

Pathogenesis and Biomarkers of Cancer-Related Ischemic Stroke

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Objective: To investigate the pathogenesis of cancer-related ischemic stroke (CRIS) and to search for reliable biomarkers of CRIS.

Methods: Patients with CRIS, only-cancer and only-ischemic stroke who were hospitalized in the First Affiliated Hospital of Guangxi Medical University from May 2022 to January 2024 were recruited, and laboratory and clinical data of the three groups were collected. Peripheral venous blood was collected and enzyme-linked immunosorbent assay (ELISA) was used to detect markers of coagulation (D-dimer) and endothelial integrity (intercellular adhesion molecule-1 (ICAM-1)).

Results: The study included 16 patients with CRIS, as well as 16 patients with only-cancer and 16 patients with only-ischemic stroke. Among patients with CRIS, the most common cancer was lung cancer, and the most common pathological type was adenocarcinoma. It was found that compared with patients with only-cancer and only-ischemic stroke, the hemoglobin and lymphocyte percentage in patients with CRIS were decreased ($P<0.05$), while the neutrophil percentage and neutrophil to lymphocyte ratio (NLR) were increased ($P<0.05$). Compared with only-ischemic stroke group, the lymphocyte absolute value in patients with CRIS was decreased ($P<0.05$), and platelet to lymphocyte ratio (PLR), globulin, prothrombin time (PT), international normalized ratio (INR) and ICAM-1 were increased ($P<0.05$). D-dimer level was higher in patients with CRIS than in only-cancer group ($P<0.05$).

Conclusions: In the present study, the increased NLR, PLR, ICAM-1 and D-dimer were expected to be biomarkers of CRIS, indicating that hypercoagulability mediated by cancer inflammation and endothelial damage may be the pathogenesis of CRIS. The novel findings in the present study will facilitate clinicians to identify the patients at high risk of CRIS. Because of the small sample size, the findings need to be validated by prospective large-sample studies in the future.

Keywords: cancer-related ischemic stroke, hypercoagulability, pathogenesis, biomarkers

Introduction

Cancer may directly mediate the pathophysiology of ischemic stroke, or lead to ischemic stroke by mediating coagulation disorders in hypercoagulable state, non-bacterial thrombotic endocarditis, endothelial injury, etc, namely “cancer-related ischemic stroke (CRIS)”.¹ As cancer treatment prolongs patient survival and the global population ages, patients with CRIS will increase.² It is estimated that 4–20% of ischemic stroke patients have cancer, and their co-prevalence is increasing.^{2–4} CRIS causes patients to suffer an additional suffering when the cancer is not yet cured, resulting in a severely poor prognosis.⁵ Studies have shown that ischemic stroke is often more severe in cancer patients than in non-cancer patients.⁶ In addition, compared with only-ischemic stroke patients, CRIS patients generally have a poorer discharge prognosis and are more likely to experience early neurological deterioration and in-hospital death.⁶ In a case-control study, 32% of CRIS patients died in hospital, compared with 13% of non-CRIS patients.⁷ These impacts put a heavier burden on individuals, families and society. What is more concerning is that the molecular mechanism of the

pathogenesis of CRIS has not been illuminated, and its reliable diagnostic markers have not been clarified. As a result, the diagnosis and treatment of CRIS has become a huge clinical challenge.

Studies have shown that about 50% of CRIS is cryptogenic stroke.⁸ Although recent research indicates that hypercoagulability may play a crucial role, the biological factors that lead to the increased risk of CRIS are still insufficiently understood. The higher plasma D-dimer levels were found to be more common in CRIS patients, but its increase could also be due to factors such as heart disease and is a non-specific biomarker.⁹ In addition, elevated levels of certain tumor markers, such as CA125 with mucin features, have been linked to cancer-related hypercoagulability. Mucins secreted by cancer cells can activate neutrophils and platelets, causing microthrombosis and leading to ischemic stroke.^{10,11} Tumor markers have also been considered as potential biomarkers for CRIS, but with less specificity. The OASIS-Cancer study reported higher levels of blood extracellular vesicles and neutrophil extracellular traps (NETs) in cancers patients and cryptogenic ischemic stroke than in control patients,^{12,13} indicating that higher levels of blood extracellular vesicles and NETs might be the potential biomarkers for CRIS, however their scalability and reproducibility may limit their clinical application. Cancer invasion, including migration and adhesion, disrupts the tight junctions between endothelial cells, causing endothelial damage, transforming endothelial cells from static to active, producing pro-inflammatory cytokines and exposing adhesion molecules, into a pro-thrombotic state, leading to ischemic stroke,^{14,15} suggesting that factors related to endothelial damage may be potential biomarkers of CRIS; however, such studies of endothelial-related markers are still limited.

Inflammatory cells and mediators are fundamental components of the tumor microenvironment, and the tumor inflammatory environment caused by genetic events related to the onset and progression of cancers work synergically with various epigenetic factors, which may alter the patient's pro-coagulation system and ultimately lead to thrombotic events.¹⁶ The presence of neutrophils and thrombocytosis may represent a response to cancer-related inflammation and thromboembolism.¹⁶ Activated neutrophils secrete tumor growth promoting factors and also enhance thrombogenesis or platelet aggregation.^{17,18} Inflammatory mediators can induce reactive thrombocytosis, platelet aggregation and degranulation and the subsequent release of platelet-derived pro-angiogenic mediators are important factors in tumor growth and key to thrombosis.^{16,19,20} The release of immune mediators can cause significant immunosuppressive effects and reduce lymphocyte counts.²⁰ These causes contribute to increased neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) in cancer patients, and NLR and PLR have been proposed as novel systemic inflammation markers to predict thrombotic events, but the relevant studies are still limited.

To improve our understanding of the mechanisms of CRIS and explore reliable biomarkers, we conducted a prospective study comparing clinical features and clot-related hematologic markers, along with endothelial damage markers among patients with CRIS, only-ischemic stroke and only-active cancer.

Materials and Methods

Patient Enrollment

This study was conducted in compliance with the Declaration of Helsinki and approved by the Medical Ethics Committee of the First Affiliated Hospital of Guangxi Medical University. Approval Number: 2022-KY-(035). Written informed consent was obtained from all patients or caregivers.

We prospectively recruited patients (aged ≥ 18 years) with active CRIS, active cancer, and ischemic stroke who were admitted to our hospital between May 2022 and January 2024. The active CRIS group was the case group, and the cancer diagnosis always preceded the onset of ischemic stroke. Active cancer was defined as cancer diagnosed or treated within the last 1 year, or known metastatic/recurrent cancer.²¹ Histopathological examination was chosen as the gold standard for cancer diagnosis. The diagnostic criteria for ischemic stroke were established according to the American Heart Association Stroke Diagnostic Criteria and confirmed by magnetic resonance imaging (MRI).²² Active cancer and ischemic stroke were controls and matched to patients in the case group by age, sex, and cancer type (if applicable), respectively. Exclusion criteria: patients with primary or secondary intracranial tumors, hematological tumors, cancer combined with neurological diseases such as cerebral hemorrhage, patients undergoing intravenous/arterial thrombolysis

or mechanical thrombolysis, patients on hemodialysis, patients with infection <14 days, platelet count <50,000/mm³, and pregnant patients.

Blood Sample Collection and Measurement

Ethylenediaminetetraacetic acid (EDTA) tubes were used to collect three group of patients with peripheral venous blood samples. Blood was collected within 14 days after ischemic stroke in the CRIS group, within 7 days of the ischemic stroke occurrence in the only-ischemic stroke group, and on the second day of admission in the only-active cancer group. The blood sample was centrifuged at a low temperature of 4 °C and at a high speed (1000×g, 15 minutes), then the supernatant was absorbed and divided into a micro-centrifuge tube and stored in a -80°C refrigerator for further measurement.

Based on previous studies, coagulation (D-dimer) and endothelial integrity (intercellular adhesion molecule-1 (ICAM-1)) were selected as blood biomarkers. D-dimer and ICAM-1 were detected by enzyme-linked immunosorbent assay (ELISA) kit (Elabscience, China).

Clinical Data Collection

Baseline data were collected on participants, including general data (age and sex); pathological type and metastasis of cancer; ischemic stroke risk factors (prior stroke/ transient ischemic attack (TIA), hypertension, diabetes, hyperlipidemia, atrial fibrillation, coronary heart disease and smoking), number of infarct lesions, symptoms of infarct (aphasia, hemiplegia, dizziness and sensory disturbance) and MRI; blood routine examination, liver and kidney functions, coagulation function. The National Institute of Health stroke score (NIHSS) was utilized to assess the severity of focal neurological dysfunction, and the modified Rankin Scale (mRS) was used to assess outcomes.

Statistical Analysis

The SPSS 25.0 software was used for statistical analysis. Categorical variables are represented by n (%); Continuous variables with normal distribution are represented by mean ± standard deviation; Continuous variables that are not normally distributed are represented by the median (lower quartile - upper quartile). In the continuous data, two groups were compared to assess the significance of differences between groups using the independent sample *t* test or rank sum test, and three groups were compared to evaluate the significance of differences between groups using ANOVA or multiple rank sum test. In the classified data, the chi-square test was used to evaluate the significance of the difference between the two groups. When three groups were compared, Bonferroni method was used for multiple comparisons based on the row × column chi-square test. *P*<0.05 was considered statistically significant.

Results

We included 16 patients with CRIS (11 males and 5 females, mean age 56.81±11.29 years), as well as 16 patients with only-cancer and 16 patients with only-ischemic stroke. There were no significant differences in age and sex among the three groups (*P* > 0.05). Among patients with CRIS, the most common cancer was lung cancer (50%), followed by nasopharyngeal cancer (18.75%) and liver cancer (12.50%). The most common pathological type is adenocarcinoma, accounting for 50%. Two patients (12.5%) developed distant cancer metastases (Table 1).

Patients with CRIS present with common symptoms of ischemic stroke, such as aphasia, hemiplegia, and dizziness. Aphasia was the most prevalent symptom in 50% of patients with CRIS, followed by hemiplegia (37.50%) and dizziness (18.75%). In patients with only-ischemic stroke, the most prevalent symptom was hemiplegia (93.75%), followed by dizziness (25.00%) and sensory disturbance (25.00%) (Table 2). However, patients with CRIS often show multiple cerebral infarction lesions on brain MRI (Table 2).

NIHSS score was used to evaluate the severity of focal neurological dysfunction and mRS score was used to evaluate the prognosis. Compared with patients with only-ischemic stroke, NIHSS score of patients with CRIS showed more severe focal neurological dysfunction (*P*<0.05), and mRS score showed worse prognosis (*P*<0.05). There were no differences in vascular risk factors, including prior stroke/TIA, hypertension, hyperlipidemia, diabetes mellitus, atrial fibrillation, coronary heart disease, smoking and alcohol consumption among the three groups (*P*>0.05) (Table 3).

Table 1 Cancer Characteristics of Patients with CRIS and Only-Cancer

Cancer Characteristics	CRIS (n=16)	Only-cancer (n=16)
Cancer types		
Lung	8 (50.00%)	8 (50.00%)
Nasopharyngeal	3 (18.75%)	3 (18.75%)
Liver	2 (12.50%)	2 (12.50%)
Colorectal	1 (6.25%)	1 (6.25%)
Bladder	1 (6.25%)	1 (6.25%)
Esophageal	1 (6.25%)	1 (6.25%)
Biological characteristics of cancer		
Adenocarcinoma	8 (50.00%)	8 (50.00%)
Distant metastasis	2 (12.5%)	3 (18.75%)

Abbreviation: CRIS, cancer-related ischemic stroke.

Table 2 Clinical Characteristics of Patients with CRIS and Only-Ischemic Stroke

Characteristics	CRIS (n=16)							Only-Ischemic Stroke (n=16)
	Total	Lung	Nasopharyngeal	Liver	Colorectal	Bladder	Esophageal	
Symptoms								
Aphasia	8 (50.00%)	4	1	0	1	1	1	2 (12.50%)
Hemiplegia	6 (37.50%)	3	1	1	1	0	0	15 (93.75%)
Dizziness	3 (18.75%)	1	2	0	0	0	0	4 (25.00%)
Sensory disturbance	0	0	0	0	0	0	0	4 (25.00%)
Infarct lesions								
Single	2 (12.50%)							12 (75.00%)
Multiple	14 (87.50%)							4 (25.00%)

Table 3 Demographic Analysis of Patients with CRIS, Only-Cancer and Only-Ischemic Stroke

	CRIS (n=16)	Only-Cancer (n=16)	Only-Ischemic Stroke (n=16)	p value
Sex (male/female)	11/5	11/5	11/5	1.000 [#]
Age (years)	56.81±11.29	57.38±11.76	58.88±7.46	0.844*
NIHSS scores	3.5 (2.25–5)	/	2 (1–3)	0.041 [☆]
mRS scores	3 (2–4)	/	2 (1–3)	0.029 [☆]
Vascular risk factors				
Prior stroke /TIA	2 (12.50%)	0 (0.00%)	0 (0.00%)	0.319 [#]
Hypertension	8 (50.00%)	4 (25.00%)	9 (56.25%)	0.169 [#]
Diabetes	0 (0.00%)	3 (18.75%)	1 (6.25%)	0.304 [#]
Hyperlipidemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	/
Atrial fibrillation	0 (0.00%)	1 (6.25%)	0 (0.00%)	1.000 [#]
Coronary heart disease	0 (0.00%)	0 (0.00%)	0 (0.00%)	/
Smoking	7 (43.75%)	8 (50.00%)	6 (37.50%)	0.776 [#]
Drinking	6 (37.50%)	4 (25.00%)	3 (18.75%)	0.609 [#]

(Continued)

Table 3 (Continued).

	CRIS (n=16)	Only-Cancer (n=16)	Only-Ischemic Stroke (n=16)	p value
Laboratory data				
WBC ($\times 10^9/L$)	7.45 $\pm$ 2.80	6.36 $\pm$ 1.58	6.86 $\pm$ 1.38	0.324*
RBC ($\times 10^{12}/L$)	4.35 $\pm$ 0.78	4.61 $\pm$ 0.62	4.61 $\pm$ 0.59	0.461*
HGB (g/L) ^{ab}	117.60 $\pm$ 20.51	134.03 $\pm$ 17.03 ^a	135.09 $\pm$ 14.90 ^b	0.011*
PLT ($\times 10^9/L$)	243.31 $\pm$ 53.81	255.36 $\pm$ 54.01	244.02 $\pm$ 42.72	0.751*
NEU ($\times 10^9/L$)	5.32 $\pm$ 2.44	3.79 $\pm$ 1.49	4.10 $\pm$ 1.41	0.055*
NEU% ^{ab}	0.70 $\pm$ 0.10	0.58 $\pm$ 0.12	0.59 $\pm$ 0.12	0.006*
LYM ($\times 10^9/L$) ^b	1.20 $\pm$ 0.72	1.80 $\pm$ 0.70	2.03 $\pm$ 0.69	0.005*
LYM% ^{ab}	0.16 $\pm$ 0.79	0.29 $\pm$ 0.11	0.30 $\pm$ 0.11	<0.001*
MONO ($\times 10^9/L$)	0.62 $\pm$ 0.21	0.54 $\pm$ 0.18	0.51 $\pm$ 0.11	0.169*
MONO%	0.09 $\pm$ 0.03	0.09 $\pm$ 0.03	0.07 $\pm$ 0.01	0.117*
PDW	0.16 (0.10–0.17)	0.14 (0.11–0.16)	0.16 (0.12–0.17)	0.534 ^Δ
PCT	0.22 $\pm$ 0.05	0.24 $\pm$ 0.05	0.20 $\pm$ 0.04	0.141*
MPV (fl)	9.21 $\pm$ 1.19	9.44 $\pm$ 1.80	8.48 $\pm$ 1.31	0.162*
PLR ^b	182.08 (156.74–414.41)	141.62 (108.69–184.81)	130.27 (89.16–158.82)	0.024 ^Δ
NLR ^{ab}	3.96 (3.04–6.41)	1.67 (1.40–2.70)	2.08 (1.34–2.79)	0.001 ^Δ
TBiL (umol/L)	9.70 (7.53–12.98)	9.85 (8.20–18.55)	11.05 (6.58–16.53)	0.888 ^Δ
DBiL (umol/L)	0.33 (0.28–0.42)	0.37 (0.26–0.46)	0.29 (0.23–0.33)	0.144 ^Δ
ALT (U/L)	17.50 (13.00–28.50)	16.00 (11.00–20.75)	14.50 (10.25–22.75)	0.550 ^Δ
AST (U/L)	24.50 (18.25–35.50)	24.00 (18.25–27.75)	23.50 (15.50–27.00)	0.645 ^Δ
TP (g/L)	67.62 $\pm$ 5.56	68.10 $\pm$ 6.39	64.51 $\pm$ 4.65	0.153*
ALB (g/L)	35.98 $\pm$ 4.25	38.50 $\pm$ 4.00	36.68 $\pm$ 2.62	0.148*
GLB (g/L) ^b	31.65 $\pm$ 3.87	29.60 $\pm$ 4.47	27.83 $\pm$ 4.15	0.044*
PAB (mg/L)	209.62 $\pm$ 62.35	239.27 $\pm$ 65.03	243.09 $\pm$ 54.85	0.246*
Ccr (mL/min)	77.06 $\pm$ 11.35	84.73 $\pm$ 27.55	80.54 $\pm$ 18.90	0.570*
CREA (umol/L)	71.63 $\pm$ 15.41	73.06 $\pm$ 17.49	73.81 $\pm$ 19.74	0.938*
UREA (mmol/L)	4.68 $\pm$ 1.12	5.64 $\pm$ 1.71	5.08 $\pm$ 1.33	0.162*
UA (umol/L)	338.25 $\pm$ 108.56	329.63 $\pm$ 86.84	318.31 $\pm$ 74.11	0.825*
PT (seconds) ^b	11.80 $\pm$ 1.06	11.37 $\pm$ 0.84	10.86 $\pm$ 0.46	0.009*
INR ^b	1.00 $\pm$ 0.08	0.96 $\pm$ 0.73	0.92 $\pm$ 0.04	0.011*
FIB (g/L)	3.81 $\pm$ 1.28	3.55 $\pm$ 0.93	3.14 $\pm$ 0.47	0.089*
ELISA				
ICAM-1 ^b	82.41 (73.41–105.32)	86.21 (51.52–103.27)	51.80 (46.45–65.39)	0.002 ^Δ
D-dimer (ng/mL) ^a	155.21 (57.52–1015.11)	177.88 (99.37–687.31)	399.17 (136.64–710.00)	0.624 ^Δ

Notes: ^aindicates a statistical difference between the CRIS group and the cancer group; ^bindicates a statistical difference between the CRIS group and the ischemic stroke group. #row x column chi-square test; *analysis of variance; ^{*}two-sample rank sum test; ^Δmultiple rank sum test.

Abbreviations: NIHSS, National Institute of Health stroke score; mRS, modified Rankin Scale; TIA, transient ischemic attack; WBC, white blood cell; RBC, red blood cell; HGB, hemoglobin; PLT, platelet; NEU, neutrophil; LYM, lymphocyte; MONO, monocyte; PDW, platelet distribution width; PCT, plateletcrit; MPV, mean platelet volume; PLR, platelet to lymphocyte ratio; NLR, neutrophil to lymphocyte ratio; TBiL, total bilirubin; DBiL, direct bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TP, total protein; ALB, albumin; GLB, globulin; PAB, prealbumin; Ccr, Creatinine Clearance Rate; CREA, Creatinine; UA, uric acid; PT, prothrombin time; INR, international normalized ratio; FIB, fibrinogen; ELISA, enzyme-linked immunosorbent assay; ICAM-1, intercellular adhesion molecule-1.

In this study, it was found that hemoglobin, neutrophil percentage, lymphocyte absolute value, lymphocyte percentage, and PLR, NLR, globulin, prothrombin time (PT), international normalized ratio (INR), and ICAM-1 were differences among the three groups ($P<0.05$). It was also found that compared with patients with only-cancer and only-ischemic stroke, the hemoglobin and lymphocyte percentage in patients with CRIS were decreased ($P<0.05$), while the neutrophil percentage and NLR were increased ($P<0.05$). Compared with only-ischemic stroke group, the lymphocyte absolute value in patients with CRIS was decreased ($P<0.05$), and PLR, globulin, PT, INR and ICAM-1 were increased

($P < 0.05$). The D-dimer levels in patients with CRIS were significantly higher than that in only-cancer group ($P < 0.05$) (Table 3).

Discussion

Cancers and ischemic stroke are common diseases leading to high disability and mortality rates worldwide, and are also the two most common causes of death.^{23,24} Studies have found that 10% of ischemic stroke patients hospitalized also had cancers, and the association may be rising.²⁵ Ischemic stroke can cause severe disability in patients with cancer, and cancer increases the risk of ischemic stroke occurring. As cancer treatment improves, the survival of cancer patients will be prolonged and the number of CRIS cases will increase. There is increasing interest in exploring the pathogenesis of CRIS and identifying reliable biomarkers.

The incidence of CRIS is related to the type and pathology of cancers.²⁶ Cancer types that are highly associated with venous thromboembolism (VTE), such as lung, pancreatic and gastric cancer, may have a higher risk of arterial thromboembolism.^{26–28} The abnormal coagulation function is one of the main mechanisms of CRIS. One study reported a case of ovarian adenocarcinoma with ischemic stroke as the first symptom. The patient had hypercoagulability and chronic thrombotic phlebitis. The disappearance of hypercoagulability after tumor resection indicates that cancer may lead to hypercoagulability in patients and thus ischemic stroke.²⁹ The study of Chung JW et al²¹ recruited 114 patients with active lung cancer and ischemic stroke, and found that patients with lung adenocarcinoma had larger cerebral ischemic lesions, and extracellular vesicles in adenocarcinoma had shorter coagulation time and stronger thrombogenic ability. In the present study, it was found that the most common cancer was lung cancer, and the most common pathological type was adenocarcinoma, which may be one of the mechanisms of ischemic stroke caused by the blood hypercoagulable state in cancer patients.

The clinical manifestations of patients with CRIS are similar to those of non-cancer patients, but they also have their own characteristics. Nearly 60% of cancer patients with unclear ischemic stroke mechanisms have multiple embolic cerebral infarction.^{30,31} In this study, aphasia was found to be the most common symptom in patients with CRIS, followed by hemiplegia and dizziness, which were similar to the clinical manifestations of traditional ischemic stroke, but multiple infarcts were common in patients with CRIS. In addition, patients with CRIS are more prone to early neurological deterioration and generally have worse prognosis.⁶ This study found that patients with CRIS had higher NIHSS and mRS scores, suggesting that patients had worse neurological function and prognosis.

In this study, we found that patients with CRIS had lower hemoglobin and lymphocyte percentage and higher neutrophil percentage and NLR compared with patients with only-cancer and only-ischemic stroke, as well as lower lymphocyte absolute value and higher PLR, globulin, PT, INR, and ICAM-1 compared with patients with only-ischemic stroke. Cancer treatment, such as blood loss due to surgery, myelosuppression due to chemoradiotherapy, decreased erythropoietin, and insufficient intake or absorption of the raw material for the synthesis of hemoglobin in advanced cancer patients, may lead to decreased hemoglobin. Cancer cells can induce neutrophils to release NETs, which bind to platelets to activate the coagulation system and increase the hypercoagulability of patients, leading to thrombosis.³²

It has been found that NLR is highly correlated with CRIS and is a biomarker of poor prognosis in cancer patients.³³ Activated neutrophils secrete a variety of pro-tumor growth factors, and the relative reduction of lymphocytes indicates decreased host cell-mediated immunity to cancer cells.¹⁷ Meanwhile, NETs produced by activated neutrophils promote thrombosis and platelet aggregation,¹⁸ leading to ischemic stroke.

PLR is an easy-to-apply blood test consisting of platelet and lymphocyte counts. Platelet aggregation and degranulation, as well as the subsequent release of platelet particles and extracellular vesicles, all play significant roles in tumor growth. Platelets stimulate tumor growth by activating proliferative signaling, anti-apoptosis effects, and releasing angiogenic factors.¹⁹ Simultaneous, platelet activation and aggregation are the key to thrombosis. In addition, the release of immunomodulators can cause significant immunosuppressive effects and a decrease in lymphocyte counts. These causes lead to increased PLR in cancer patients, which increases the risk of thromboembolism in cancer patients.^{16,20}

We also found that PT and INR were higher than in the control group, indicating coagulation dysfunction, which was consistent with previous studies.^{34,35} Under physiological conditions, vascular endothelium is in a static state. After injury, endothelial cells change from a static type to an active type and into a thrombogenic state. Activated endothelial

cells showed high expression levels of ICAM-1.¹⁵ Cancer cells are aggressive, and after binding with some non-specific immune signaling molecules (such as selectin, chemokines and their receptors), cancer cells invade, migrate and adhere, breaking the tight connection between endothelial cells, causing endothelial damage, and thus thrombosis.³⁶ Cancer cells can also activate the body's immune system, activate immune cells, and release amounts number of inflammatory factors to damage the vascular endothelium and promote thrombosis.³⁶

There are some limitations to this study. First, the study was conducted in the First Affiliated Hospital of Guangxi Medical University and the findings may not be generalized to other cities and hospitals. Second, while we matched on age, sex, and cancer type, it was unpractical for enrollment reasons to make full matches on other potentially significant factors, such as vascular risk factors and cancer diagnosis time (for the cancer group). As a result, some baseline features may be unbalanced between groups. Third, the small sample size limited subgroup analysis by individual cancer type and prevented multivariate adjustment. Fourth, although the study was prospective, it was cross-sectional and the blood biomarker samples were collected at a single point in time, which failed to better observe the relationship between these markers over time. Fifth, the study was limited to solid cancers patients, and the findings may not be generalizable to blood cancers or primary brain tumors. Therefore, future multi-center, prospective and larger sample size studies are needed to comprehensively understand the pathogenesis of CRIS and search for reliable biomarkers.

In summary, the study found that the increased NLR, PLR, ICAM-1 and D-dimer were expected to be biomarkers of CRIS, indicating that hypercoagulability mediated by cancer inflammation and endothelial damage may be the pathogenesis of CRIS. The novel findings in the present study will facilitate clinicians to identify the patients at high risk of CRIS and to take some diagnostic and therapeutic strategies.

Data Sharing Statement

Anonymized data not published within this article will be made available by request from any qualified investigator.

Ethics Approval

This study was performed in line with the principles of the Declaration of Helsinki. The present study has been approved by the Medical Ethics Committee of the First Affiliated Hospital of Guangxi Medical University. The approval number is 2022-KY-(035).

Consent to Participate

Informed consent was obtained from all individual participants included in the study.

Consent to Publish

The authors affirm that human research participants provided informed consent for publication.

Author Contributions

Gengyu Cen and Jun Wang contributed equally to this work and share first authorship. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no relevant financial or non-financial interests to disclose.

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