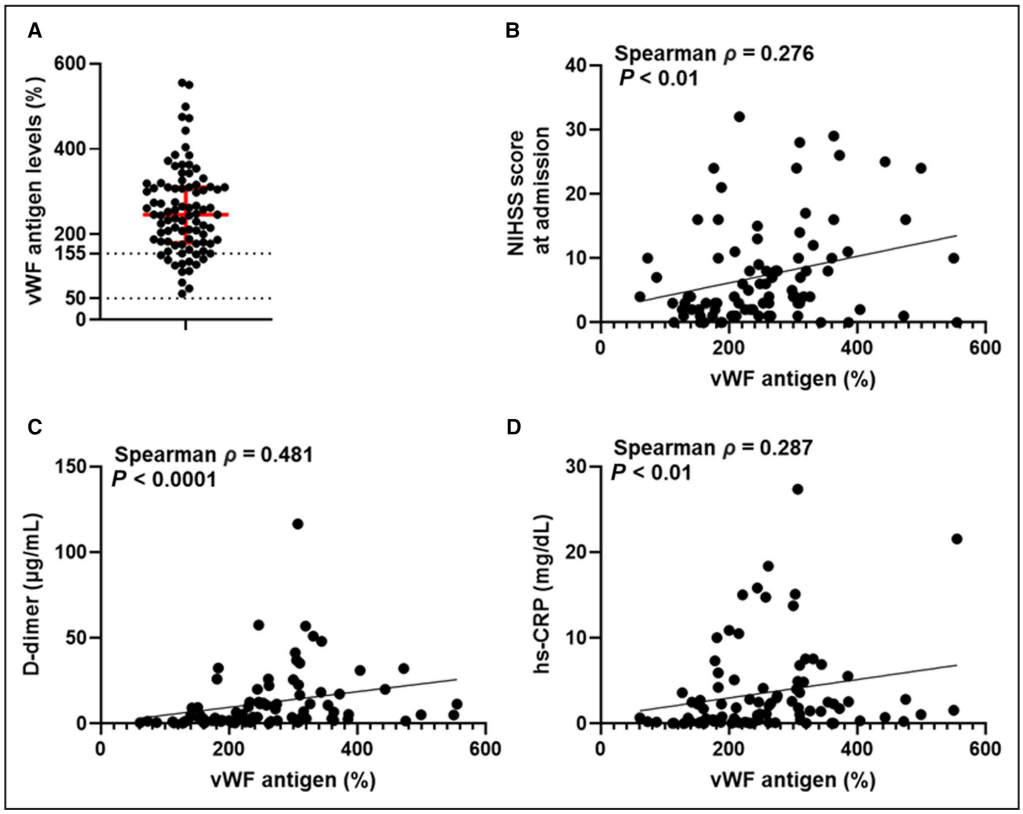

Figure 1. The distribution of vWF antigen levels and correlation between vWF antigen levels and NIHSS score, D-dimer levels, and hs-CRP levels.

A, The 50%–155% range is considered to be the normal value of vWF antigen levels, which are shown as dotted lines. The red colored line and bars are median (246) and IQR (180.3–310.3). **B**, The NIHSS score at admission. **C**, D-dimer levels (μg/mL). **D**, hs-CRP levels (mg/dL). Blood samples were obtained immediately after patient admission and before any treatment was initiated. The Spearman rank correlation test was used in B, C, and D. hs-CRP indicates high-sensitivity C-reactive protein; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; and vWF, von Willebrand factor.

had a significantly higher modified Rankin Scale score than the low-vWF group (median, 4 [IQR, 1–6] versus 6 [IQR, 4.75–6]; *P*<0.01), suggesting that patients in this group had poor functional outcomes. Evaluation of survival rates at 1 year after the stroke using the Kaplan–Meier method revealed that the high-vWF group had a significantly lower survival rate than the low-vWF group (low-vWF group: 65.9% [95% CI, 53.3–81.5]; high-vWF group: 43.5% [95% CI, 31.1–60.4]; log rank, *P*<0.001) (Figure 2B).

Finally, we performed logistic regression analyses to examine whether vWF antigen levels at stroke onset could predict death within 1 year. We found that high vWF antigen levels were an independent predictor of death within 1 year after adjusting for potential confounders (odds ratio, 6.77 [95% CI, 1.49–30.78]; *P*<0.05; Table 3).

DISCUSSION

The major findings of this study were that (1) patients with cancer-associated ischemic stroke and high vWF antigen levels experienced more severe stroke than those with low vWF antigen levels; (2) vWF antigen levels were not associated with the rate of stroke recurrence in these patients; and (3) high vWF antigen levels at stroke onset were an independent predictor of death within 1 year of stroke onset in patients with cancer-associated stroke.

Compared with a normal range of vWF antigen levels, patients with cancer-associated stroke have increased vWF antigen levels (Figure 1A). We have 2 possible explanations for increased vWF antigen values in this study population. First, patients with ischemic stroke have increased vWF antigen levels compared with the control population.[14,15] Second, several cohorts of patients with cancer also have increased levels of vWF antigen levels compared with healthy controls.[6] Taken together, the combination of ischemic stroke and cancer could increase the levels of vWF antigen. Therefore, patients with cancer-associated stroke may have elevated vWF antigen levels compared with normal controls.

Patients with cancer-associated stroke have some unique clinical characteristics, such as fewer traditional stroke risk factors, increased stroke severity, elevated D-dimer and C-reactive protein levels, embolic-like

Table 1. Baseline Characteristics of Patients With Stroke and Cancer Belonging to the Low- and High-vWF Groups

	Low vWF (61–244 [%]), n=44	High vWF (246–555 [%]), n=46	*P* value
Age, y	76.5 (70–81.75)	75 (69–82)	0.616
Female	12 (27)	21 (46)	0.071
Past medical history			
Hypertension	25 (57)	27 (59)	0.857
Diabetes	13 (30)	9 (20)	0.271
Hyperlipidemia	15 (34)	17 (40)	0.777
Prior history of stroke	12 (27)	9 (20)	0.388
Cancer status			
Advanced cancer stage	27 (61)	31 (67)	0.374
Metastasis	23 (52)	26 (57)	0.620
Prestroke cancer treatment			
Cancer surgery	14 (32)	6 (13)	0.0367
Chemotherapy	26 (59)	23 (51)	0.449
Radiotherapy	5 (11)	4 (10)	0.698
No treatment	7 (16)	15 (33)	0.0654
Cancer site			0.15
Lip, mouth, and pharynx	4 (9)	3 (7)	
Esophagus	2 (5)	3 (7)	
Gastrointestinal tract	1 (2)	3 (7)	
Colon and rectum	4 (9)	8 (17)	
Liver	2 (5)	2 (4)	
Gallbladder	0 (0)	4 (9)	
Pancreas	4 (9)	8 (17)	
Lung	12 (27)	4 (9)	
Breast	5 (11)	2 (4)	
Uterus	0 (0)	1 (2)	
Prostate	4 (9)	3 (7	
Bladder	3 (7)	0 (0)	
Thyroid	0 (0)	1 (2)	
Hematopoietic	2 (5)	3 (7)	
Other	1 (2)	1 (2)	

Data are shown as the median (IQR) or n (%). IQR indicates interquartile range; and vWF, von Willebrand factor.

infarctions in multiple vascular territories, and high rates of recurrent stroke than those without cancer.[16] In this study, the patients in the high-vWF group had more severe neurological deficits, elevated D-dimer and hs-CRP levels, and more lesions than those in the low-vWF group (Table 2). Moreover, vWF antigen levels were positively correlated with D-dimer and hs-CRP concentrations (Figure 1C and 1D). These findings suggest that patients with high vWF antigen levels share characteristics of cancer-associated stroke. In addition, we observed that 15% of patients in the high-vWF group had systemic venous thrombosis as a complication on admission (Table 2), suggesting that patients with increased vWF antigen levels might be predisposed to coagulopathy. Taken together, we surmised that increased vWF antigen values could reflect the clinical status of patients with cancer-associated stroke and thus be helpful in characterizing this group of patients, especially given that coagulopathy is an important cause of cancer-associated stroke.[17]

Unexpectedly, we found that the high-vWF group had a similar annual stroke recurrence rate (8.7%) to that of the low-vWF group (6.8%). These recurrence rates were lower than those reported by previous studies (16% at 6 months[2] and 26% at a median follow-up time of 48 days[18]). We have 2 possible reasons for the low stroke recurrence rates observed in our study. First, we might have missed some stroke recurrence cases and therefore underestimated the stroke recurrence rates. Stroke recurrence was confirmed in an outpatient clinic or via telephone interview by the attending physician. Therefore, stroke recurrence would have been difficult to detect in patients with mild to no stroke recurrence symptoms. Second, we found that

Table 2. Clinical Features of Stroke in Patients With Cancer With Different vWF Antigen Levels

	Low vWF (61–244 [%]), n=44	High vWF (246–555 [%]), n=46	*P* value
NIHSS at admission	3 (1–8.5)	7 (3–11.25)	0.0392
Platelets (× 10^4/μL)	22.8 (17.6–29.1)	16.0 (8.2–25.0)	0.0003
hs-CRP, mg/dL	0.6 (0.1–2.8)	2.5 (1.1–5.2)	0.0055
D-dimer, μg/mL	1.9 (1.1–4.9)	11.4 (3.4–25.9)	<0.0001
Stroke subtypes			
Cryptogenic	16 (36)	32 (70)	0.0016
Cardioembolism	10 (22)	9 (20)	0.713
Large-artery atherosclerosis	8 (18)	4 (9)	0.186
Small vessel occlusion	4 (9)	0 (0)	0.0364
Other	6 (14)	1 (2)	0.0424
Imaging analysis			
Multiple lesions	12 (27)	28 (62)	0.0009
Complication at admission			
Systemic venous thromboembolism	0 (0)	7 (15)	0.0070
Acute therapy for stroke			
tPA treatment	3 (7)	2 (4)	0.609
Endovascular therapy	8 (18)	4 (9)	0.186
Secondary prevention for stroke			
Antiplatelet therapy	21 (48)	5 (11)	0.0001
Anticoagulation therapy	27 (62)	36 (78)	0.079

Data are shown as the median (IQR) or n (%). hs-CRP indicates high-sensitivity C-reactive protein; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; tPA, tissue-type plasminogen activator; and vWF, von Willebrand factor.

78% of patients in the high-vWF group received anticoagulant therapy as a secondary stroke prevention (Table 2), even though only 9 (20%) patients were diagnosed as having cardioembolic stroke. Meanwhile, 62% of patients in the low-vWF group received anticoagulant therapy. Moreover, the use of anticoagulant medication in our study was higher than that previously reported (<40%).[2] In addition, we found that all strokes recurred within 100 days after stroke onset in both groups (Figure 2A). This finding highlights that patients with cancer-associated stroke may be at an especially elevated risk for stroke recurrence during this 100-day period. At present, there are limited guidelines for managing cancer-associated stroke. Although further studies are required, anticoagulant therapy might be a novel strategy for preventing the recurrence of cancer-associated stroke.

Two previous studies showed that patients with stroke with elevated vWF antigen levels had an increased risk of death.[10,19] However, to the best of our knowledge, this is the first multicenter, prospective study to demonstrate that high vWF antigen levels are also an independent predictor of death among patients with cancer-associated stroke. Moreover, we

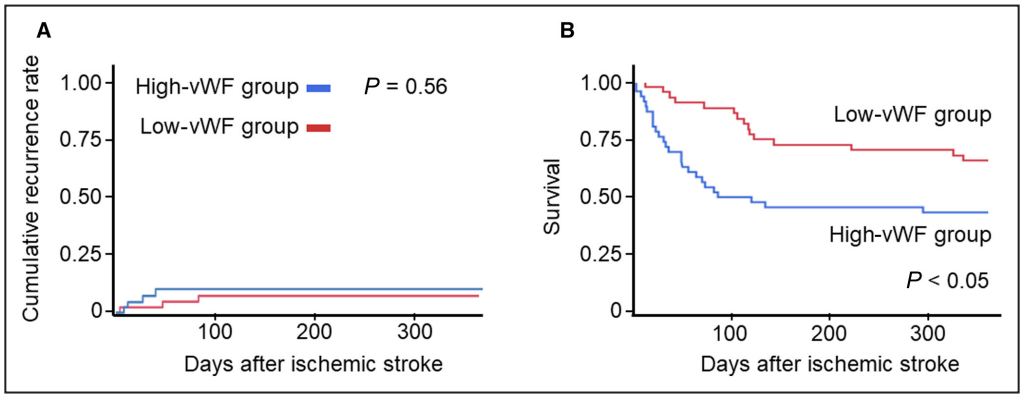

Figure 2. Stroke recurrence and poststroke survival within 1 year of the initial stroke.
A, Stroke recurrence and (**B**) survival rates were estimated using the Kaplan–Meier method. Death was treated as a competing risk in the stroke recurrence analysis. vWF indicates von Willebrand factor.

Table 3. Elevated vWF Antigen Levels at Stroke Onset Predict Death Within 1 Year of Stroke in Patients With Cancer

	OR (95% CI)	*P* value
High-vWF group (unadjusted)	2.51 (1.07–5.90)	0.0343
High-vWF group (model 1)	2.95 (1.19–7.36)	0.0201
High-vWF group (model 2)	5.46 (1.57–18.93)	0.0075
High-vWF group (model 3)	5.66 (1.58–20.23)	0.0077
High-vWF group (model 4)	6.77 (1.49–30.78)	0.0133

Model 1: vWF+age+sex; model 2: model 1+cancer stage; model 3: model 2+NIHSS score at admission; model 4: model 3+D-dimer and hs-CRP levels. hs-CRP indicates high-sensitivity C-reactive protein; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; and vWF, von Willebrand factor.

demonstrated that the predictive power of vWF antigen levels was retained even after adjustment for cancer stage and baseline stroke severity. vWF is mainly synthesized in vascular endothelial cells and has a primary role in hemostasis. Interestingly, vWF also promotes proinflammatory signaling, regulates angiogenesis, and modulates vascular permeability, which may contribute not only to cancer progression but also to ischemic injury. Consequently, reducing vWF antigen levels or inhibiting vWF signaling may be a feasible strategy for attenuating cancer progression and ischemic injury and, thus, improving the prognosis of patients with cancer-associated stroke. Recently, innovative therapeutic approach for vWF is just beginning to emerge. Caplacizumab is an anti-vWF humanized, bivalent variable-domain-only immunoglobulin fragment that can inhibit interaction between vWF and platelets, resulting in decreased formation of microthrombi.[20] Caplacizumab is already approved by the US Food and Drug Administration for treatment for acquired thrombotic thrombocytopenic purpura.[21] Further development of innovative treatment for cancer-associated stroke is expected.

In our study, the high-vWF group had lower platelet counts than the low-vWF group (Table 2). Patients with cancer are prone to hemostatic perturbations, which increases the risk of thrombosis and bleeding. Platelets are an important factor in hemostasis dysregulation during cancer; however, the underlying mechanisms are not well understood. A previous study using a mouse model of human pancreatic cancer demonstrated that platelet counts were decreased, while reticulated platelets were elevated in tumor-bearing mice compared with control mice. These findings suggest that the clearance of activated platelets is increased in tumor-bearing mice.[22] In addition, Chen et al reported that the binding of vWF to platelets facilitated their rapid clearance by inducing glycoprotein Ibα-mediated signaling in response to refrigeration.[23] Thus, the increased vWF antigen levels observed in patients with cancer might contribute to the reduction of platelet counts by promoting the clearance of activated platelets. The molecular mechanisms underlying the reduction in platelet counts in patients with cancer should be addressed in future studies.

Study Limitations

First, we adjusted cancer stage to determine if vWF antigen levels could predict death within 1 year of stroke onset; however, because of the small number of patients included in the study, we did not stratify by cancer site or cancer treatment. Again, because of the small sample size, we could not examine whether the antithrombotic medication influenced stroke recurrence (low vWF, 3 [6.8%] versus high vWF, 4 [8.7%]). Finally, we did not have access to ADAMTS13 data in this study. ADAMTS13 cleaves hemostatically active, ultra-large vWF to form the less active, low-molecular-weight vWF. As such, ADAMTS13 is an important regulator of VWF distribution and hemostatic activity. These points should be addressed in a future study.

SUMMARY

High vWF antigen levels at stroke onset were associated with adverse outcomes among patients with cancer-associated stroke. Thus, vWF antigen levels may be a useful biomarker to identify patients with a poor prognosis and guide future therapeutic interventions.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Data S1

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