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D-dimer and diffusion-weighted imaging pattern as two diagnostic indicators for cancer-related stroke

A case–control study based on the STROBE guidelines

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Abstract

The aim of this study was to evaluate the risk factors and elucidate the clinical characteristics of cancer-associated ischemic stroke to differentiate it from conventional ischemic stroke in China and East Asia. Between June 2012 and June 2016, a retrospective analysis was performed on 609 stroke patients with cancer. They were divided into 3 groups: cancer-stroke group (CSG, 203 cases), stroke group (SG, 203 cases), and cancer group (CG, 203 cases). The D-dimer levels and diffusion-weighted imaging lesion (DWI) pattern were compared to an age- and sex-matched control group. The most common cancer types were colorectal cancer (20.2%) and lung cancer (18.72%). The average D-dimer level in stroke patients and cancer patients were 0.34 and 1.50 mg/L, respectively. The descending levels of D-dimer from cancer types were lung cancer (2.06 mg/L), pancreas (1.74 mg/L), gastric (1.61 mg/L), among others. Univariate analysis of the CSG and the others shows there were significant differences in the prevalence of the levels of D-dimer and DWI pattern, hypertension, diabetes mellitus, and thrombus. CSG has a unique pathological characteristic including high plasma D-dimer levels and multiple vascular lesions. The results show that D-dimer and DWI can be used as diagnostic index in clinical practice.

Abbreviations: APTT = activated partial thromboplastin time, AUC = area under the curve, CAS = group in which the tumor occurred simultaneously with stroke, CG = cancer without stroke group, CSG = cancer-stroke group, CSH = group of cancer patients with a history of stroke, DD = D-dimer, DWI = diffusion-weighted imaging, FIB = fibrinogen, HDL = high-density lipoprotein cholesterol, INR = international normalized ration, LDL = low-density lipoprotein cholesterol, n-CSG = stroke patients without risk factors, PT = prothrombin time, r-CSG = patients with normal stroke mechanism, ROC = receiver-operating characteristic, SG = cancer-free stroke group, TCS = group whose cancer occurred after treatment, TOAST = trial of Org 10172 in acute stroke treatment, TT = thrombin time.

Keywords: cancer, colorectal cancer, D-dimer, diffusion weighted imaging, lung cancer, stroke

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1. Introduction

Neoplasms, cardiovascular diseases, cerebrovascular diseases are 3 major killers among humans all over the world.[1–6] The relationship between cancer and thrombosis was first proposed in 1865 by Trousseau, who discovered migratory thrombosis as a manifestation of concealing gastric cancer. Approximately, 15% of the cancer patients were reported to exhibit thromboembolic complications at autopsy, and 50% had clinical manifestations of stroke.[7–9] Researchers have proposed that stroke might be the first manifestation of an underlying malignancy, coagulation abnormalities, or embolic pathologies.[10] Some studies have reported that stroke is a common cerebrovascular accident among cancer patients[11,12] and that the most common mechanisms of stroke in cancer patients appear to be central nervous system tumor and coagulopathy. Cancer-related thrombosis, known as Trousseau syndrome, is caused by coagulopathy, which indicates that cancer-associated hypercoagulation plays a pivotal role in cancer-related stroke.[13] Lung cancer is associated with an increased risk of subsequent stroke within 1 year after diagnosis for men and 2 years after diagnosis for women.[14] Plasma D-dimer levels are above the normal range in patients with gynecologic tract tumors.[15] Studies have demonstrated that ovarian cancer and breast cancer patients have an increased risk of developing ischemic stroke. Age, hypertension, diabetes, and chemotherapy treatment are independent risk factors.[16] However, there are few large-sample retrospective research of cancer-related stroke and high-risk tumor types, among cancer patients in China Mainland. Several studies on this topic have reached

similar conclusions: the D-dimer levels and multiple vascular territory lesions of DWI pattern are 2 significant characteristics differentiating cancer-stroke from conventional stroke.[11,17–19] Based on the hypothesis that hypercoagulation has close relationship with the pathophysiology of stroke in cancer patients without conventional stroke mechanisms, we guessed whether similar findings could be observed in a large cancer-stroke population versus a matched control group in China Mainland. We searched the PubMed and Embase database for similar studies in the United States and Europe and found that the sample sizes in all such studies were <200 and that some studies did not provide clear statistical evidence for the diagnostic significance of the D-dimer levels or multiple vascular territory lesions. Thus, we collected current data in Shanghai and tried to take advantage of a larger sample of statistical data to confirm whether the two characteristics can be used as diagnostic indicators in China.

Previous studies have evaluated the characteristics of ischemic stroke in patients with cancer. There are few large-scale studies on stroke in cancer-affected persons. The present study aims to confirm whether the plasma D-dimer levels can predict ischemic stroke in cancer patients. The highlights of this study are the large sample of patients investigated and the combined analysis of the D-dimer levels and diffusion-weighted imaging (DWI) pattern. The purpose of this study was to evaluate the risk factors in cancer-stroke patients and elucidate the clinical characteristics of cancer-associated ischemic stroke to differentiate the latter from the conventional ischemic stroke and understand whether the D-dimer levels and DWI pattern can be used as diagnostic indices for cancer-related stroke.

2. Methods

2.1. Patient population

To assess the precise mechanisms of stroke in cancer patients, we retrospectively analyzed cancer patients with acute ischemic stroke or a stroke history registered at Xinhua Hospital, Shanghai Jiao Tong University, from 2012 to 2016. Cancer-stroke subjects who displayed no evidence of acute infarction or chronic infarction on neuroimaging, serious infection disease, chronic renal failure, hematological malignancies, or brain tumor were excluded from the study.

2.1.1. Cancer-stroke group. Between June 2012 and June 2016, the total number of patients with cerebral infarction was 7548. Among them, the number of cancer patients with cerebral infarction was 317. Cancer patients with brain tumor, hematological malignancies, and infectious diseases were excluded. Eventually, 203 subjects met our selection criteria. According to the time of cancer onset, the cancer-stroke group (CSG) was divided into 3 groups: a group in which the tumor occurred simultaneously with stroke (diagnosis of cancer and acute stroke occurred within 3 months) (75, 36.95%, CAS), a group in whom stroke occurred after cancer treatment (the diagnosis of cancer and acute stroke occurred >3 months apart, and cancer treatment was received) (63, 30.05%, TCS), and a group of cancer patients with a history of stroke (65, 30.02%, CSH). Clinical diagnostic interviews were conducted by 2 experienced neurologists. The patients in the cancer-related stroke group were classified into 2 subgroups according to the criteria of the Trial of Org 10172 in Acute Stroke Treatment (TOAST): patients with a normal stroke mechanism (stroke patients with normal risk factors, r-CSG) and stroke patients without risk factors (n-CSG).

2.1.2. Stroke group. Two hundred three subjects were selected from the patients with conventional stroke mechanisms (cancer-free stroke group [SG]). The patients were classified as non-cancer patients if they had never been diagnosed with cancer. SG patients were selected with the same hospital admission time, sex, age, and number of cases as the CSG patients. The exclusion criteria were body and CNS tumors, serious infections, hematologic diseases, and vital organ failure.

2.1.3. Cancer group. Two hundred three patients were selected in the cancer group (CG) (cancer without stroke) The patients with cancer were classified as nonstroke patients if they had never been diagnosed with stroke. Overall, 203 subjects were selected from patients with body cancer (cancer without stroke group CG). CG patients were selected with the same hospital admission time, sex, age, type of cancer, and number of cases as the CSG patients. The exclusion criteria were infarction, serious infections, blood diseases, nervous system tumors, and vital organ failure.

Control groups with ischemic infarction or cancer were established by a one-to-one assignment of age- and sex-matched control subjects (N: 203, 63 females, 140 males). Control subjects were further selected with respect to the date of hospital admission to avoid bias from time-dependent differences in the diagnostic workup during the last 5 years. Consequently, age- and sex-matched patients with stroke or cancer who were admitted to the hospital within the same time frame (less than a month), as the index patients were chosen for this study (Fig. 1).

2.2. Demographic and clinical characteristic

Hypertension was diagnosed when the systolic/diastolic blood pressure was consistently >140/90 mmHg. Diabetes mellitus was defined as a fasting blood glucose level ≥126 mg/dL and a glycosylated hemoglobin A1c concentration ≥6.5%. Demographic data, including age, sex, atrial fibrillation, myocardial infarction, thrombus, tumor metastasis, and treatment results, were obtained from medical records.

Laboratory data, including prothrombin time (PT), prothrombin time international normalized ration, activated partial thromboplastin time, thrombin time (TT), erythrocyte, hemoglobin platelet count, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and plasma levels of D-dimer and fibrinogen, were collected. All patients received infarction National Institute of Health Stroke Scale score, electrocardiography, and arteriovenous ultrasound.

2.3. Imaging data

Three-tesla magnetic resonance imaging (MRI) was performed at admission. DWI, T1- and T2-weighted images, fluid-attenuated inversion recovery images, and 3-dimensional time-of-flight magnetic resonance angiography were obtained. Cerebral computed tomography (CT) was chosen for patients with MRI contraindication. For subjects with brain MRI, the distributions of ischemic lesions were divided into single brain infarction, multiple cerebral infarction, and lacuna cerebral infarction. Stroke subtypes were assigned using the criteria of the TOAST.

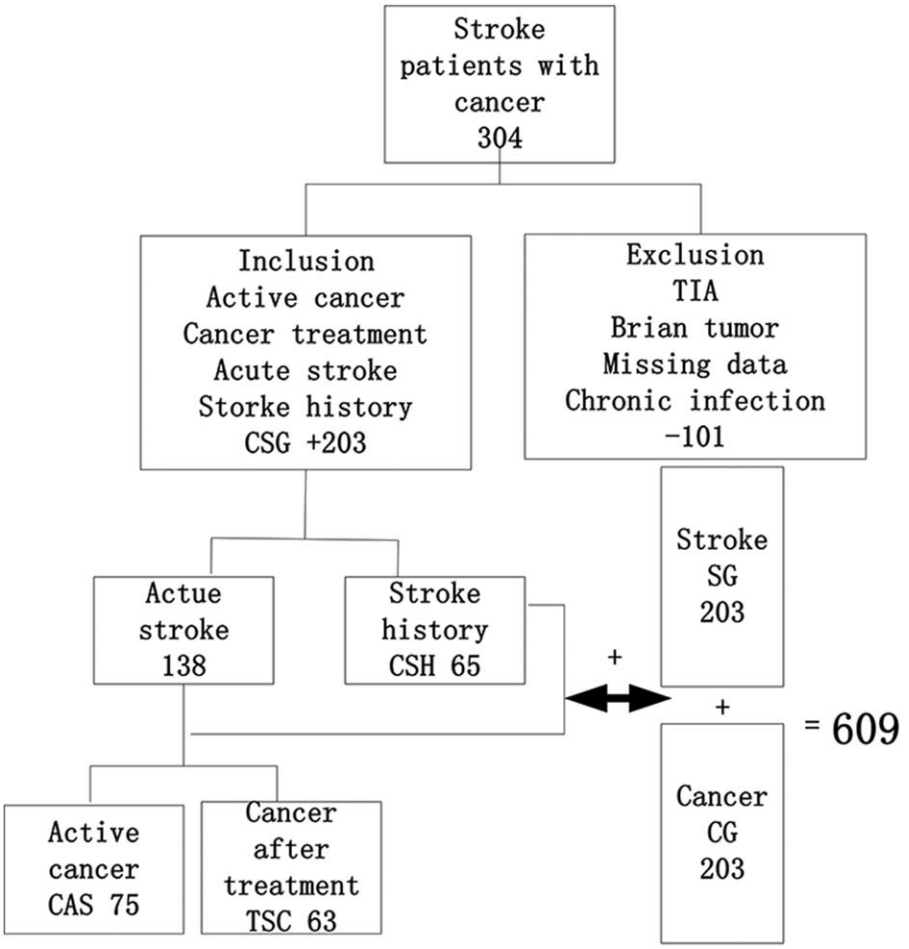

Figure 1. Selection of patients with cancer, showing inclusion and exclusion criteria as well as subgroup assignment and patient numbers.

2.4. Statistical analysis

The SPSS17.0 software (SPSS Inc, Chicago, IL) was applied for data analysis. A P value $<.05$ was considered statistically significant. Differences in the frequency of categorical variables were reviewed using the χ^2 test or Fisher exact test. Outcome values were compared using the t test and general linear model analysis. A receiver-operating characteristic (ROC) curve analysis with area under the curve (AUC) was used to calculate the discriminatory ability of the d-dimer and DWI pattern for r-CSG and n-CSG.

2.5. Ethics Statement

The study was approved by the Ethics Committee of the Xinhua Hospital, Shanghai Jiao Tong University.

3. Results

This study suggests that the most common cancer types were colorectal cancer (20.2%), lung cancer (18.72%), prostate cancer (10.84%), gastric cancer (10.84%), urologic neoplasm (9.36%), breast cancer (7.88%), and gynecological cancer (6.4%) (Fig. 2). The average D-dimer levels in stroke patients without cancer were 0.34 mg/L, whereas the D-dimer levels for cancer patients were 1.0427 mg/L ($P<.05$). The average of D-dimer in each group was ranked in descending order: 1.50 mg/L CAS, 1.01 mg/L CS, 0.88 mg/L TCS, 0.56 mg/L CSH, 0.34 mg/L SG, 0.59 mg/L CG. The average of D-dimer by types of cancer was ranked from high to low as lung cancer (2.06 mg/L), pancreatic cancer (1.74 mg/L), and gastric cancer (1.61 mg/L) (Fig. 3).

Vascular risk factors of patients were more common in the SG group than in the CS group. DWI pattern of multiple lesions that involved multiple arterial territories were more frequent in the CSG than in the SG (Table 1).

Among all laboratory indicators, PT ($P<.005$), TT ($P<.001$), plasma levels of D-dimer ($P<.01$), erythrocytes ($P<.01$), and hemoglobin ($P<.01$) in patients with cancer were significantly higher than those in CFS patients. The mortality rate was significantly higher in patients with cancer (29, 15.3%) than in control subjects (4, 1.97%) ($P<.01$) (Table 1). The prevalence of deep vein thrombosis and pulmonary embolism was significantly higher in patients with cancer (6, 2.90%) than in control subjects (0, 0.0%) ($P<.01$) (Table 1). The D-dimer levels varied significantly among different groups; except TCS compared with CAS ($P>.05$), and those of cancer patients with metastatic disease were significantly higher than those of patients without metastasis ($P<.01$) (Table 2). The AUC for D-dimer level and DWI pattern was 0.864 (0.801–0.967) and 0.839 (0.580–0.755) (95% confidence interval). This indicates that the D-dimer levels and DWI pattern are both reliable indicators for the diagnosis of n-CSG.

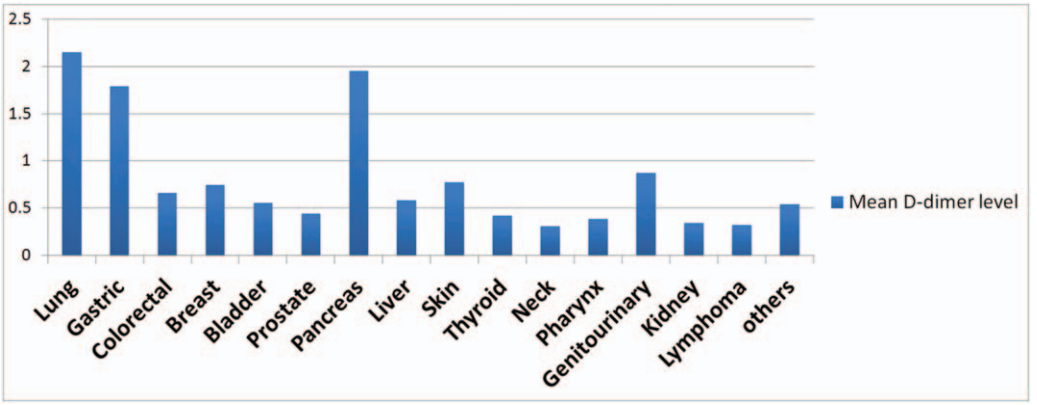

Figure 2. Selection of patients with cancer, showing inclusion and exclusion criteria as well as subgroup assignment and patient numbers.

4. Discussion and conclusion

Stroke remains as one of the highest mortality in neurological diseases.[20–24] The current evidence suggests that a first-ever stroke may reveal an undiagnosed underlying malignancy.[10] To date, this study is the first case–control report in China and is somewhat representative of East Asia. We identify the probability of cerebral infarction in different cancer patients, as in the Schwarzbach et al's study.[11] Because the sample size used intudy is much bigger than those used in other articles,[11,25] our results shall be convincing.

Several studies have reported that lung cancer has the highest incidence in stroke patients, whereas we concluded that colorectal cancer has the highest incidence.[11,17,26] The possible reasons for this discrepancy might be attributed to the different clinical studies performed or the fact that this was a single-center retrospective study, and the difference between colorectal cancer and lung cancer was <2%. Nevertheless, the physicians should be highly alert, not just for patients with lung cancer, as a result of colorectal cancer as a possible risk factor for stroke (Table 3).

Various factors must be considered when determining the etiology of stroke in cancer patients. Chronic inflammation and activated coagulation system seem to play a role in stroke onset, the extent of which depends on the activity and severity of the underlying cancer.[27] Traditional cerebrovascular risk factors in the general population such as age, hypertension, coronary artery disease, hypercholesterolemia, diabetes, and family history of stroke should be assessed, but cancer patients frequently have stroke as a cancer-related event, in which the malignancy directly or indirectly contributes to the cerebrovascular insult.[28]

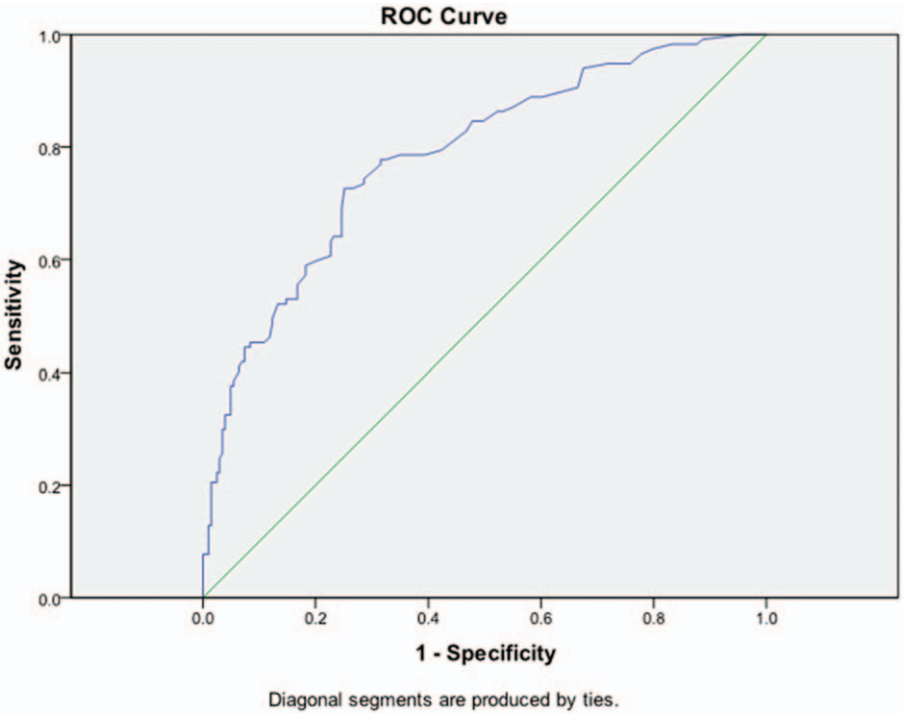

Figure 3. ROC analysis of D-dimer levels and DWI pattern. DWI = diffusion-weighted imaging, ROC = receiving-operating characteristic.

Table 1

Risk factors and lesion patterns in patients with cancer and control subjects.

Basic information	Stroke patients with cancer (N = 203)	Stroke patients (N = 203)	P
Male	140 (69.0%)	140 (69.0%)	1.000
Female	63 (31.0%)	63 (31.0%)	1.000
Age, mean	75.65 ± 9.80	75.65 ± 9.80	1.000
Hypertension (level 1)	11 (5.4%)	7 (3.5%)	.282
Hypertension (level 2)	24 (11.8%)	17 (8.4%)	.249
Hypertension (level 3)	36 (17.7%)	78 (38.4%)	.000
Diabetes mellitus	47 (23.2%)	72 (35.5%)	.004
Atrial fibrillation	16 (7.9%)	24 (11.8%)	.243
Thrombus	6 (2.9%)	0 (0.0%)	.000
Coronary heart disease	13 (6.4%)	16 (7.9%)	.035
Atherosclerosis	7 (3.9%)	7 (3.9%)	1.000
Acute myocardial infarction	7 (3.9%)	4 (2.0%)	.210
History of stroke	13 (9.4%) (CAS + TCS)	24 (11.8%)	.042
Mortality rate	32 (15.3%)	4 (2.0%)	.000
Single acute cerebral infarction	40 (28.8%)	93 (45.8%)	.002
Multiple acute cerebral infarction	52 (37.4%)	41 (20.2%)	.001
Lacunar infarction	47 (23.7%)	69 (34.0%)	1.000
Distant metastasis	22.0%	—	—

TCS = group whose cancer occurred after treatment.

Stroke patients with active cancer had significantly higher D-dimer levels than did those without cancer. Our data suggest that coagulopathy associated with cancer might cause stroke. To determine whether elevated D-dimer levels are the result of the cancer, we also included cancer patients without stroke in the analysis: the average D-dimer levels of CG (0.59 mg/L) were higher than those of SG (0.34 mg/L), but still lower than those of CSG (1.01 mg/L). This result indicates that elevated D-dimer levels are probably the result of the stroke and that the cancer D-dimer levels, although they are higher than the normal range, are not sufficient to diagnose cancer-related stroke because 14.77% of cancer-free stroke patients also have abnormal D-dimer levels. Patients who had mildly elevated D-dimer (≥0.55 mg/L) and multiple infarctions on MRI had increased likelihood of occult malignancy.[29]

Table 2

Comparison of D-dimer levels between different groups.

CSG		Control		P
CAS	1.50 ± 2.65	SG	0.33 ± 0.58	.000
TCS	0.88 ± 1.68	SG	0.33 ± 0.58	.000
CSH	0.56 ± 0.75	SG	0.33 ± 0.58	.012
TCS	0.88 ± 1.68	CAS	1.50 ± 2.65	.112
CSH	0.56 ± 0.75	CAS	1.50 ± 2.65	.007
TCS	0.88 ± 1.68	CSH	0.56 ± 0.75	.165

CAS = group in which the tumor occurred simultaneously with stroke, CSH = group of cancer patients with a history of stroke, SG = cancer-free stroke group, TCS = group whose cancer occurred after treatment

Cancer treatments may contribute to a low-grade activated coagulation that results in systemic or cerebral arteriovenous thrombosis, which usually, but not exclusively, occurs in the setting of advanced malignant disease.[30] Our data show that the average D-dimer levels of TCS (0.88 mg/L) were higher than that of CSH (0.56 mg/L). In conclusion, cancer treatment, cancer itself, and stroke itself can all cause elevated D-dimer levels. Additionally, an evaluation of D-dimer levels can be used for diagnosis, for risk evaluation, and as a treatment marker in thrombogenic states such as deep vein thrombosis.

The infarct pattern in cancer patients with stroke is rarely reported. DWI pattern of multiple lesions involving multiple arterial territories were observed more frequently in the CSG than in the SG. Among our active cancer patients, multiple territory infarctions were found in 37.43% of the cancer-related stroke patients. These data indicate that MRI features alone have an inadequate sensitivity for the prediction of hidden malignancies. Previous studies have speculated that the D-dimer levels and DWI pattern may have diagnostic significance in the contest of the statistical analysis of large amounts of data. The results reported here, relative to the comparison of the two ROC analyses, support the argument that the D-dimer levels and DWI pattern are both reliable for diagnosing n-CSG. The D-dimer levels are of great significance for the diagnosis, although the significance of the DWI pattern in the diagnosis of n-CSG is relatively weak (Figs. 2 and 3).

Extraordinary high D-dimer levels or a combination of D-dimer levels and MRI findings may be used as a screening tool to detect

Table 3

Laboratory data in stroke patients with cancer and stroke patients and cancer patients.

	CSG	SG	CG	P_1	P_2	P_3
PT	11.8 ± 3.77	11.04 ± 2.28	10.76 ± 1.22	.017	.000	.313
INR	1.04 ± 1.97	1.14 ± 1.97	0.98 ± 0.10	.491	.002	.054
APTT	31.83 ± 5.61	31.51 ± 4.28	32.11 ± 4.37	.525	.171	.031
FIB	3.81 ± 1.31	3.80 ± 2.69	3.72 ± 2.49	.994	.665	.052
TT	14.19 ± 2.31	13.48 ± 1.433	13.19 ± 2.41	.000	.000	.074
DD	1.01 ± 1.94	0.33 ± 0.58	0.59 ± 0.84	.000	.005	.026
Erythrocyte	3.82 ± 0.62	4.08 ± 0.59	3.68 ± 0.61	.000	.022	.004
Hemoglobin	118.29 ± 21.04	130.15 ± 28.69	115.76 ± 22.09	.000	.254	.030
Platelet	197.44 ± 85.98	184.41 ± 60.47	185.33 ± 73.92	.840	.137	.215
Triglycerides	1.38 ± 0.66	2.37 ± 12.82	1.30 ± 0.71	.304	.311	.023
HDL	1.20 ± 0.33	3.61 ± 17.92	3.22 ± 14.22	.073	.100	.095
LDL	2.60 ± 0.79	3.65 ± 11.47	33.21 ± 0.79	.222	.187	.068

APTT = activated partial thromboplastin time, CG = cancer without stroke group, CSG = cancer-stroke group, DD = D-dimer, FIB = fibrinogen, INR = international normalized ration, HDL =high-density lipoprotein, LDL = low-density lipoprotein, P_1 = the comparation between CSG and SG, P_2 = the comparation between CSG and CG, P_3 = the comparation between CSG, SG, and CG, SG = cancer-free stroke group, TT = thrombin time.

malignancy in stroke patients.[29] Current evidence shows that when presented with multiple bihemispheric infarction on DWI and an unknown etiology, clinicians must consider the possibility of a concealed cancer.[31] In stroke patients with cancer, the D-dimer levels and DWI lesion pattern may be helpful in the early identification of cancer (especially coagulopathy associated with cancer) and possibly in guiding secondary prevention for stroke.[30]

In our patients, there was a significant difference in the occurrence of embolic events and mortality rate between CSG and SG.[32,33] Six patients had deep vein thrombus in CSG, and no patient had deep vein thrombus in SG. In addition to venous thrombosis, arterial occlusion and angina symptoms are relatively common among cancer patients.[34] Some studies have shown that lung cancer patients have a higher risk of developing pulmonary embolism than do cancer-free patients. Surgery and chemotherapy were also associated with an increased risk of embolism.[35]

The published mortality rate in cancer-related stroke patients ranges from 25% to 30%, compared with 14% mortality rate in stroke patients without cancer.[36] In our study, the mortality rate in patients with cancer was >15.27% during hospitalization; of the deaths recorded, 10 cases occurred in lung cancer patients, 6 cases in gastric cancer patients, 4 cases in colorectal cancer patients, and 3 cases in pancreatic cancer patients. Lung cancer patients are, as expected, the ones with the highest mortality rate; however, other types of cancer should not be ignored.

Our results also show that the D-dimer levels are correlated with the stage of the disease and the number of metastases. According to our study, the cancer of the neck had the lowest D-dimer level (0.31 mg/L). Head-neck tumors can produce cerebral ischemia by local vascular compression. Increasing amount of data show that chemotherapy can exert significant toxicity on the nervous system. Radiation therapy administered to the head and neck, typically in the setting of head and neck cancers, may induce severe carotid atherosclerosis after a delay.[37,38] The dose and types of radiotherapy and the chemotherapy regimen are serious factors.[39] These issues need further investigation.

The stroke mechanisms in cancer patients may differ from those in stroke patients without cancer. Thus, the treatment and preventive strategies in these 2 groups may differ. Early recognition of acute stroke may allow the cancer patient to access surgical or medical intervention and improve their overall outcome. In addition, secondary prevention therapies of stroke are guided by the etiology of the initial cerebrovascular event. Anticoagulants reduce the incidence of thromboembolic events in patients with metastatic or locally advanced cancer who are receiving chemotherapy.[40] Thus, additional consideration must be given to the causes of stroke that are unique to the cancer patient.

Limitations to our study include its retrospective nature and the lack of late follow-up. The results presented in this study can be summarized as follows: hypercoagulopathy could be a major pathophysiologic mechanism of stroke related to cancer, which is very distinct from the mechanisms of conventional stroke; considering extraordinarily high D-dimer levels or a combination of D-dimer levels and MRI findings as modern diagnostic evaluations is essential for the correct management of these patients.

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Author contributions

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Formal analysis: Yijun Shen.
Investigation: Yijun Shen, Tian Li, Chengming Chen.
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References

[1] Gu C, Li T, Jiang S, et al. AMP-activated protein kinase sparks the fire of cardioprotection against myocardial ischemia and cardiac ageing. Ageing Res Rev 2018;47:168–75.
[2] Li T, Yang Z, Jiang S, et al. Melatonin: does it have utility in the treatment of haematological neoplasms? Br J Pharmacol 2018;175: 3251–62.
[3] Li T, Jiang S, Yang Z, et al. Targeting the energy guardian AMPK: another avenue for treating cardiomyopathy? Cell Mol Life Sci 2017;74:1413–29.
[4] Yu Z, Tian X, Peng Y, et al. Mitochondrial cytochrome P450 (CYP) 1B1 is responsible for melatonin-induced apoptosis in neural cancer cells. J Pineal Res 2018;65:e12478.
[5] Proietti S, Catizone A, Masiello MG, et al. Increase in motility and invasiveness of MCF7 cancer cells induced by nicotine is abolished by melatonin through inhibition of ERK phosphorylation. J Pineal Res 2018;64:e12467.
[6] Haro M, Orsulic S. A paradoxical correlation of cancer-associated fibroblasts with survival outcomes in B-cell lymphomas and carcinomas. Front Cell Dev Biol 2018;6:98.
[7] Graus F, Rogers LR, Posner JB. Cerebrovascular complications in patients with cancer. Medicine 1985;64:16–35.
[8] Davis CK, Jain SA, Bae ON, et al. Hypoxia Mimetic Agents for Ischemic Stroke. Front Cell Dev Biol 2018;6:175.
[9] Chen R, Lai UH, Zhu L, et al. Reactive oxygen species formation in the brain at different oxygen levels: the role of hypoxia inducible factors. Front Cell Dev Biol 2018;6:132.
[10] Taccone FS, Jeangette SM, Blecic SA. First-ever stroke as initial presentation of systemic cancer. J Stroke Cerebrovasc Dis 2008;17: 169–74.
[11] Schwarzbach CJ, Schaefer A, Ebert A, et al. Stroke and cancer: the importance of cancer-associated hypercoagulation as a possible stroke etiology. Stroke 2012;43:3029–34.
[12] Nam KW, Kim CK, Kim TJ, et al. Intravenous thrombolysis in acute ischemic stroke with active cancer. BioMed Res Int 2017;2017:4635829.
[13] Rickles FR, Edwards RL. Activation of blood coagulation in cancer: Trousseau's syndrome revisited. Blood 1983;62:14–31.
[14] Chen PC, Muo CH, Lee YT, et al. Lung cancer and incidence of stroke: a population-based cohort study. Stroke 2011;42:3034–9.
[15] Tadokoro Y, Sakaguchi M, Yagita Y, et al. Ischemic stroke in patients with solid gynecologic tract tumors and coagulopathy. Eur Neurol 2013;70:304–7.
[16] Kuan AS, Teng CJ, Wu HH, et al. Risk of ischemic stroke in patients with ovarian cancer: a nationwide population-based study. BMC Med 2014;12:53.
[17] Bang OY, Seok JM, Kim SG, et al. Ischemic stroke and cancer: stroke severely impacts cancer patients, while cancer increases the number of strokes. J Clin Neurol 2011;7:53–9.
[18] Min J, Farooq MU. Detecting nonvalvular atrial fibrillation and anticoagulant therapy in cardioembolic ischemic stroke. Postgrad Med 2016;128:620–8.
[19] Li T, Jiang S, Lu C, et al. Melatonin: another avenue for treating osteoporosis? J Pineal Res 2019;66:e12548.
[20] Roque C, Mendes-Oliveira J, Duarte-Chendo C, et al. The role of G protein-coupled estrogen receptor 1 on neurological disorders. Front Neuroendocrinol 2019;100786.
[21] Liberale L, Carbone F, Montecucco F, et al. Ischemic stroke across sexes: what is the status quo? Front Neuroendocrinol 2018.
[22] Liberale L, Carbone F, Montecucco F, et al. Ischemic stroke across sexes: what is the status quo? Front Neuroendocrinol 2018;50:3–17.
[23] Huang H, Song S, Banerjee S, et al. The WNK-SPAK/OSR1 kinases and the cation-chloride cotransporters as therapeutic targets for neurological diseases. Aging Dis 2019;10:626–36.
[24] Ma Y, Liu Y, Zhang Z, et al. Significance of complement system in ischemic stroke: a comprehensive review. Aging Dis 2019;10:429–62.

[25] Seok JM, Kim SJ, Song P, et al. Clinical presentation and ischemic zone on MRI in cancer patients with acute ischemic stroke. Eur Neurol 2012;68:368–76.
[26] Fan J, Shang D, Han B, et al. Adoptive cell transfer: is it a promising immunotherapy for colorectal cancer? Theranostics 2018;8:5784–800.
[27] Lee EJ, Nah HW, Kwon JY, et al. Ischemic stroke in patients with cancer: is it different from usual strokes? Int J Stroke 2014;9:406–12.
[28] Arboix A. [Cerebrovascular disease in the cancer patient]. Rev Neurol 2000;31:1250–2.
[29] Guo YJ, Chang MH, Chen PL, et al. Predictive value of plasma D-dimer levels for cancer-related stroke: a 3-year retrospective study. J Stroke Cerebrovasc Dis 2014;23:e249–54.
[30] Kim SG, Hong JM, Kim HY, et al. Ischemic stroke in cancer patients with and without conventional mechanisms: a multicenter study in Korea. Stroke 2010;41:798–801.
[31] Kwon HM, Kang BS, Yoon BW. Stroke as the first manifestation of concealed cancer. J Neurol Sci 2007;258:80–3.
[32] Arkel YS. Thrombosis and cancer. Semin Oncol 2000;27:362–74.
[33] Murthy SB, Karanth S, Shah S, et al. Thrombolysis for acute ischemic stroke in patients with cancer: a population study. Stroke 2013;44: 3573–6.
[34] Amer MH. Cancer-associated thrombosis: clinical presentation and survival. Cancer Manag Res 2013;5:165–78.
[35] van Herk-Sukel MP, Shantakumar S, Penning-van Beest FJ, et al. Pulmonary embolism, myocardial infarction, and ischemic stroke in lung cancer patients: results from a longitudinal study. Lung 2013;191:501–9.
[36] Zhang YY, Cordato D, Shen Q, et al. Risk factor, pattern, etiology and outcome in ischemic stroke patients with cancer: a nested case-control study. Cerebrovasc Dis 2007;23:181–7.
[37] Plummer C, Henderson RD, O'Sullivan JD, et al. Ischemic stroke and transient ischemic attack after head and neck radiotherapy: a review. Stroke 2011;42:2410–8.
[38] Hsu CW, Huang YB, Kuo CC, et al. Evaluating the primary prevention of ischemic stroke of oral antithrombotic therapy in head and neck cancer patients with radiation therapy. BioMed Res Int 2016;2016: 6205158.
[39] Huang YS, Lee CC, Chang TS, et al. Increased risk of stroke in young head and neck cancer patients treated with radiotherapy or chemotherapy. Oral Oncol 2011;47:1092–7.
[40] Agnelli G, Gussoni G, Bianchini C, et al. Nadroparin for the prevention of thromboembolic events in ambulatory patients with metastatic or locally advanced solid cancer receiving chemotherapy: a randomised, placebo-controlled, double-blind study. Lancet Oncol 2009;10:943–9.