Am J Cancer Res 2025;15(9):4054-4066
www.ajcr.us /ISSN:2156-6976/ajcr0167767

Original Article

Association of red blood cells, D-dimer, and 13-(S)-HODE with cancer-related ischemic stroke: a case-control study

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Received July 29, 2025; Accepted September 21, 2025; Epub September 25, 2025; Published September 30, 2025

Abstract: This study aimed to investigate the clinical characteristics of CRIS and potential laboratory indicators. Acute ischemic stroke (AIS) patients were retrospectively enrolled and categorized into two groups: a cancer-related ischemic stroke (CRIS) group (n = 41) and a non-cancer ischemic stroke group (NC-IS) (n = 213). Baseline characteristics were balanced using 1:1 propensity score matching, adjusting for age, sex, and comorbidities, resulting in 41 patients per group. Serum levels of 13-(S)-hydroxyoctadecadienoic acid [13-(S)-HODE] and nine routine laboratory indicators were measured. Univariate and multivariate logistic regression identified CRIS-associated indicators. Independently associated indicators were evaluated using ROC curve analysis. Additionally, cancer patients without stroke (CNSP, n = 40) and healthy controls (NC, n = 41) were matched to compare routine indicators. Respiratory (34.1%) and digestive (29.3%) cancers were the most common in CRIS patients. Stroke occurred within six months of cancer diagnosis in 36.6% of patients, and 75.6% had multifocal cortical-subcortical infarctions. Multivariate regression confirmed that decreased red blood cells (RBCs) (OR = 0.444, 95% CI: 0.205-0.961), elevated D-dimer (OR = 2.41, 95% CI: 1.67-3.48), and decreased 13-(S)-HODE (OR = 3.20, 95% CI: 1.92-5.33) were independent risk factors for CRIS. The AUCs for the three indicators and the combined model were: RBC, 0.642; D-dimer, 0.739; 13-(S)-HODE, 0.722; combined model, 0.819 (95% CI: 0.729-0.908). CRIS patients had significantly higher D-dimer than CNSP patients (P = 0.001), and lower RBC, lower creatinine, and higher D-dimer than NCs (all P < 0.01). A combined model incorporating decreased RBC, elevated D-dimer, and decreased 13-(S)-HODE demonstrated a significant association with CRIS, showing potential for aiding the distinction of CRIS from NC-IS.

Keywords: Cancer-related ischemic stroke, cancer, 13-(S)-HODE, D-dimer

Introduction

The lifetime incidence of cancer is approximately 40% [1]. With declining cancer mortality and extended patient survival [2], the management of cancer-related chronic diseases has gained increasing attention, particularly concerning acute ischemic stroke (AIS). AIS is defined as ischemic cell death resulting from insufficient blood supply to the brain, spinal cord, or retina [3]. Compared to the general population, cancer patients face a heightened risk of AIS [4, 5]. AIS occurring after a cancer diagnosis is termed cancer-related ischemic stroke (CRIS), in contrast to non-cancer ischemic stroke (NC-IS).

The absolute incidence of CRIS varies across different cancer types. A large-scale study published in *The Lancet* in 2019 indicated that patients with specific cancers, such as oral, lung, central nervous system, and hematologic malignancies, have a higher incidence of stroke than non-cancer patients. For instance, the 5-year cumulative incidence of CRIS in lung cancer and leukemia patients is 2.5-5.4% and 1.7-7.9%, respectively [6]. Although the data are more fragmented, studies focusing on various cancer types and clinical contexts suggest that head and neck cancers, as well as those from the digestive system (e.g., pancreatic cancer), are associated with an even higher incidence of stroke [7, 8].

https://doi.org/10.62347/RHLH9776

The mechanisms underlying CRIS are complex: tumor cells can directly secrete procoagulant factors [9, 10]; tumor compression of the neurovascular system can cause ischemia; chemotherapy, radiotherapy, immunotherapy, and surgical immobilization can promote thrombosis [11]; and traditional stroke risk factors (e.g., dyslipidemia, hypertension) may also contribute. CRIS may present with distinct clinical features and laboratory indicator profiles, which could aid in distinguishing it from NC-IS. Although existing studies have explored the role of blood indicators such as D-dimer, C-reactive protein (CRP), fibrinogen, and RNA markers in identifying CRIS [12], other studies have focused on imaging markers, such as enlarged perivascular spaces in the basal ganglia, for diagnosing CRIS [13]. Additionally, some investigations have examined whether alterations in the gut microbiota in CRIS patients affect clinical prognosis [14]. However, specific and reliable blood markers for CRIS are still lacking, often leading to delayed diagnosis and suboptimal treatment outcomes.

Among hydroxyoctadecadienoic acids (HODEs), 13-(S)-Hydroxyoctadecadienoic acid [13-(S)-HODE] is a common isomer and an oxidative metabolite of linoleic acid [15]. It is enriched in atherosclerotic plaques [16]. Previous research has suggested that serum HODE levels are higher in AIS patients compared to healthy individuals [17]. Notably, tumor cells can uptake linoleic acid and secrete 13-(S)-HODE [18], and the downstream signaling factor of 13-(S)-HODE, PPARγ, is involved in tumor growth regulation [19]. However, no studies have specifically explored changes in 13-(S)-HODE levels in CRIS patients, who have both cancer and stroke.

To elucidate the clinical characteristics of CRIS and explore potential biomarkers, we conducted a retrospective study comparing the clinical features, laboratory indicators (including common clinical tests and serum 13-(S)-HODE levels), and the efficacy of combining multiple indicators for identifying CRIS between CRIS and NC-IS patients.

Materials and methods

Ethical approval and participant enrollment

This retrospective cohort study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Chongqing Medical University (Approval No. CY2025-0558-02) and adhered to the principles of the Declaration of Helsinki. Using historical samples and anonymized data, we screened patients hospitalized between January 2025 and May 2025.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) Age ≥ 18 years; (2) Primary diagnosis of acute ischemic stroke (AIS), with the diagnostic criteria referring to the *2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke* [20] issued by the American Heart Association/American Stroke Association (AHA/ASA) and the *Chinese Guidelines for Diagnosis and Treatment of Acute Ischemic Stroke 2023* [21], respectively; (3) Meeting all the following clinical and imaging criteria: ① Acute onset, defined as the time from symptom onset to hospital admission ≤ 72 hours; ② Presence of focal neurological deficit symptoms; ③ Imaging examinations (magnetic resonance imaging [MRI] or computed tomography angiography [CTA]) indicating the presence of a responsible lesion; (4) For the CRIS group: Patients must have a confirmed diagnosis of cancer prior to admission for AIS; patients with a new diagnosis of cancer made during the stroke workup were excluded from this group.

The exclusion criteria were as follows: (1) Severe liver or kidney dysfunction; (2) Primary or secondary intracranial tumors, or hematologic malignancies; (3) Receipt of intravenous/intra-arterial thrombolysis or vascular intervention within 24 hours before blood sample collection; (4) Presence of fever or a confirmed diagnosis of infectious disease; (5) Pregnancy; (6) Incomplete clinical data. Based on retrospective screening using the above criteria and electronic medical records, patients diagnosed with cancer before admission (confirmed by histological examination) were assigned to the experimental group (n = 41), termed the CRIS group. The remaining patients formed the initial control group (n = 213), termed the NC-IS group. To balance potential baseline confounders between the CRIS and NC-IS groups, we performed 1:1 propensity score matching (PSM). The matching variables included sex, age, medical history (diabetes mellitus [DM], hypertension, coronary heart disease [CHD], atrial fibrillation [AF]), lifestyle habits (smoking,

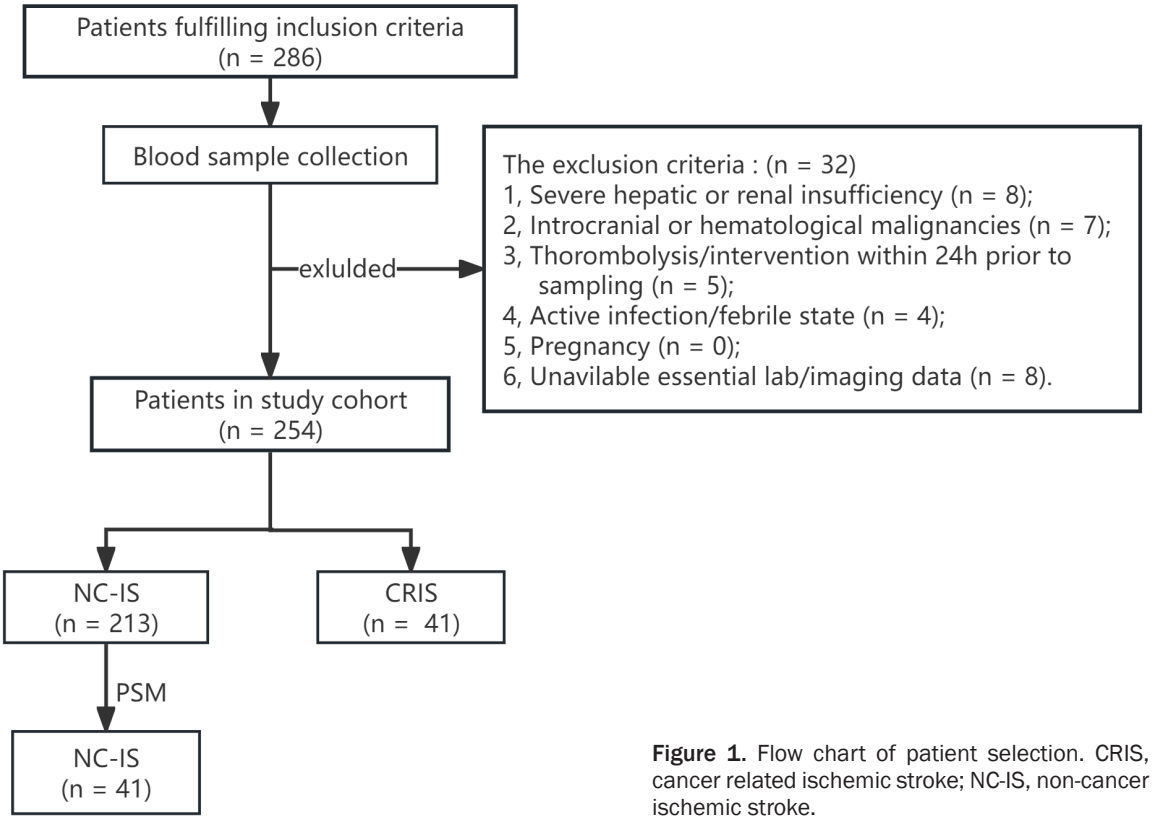

Figure 1. Flow chart of patient selection. CRIS, cancer related ischemic stroke; NC-IS, non-cancer ischemic stroke.

alcohol consumption), body mass index (BMI), and National Institutes of Health Stroke Scale (NIHSS) score at admission. The caliper value was set to 0.03. This resulted in balanced baseline characteristics for the final CRIS group (n = 41) and NC-IS group (n = 41) used in subsequent analyses (**Figure 1**).

Additionally, to explore differences between CRIS patients, cancer-only patients, and healthy individuals, we added two retrospectively matched cohorts. Based on the baseline characteristics of the CRIS group, cancer and no stroke patients (CNSP) were manually matched 1:1 from various departments of the same hospital during the same period. The matching variables included sex, age, chronic disease history (DM, hypertension, CHD, AF), lifestyle habits (smoking, alcohol consumption), cancer primary site, and cancer pathological type. One patient with Bartholin's gland carcinoma was excluded due to low incidence and lack of a match, resulting in a final CNSP group of n = 40. Forty-one normal controls (NC) were matched from the hospital's physical examination center during the same period using the following variables: sex, age, chronic disease history (DM, hypertension, CHD, AF), and lifestyle habits (smoking, alcohol consumption).

Clinical data collection

Clinical data were retrospectively extracted from the Hospital Information System (HIS) and included the following general data: age, sex, and BMI. Cancer-related factors included the time interval between cancer diagnosis and stroke onset, cancer pathological type, metastasis status, and treatment methods. Stroke-related data included the Trial of Org 10172 in Acute Stroke Treatment (TOAST) subtype, NIHSS score at admission, and the location and size of cerebral infarction lesions. Risk factors included DM, hypertension, CHD, AF, smoking, and alcohol abuse. Laboratory test results included complete blood count, renal function, D-dimer, and lipid profile data. Outcomes included NIHSS score at discharge, hemorrhagic transformation, and mortality.

Biomarker selection and measurement

The laboratory indicators compared included 13-(S)-HODE and nine common clinical tests.

Table 1. The baseline information and cancer characteristics of CRIS patients

Characteristics	Number of patients (n = 41)
Sex	
Male	25 (61.0%)
Female	16 (39.0%)
Age (years)	
40-49	2 (4.8%)
50-59	5 (12.2%)
60-69	13 (31.7%)
70-79	10 (24.4%)
80-89	11 (26.9%)
Length of stay	
< 5 days	3 (7.3%)
6-10 days	16 (39.0%)
11-20 days	22 (53.7%)
Mortality in hospital	2 (4.9%)
Hemorrhagic transformation in hospital	2 (4.9%)
Antithrombotic use	
Antiplatelet agents	14 (34.1%)
Anticoagulants	4 (9.8%)
Cancer primary site	
Respiratory System	14 (34.1%)
Digestive System	12 (29.3%)
Urinary System	7 (17.1%)
Endocrine System	3 (7.3%)
Female Genital System	3 (7.3%)
Breast	2 (4.9%)
Cancer stage	
Localized	18 (43.9%)
Regional	13 (31.7%)
Distant	10 (24.4%)
Proportion of adenocarcinoma	25 (61.0%)
Cancer treatment	
Surgical	26 (63.4%)
Chemotherapy	13 (31.7%)
Radiotherapy	4 (9.8%)
Hormonal therapy	4 (9.8%)
Targeted therapy	10 (24.4%)

Abbreviation: CRIS, cancer-related ischemic stroke.

For the CRIS and NC-IS group patients, 5 mL of venous blood was collected via peripheral venipuncture at admission. The samples were immediately centrifuged at room temperature (3000 rpm, 10 minutes). The clear supernatant was transferred to cryovials and stored at -80°C. Serum 13-(S)-HODE levels were measured using a commercially available ELISA kit (Enzo Life Sciences, USA) according to the manufacturer's instructions. Due to the lack of historically frozen serum samples, 13-(S)-HODE was not measured in the CNSP and NC groups. For the nine routine clinical tests, the results from admission (CRIS, NC-IS) or physical examination (CNSP, NC) were retrospectively extracted for all four groups.

Statistical analysis

Statistical analyses were performed using SPSS software (version 26.0, USA), and figures were generated using GraphPad software (version 9.5, USA). Given the relatively small sample size, the normality of continuous variables was assessed using the Shapiro-Wilk test. Normally distributed continuous variables are presented as means ± standard deviations and were compared using independent samples t-tests (CRIS vs. NC-IS) or paired samples t-tests (CRIS vs. NC, CRIS vs. CNSP). Non-normally distributed continuous variables are presented as medians (interquartile ranges) and were compared using the Mann-Whitney U test (CRIS vs. NC-IS) or Wilcoxon signed-rank test (CRIS vs. NC, CRIS vs. CNSP). Categorical variables are presented as numbers (percentages) and were compared using the Chi-square test (CRIS vs. NC-IS) or the McNemar test (CRIS vs. NC, CRIS vs. CNSP). Binary logistic regression analysis was used to assess the impact of each indicator on the risk of CRIS in the PSM-matched CRIS and NC-IS groups, with odds ratio (OR) as the measure of association. A two-tailed $P < 0.05$ was considered statistically significant. The discriminatory power of significantly different laboratory results for distinguishing CRIS patients from NC-IS patients was evaluated using receiver operating characteristic (ROC) curves, calculating the area under the

Table 2. Clinical characteristics at ischemic stroke onset in CRIS patients

Cancer types	Number of patients
Stroke sub-types	
large artery atherosclerosis	14 (34.1%)
Small artery diseases	11 (26.8%)
Cardioembolism	10 (24.4%)
Other	4 (9.8%)
Undermined	2 (4.9%)
Location of infarcts	
Cortical/subcortical	31 (75.6%)
Deep cerebral hemisphere (basal ganglia, internal capsule, etc.)	16 (39.0%)
Cerebellar	7 (17.1%)
Brainstem	7 (17.1%)
Size of the infarcts	
Only small lesions (< 20 mm)	17 (41.5%)
Only large lesions (≥ 20 mm)	4 (9.8%)
Large lesion mixed with small lesion	20 (48.8%)
Lesion patterns of arterial territory	
Single arterial territory	15 (36.6%)
Unilateral anterior circulation	18 (43.9%)
Bilateral anterior circulation	1 (2.4%)
Posterior circulation	4 (9.8%)
Both anterior and posterior circulations	3 (7.3%)
NIHSS at admission (Median (Q1-Q3))	4 (2, 12)
NIHSS at discharge (Median (Q1-Q3))	3 (1, 9)

Abbreviations: CRIS, cancer-related ischemic stroke; NIHSS, the National Institutes of Health Stroke Scale.

curve (AUC) and its 95% confidence interval (CI).

Results

Clinical characteristics of CRIS patients

Baseline characteristics of the CRIS group: We enrolled 41 patients in the CRIS group: 25 males (60.98%) and 16 females (39.02%), with a mean age of 70.15 ± 11.47 years. The mean hospital stay was 10.90 ± 4.16 days. Two patients (4.87%) died during hospitalization, and two patients (4.87%) experienced hemorrhagic transformation. During hospitalization, 14 patients received antiplatelet therapy, and 4 received anticoagulant therapy (**Table 1**).

Distribution of tumor types: The most common malignancies were cancers of the respiratory system (14 cases, 34.1%) and the digestive system (12 cases, 29.3%), followed by cancers of the urinary system (7 cases, 17.1%). The endocrine system and female genital system each accounted for 3 patients (7.3%), with breast cancer identified in 2 patients (4.9%). Adenocarcinoma was the predominant histological type (25 cases, 61.0%). Regarding disease stage at presentation, 18 patients (43.9%) had localized disease, 13 (31.7%) had locoregional metastasis, and 10 (24.4%) had distant metastasis. Among treatment modalities, surgery was the most common, performed in 63.41% of patients (**Table 1**).

Characteristics of stroke onset: Among the 41 CRIS patients, stroke attribution according to the TOAST classification was as follows: large-artery atherosclerosis (LAA) (14 cases), small-artery occlusion (SAD) (11 cases), cardioembolism (CE) (10 cases), stroke of other determined etiology (4 cases), and stroke of undetermined etiology (2 cases). Brain CT/MRI revealed that cerebral infarcts in CRIS patients predominantly involved cortical and subcortical regions (31 patients, 75.61%), followed by deep cerebral hemispheres (16 patients, 39.02%). Regarding

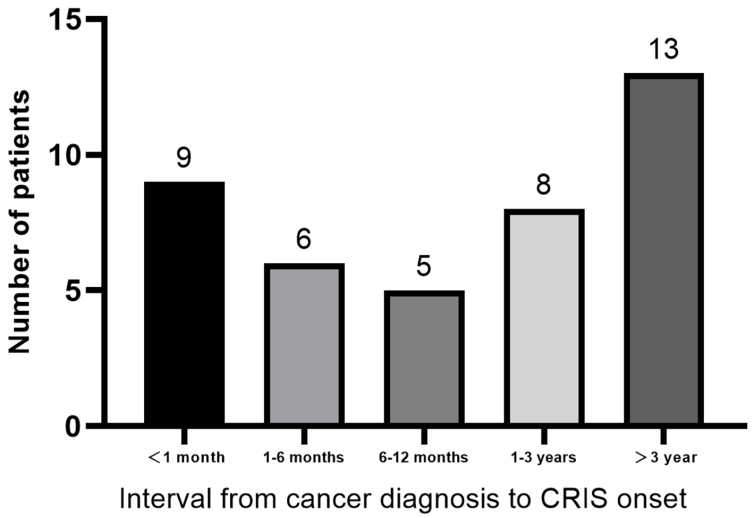

Figure 2. Time distriibution of CRIS onset. CRIS, cancer related ischemic stroke.

infarct size, many patients presented with small lesions or a combination of large and small lesions. The median (interquartile range) NIHSS scores at stroke onset and discharge were 4 (2, 12) and 3 (1, 9), respectively (**Table 2**). The temporal distribution of stroke onset relative to cancer diagnosis is shown in **Figure 2**. Among the 41 CRIS patients, 36.6% (15/41) experienced stroke within six months of cancer diagnosis.

Comparison of laboratory indicators between the CRIS and NC-IS groups

Matching of baseline characteristics: We initially collected data from 213 NC-IS patients. PSM successfully balanced baseline confounders between the CRIS and NC-IS groups (matching variables: sex, age, DM, hypertension, CHD, smoking history, alcohol history, AF, BMI, admission NIHSS score), resulting in 41 matched pairs. Comparisons of baseline clinical variables before and after matching are shown in **Table 3**. After matching, baseline characteristics were balanced between the groups. Notably, the distribution of the time from stroke onset to blood sampling - which was not included as a matching variable - was also well balanced between the two groups, suggesting adequate preparation for subsequent analysis (**Table 3**).

Association of laboratory indicators with CRIS status: Binary univariate logistic regression analysis of the matched CRIS and NC-IS groups revealed that among patients with established AIS, the following indicators were significantly associated with CRIS status: RBC, D-dimer, TG, and 13-(S)-HODE (**Table 4**). Subsequent binary multivariate logistic regression analysis of these four indicators revealed that RBC, D-dimer, and 13-(S)-HODE remained significantly associated with CRIS status (**Table 5**).

Ability of indicators to distinguish CRIS from NC-IS: ROC curve analysis demonstrated that among patients with established AIS, RBC, D-dimer, and 13-(S)-HODE had value in distinguishing CRIS from NC-IS. The AUCs were as follows: RBC 0.642 (95% CI: 0.521-0.761, $P = 0.0267$) (**Figure 3A**); D-dimer 0.739 (95% CI: 0.630-0.848, $P < 0.001$) (**Figure 3B**); and 13-(S)-HODE 0.722 (95% CI: 0.607-0.836, $P = 0.0006$) (**Figure 3C**). The combined model of these three indicators achieved an AUC of 0.819 (95% CI: 0.729-0.908, $P = 0.0001$) (**Figure 3D**). The optimal cutoff values for distinguishing CRIS from NC-IS, determined by the Youden index, were as follows: RBC 4.15 × 10^{12}/L, D-dimer 1.39 mg/L, and 13-(S)-HODE 384.167 ng/mL. The CRIS recognition rate, NC-IS recognition rate, overall correct classification rate, proportion of CRIS in test-positive cases, and proportion of NC-IS in test-negative cases for each indicator at its cutoff are presented in **Table 6**.

Comparison of laboratory indicators among the CRIS, CNSP, and NC groups

Using the manual 1:1 matching method, we collected data from 40 CNSP patients (one excluded due to rare tumor types) and 41 NC patients. Baseline characteristics were balanced after matching (Supplementary Table 1). Due to differences in case collection methods and the lack of frozen serum samples for CNSP and NC groups, 13-(S)-HODE was only used in the core analysis comparing CRIS and NC-IS. The nine remaining routine clinical indicators were compared across groups. Compared with the NC-IS group, the CRIS group had significantly lower

Table 3. Comparison baseline characteristics between CRIS group and NC-IS group before and after PSM

Characteristics	Before PSM				After PSM			
	CRIS (41)	NC-IS (213)	*P* value	SMD	CRIS (41)	NC-IS (41)	*P* value	SMD
Age (year)	70.2 ± 11.5	70.94 ± 11.7	0.690	0.060	70.2 ± 11.5	69.5 ± 11.2	0.756	0.062
Sex			0.742	0.057			0.820	0.049
Male	25 (61.0%)	124 (58.2%)			25 (61.0%)	26 (63.4%)		
Female	16 (39.0%)	89 (41.8%)			16 (39.0%)	15 (36.6%)		
DM	16 (39.0%)	69 (32.4%)	0.410	0.138	16 (39.0%)	17 (41.5%)	0.822	0.125
Hypertension	31 (75.6%)	149 (70.0%)	0.465	0.135	31 (75.6%)	30 (73.1%)	0.800	0.057
CHD	8 (19.5%)	37 (17.4%)	0.742	0.054	8 (19.5%)	8 (19.5%)	1.000	0
Smoking	11 (26.8%)	90 (42.3%)	0.065	0.330	11 (26.8%)	12 (29.3%)	0.806	0.054
Drinking	5 (12.2%)	25 (11.7%)	0.934	0.015	5 (12.2%)	6 (14.6%)	0.532	0.071
AF	7 (17.1%)	77 (36.2%)	0.017*	0.442	7 (17.1%)	6 (14.6%)	0.905	0.068
BMI	23.1 (20.2, 25.9)	24.9 (22.9, 26.7)	0.001*	0.550	23.1 (20.2, 25.9)	23.4 (21.6, 25.3)	0.591	0.047
NIHSS	4 (2, 11.5)	4 (2, 10)	0.845	0	4 (2, 11.5)	4 (2, 9.5)	0.915	0
Onset-to-sampling time (hour)	/	/	/	/	5 (2.0, 39.5)	15 (6.5, 26)	0.197	0.187

Note: Continuous data: mean ± SD or median (IQR); categorical data: n (%); **P*-value < 0.05. Abbreviations: CRIS, cancer related ischemic stroke; NC-IS, non-cancer ischemic stroke; PSM, propensity score matching; NC, normal control; SMD, standardized mean difference; DM, Diabetes mellitus; CHD, coronary heart disease; AF, atrial fibrillationl; BMI, body mass indexuric acid; NIHSS, the National Institutes of Health Stroke Scale.

Table 4. Univariate binary logistic regression analysis of CRIS

Risk factors	OR (95% CI)	*P* value
WBC	0.997 (0.872-1.139)	0.960
RBC	0.517 (0.274-0.976)	0.042*
PLT	0.994 (0.988-1.001)	0.089
D-Dimer	1.298 (1.030-1.636)	0.027*
Crea	0.988 (0.972-1.003)	0.126
UA	0.997 (0.992-1.001)	0.138
TG	0.587 (0.316-1.090)	0.043*
HDL-C	0.500 (0.215-1.163)	0.107
LDL-C	0.898 (0.587-1.373)	0.619
13-(s)-HODE	0.997(0.994-0.999)	0.002*

Note: **P*-value < 0.05. Abbreviations: CRIS, cancer related ischemic stroke; WBC, White blood cell count; RBC, Red blood cell count; PLT, Platelet count; UA, Uric acid; TG, Triglycerides; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; 13-(S)-HODE, 13-(s)-hydroxyoctadecadienoic acid.

RBC (P = 0.027), higher D-dimer (P = 0.001), and lower TG (P = 0.020) levels, consistent with the previous univariate logistic regression analysis (Supplementary Table 2). Compared with the CNSP group, the CRIS group had significantly higher D-dimer (P = 0.001), but no significant differences were found for other indicators (Supplementary Table 3). Compared with the NC group, the CRIS group had significantly lower RBC (P = 0.001), higher D-dimer (P = 0.001), and lower serum creatinine (Cr) (P = 0.036), with no significant differences in other indicators (Supplementary Table 4).

Discussion

This study collected clinical data from CRIS patients, analyzed their clinical characteristics, and compared laboratory parameters and serum 13-(S)-HODE levels with those of NC-IS patients.

CRIS patients are predominantly elderly males, consistent with the high-risk demographic for cancer [22]. All CRIS patients underwent CTA or MR imaging, confirming the nature of the infarcts. The lesions were mostly large lesions mixed with small lesions; many cases involved both the anterior and posterior circulation. Navi et al. also suggested multifocal involvement in CRIS patients [23]. This widespread, multifocal involvement aligns with the characteristics of multimechanism embolization induced by tumors.

Table 5. Multivariate logistic regression analysis of CRIS

Risk factors	OR (95% CI)	*P* value
RBC	0.444 (0.205-0.961)	0.039*
D-Dimer	1.310 (1.010-1.699)	0.042*
TG	0.591 (0.3267-1.598)	0.196
13-(s)-HODE	0.995 (0.992-0.998)	0.001*

Note: **P*-value < 0.05. Abbreviations: CRIS, cancer-related ischemic stroke; OR, odds ratio; RBC, Red blood cell count; TG, Triglycerides; 13-(S)-HODE, 13-(s)-hydroxyoctadecadienoic acid.

In this study, cancers of the respiratory system (34.1%) and digestive system (29.3%) were the most common primary tumors in CRIS. The association of these tumor types with high stroke risk is supported by multiple studies: Chungi et al. studied 114 patients with active lung cancer and ischemic stroke, finding larger ischemic lesions in lung adenocarcinoma patients [24]; cancer diagnosis increases short-term stroke risk, particularly in lung, pancreatic, and colorectal cancers [25]; and another study involving over 1200 patients also indicated that genitourinary, breast, and gastrointestinal cancers are common in CRIS [26]. We observed a high proportion of adenocarcinoma (61.0%) in CRIS. Studies have also shown that adenocarcinomas - particularly pancreatic, ovarian, and lung cancers - are more prone to thrombotic events. This is attributed to the procoagulant activity of adenocarcinoma-derived extracellular vesicles, which shorten clotting time and enhance thrombus formation, increasing the likelihood of arterial thrombotic events such as stroke [27]. However, not all CRIS patients in this study received anticoagulation. Key reasons include a delayed anticoagulation safety window due to large infarct size and the lack of evidence-based guidelines for anticoagulation in CRIS, despite increasing research. While current understanding parallels venous thromboembolism in suggesting that anticoagulation is crucial for CRIS, and some small-scale studies indicate its efficacy in preventing CRIS episodes [28], the benefit of thrombosis prevention must be carefully weighed against bleeding risks. There is an urgent need for research targeting specific high-risk subgroups (e.g., patients with metastatic adenocarcinoma) to explore the benefit-risk.

Approximately 36.59% of the CRIS patients in this study experienced stroke within six months

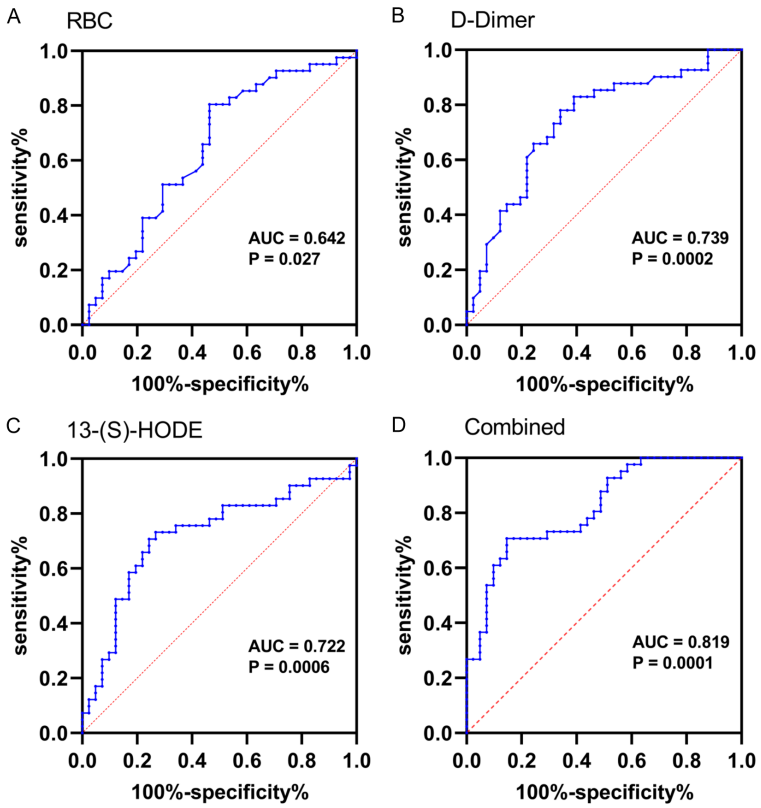

Figure 3. ROC curves for discrimination between CRIS and NCIS patients. A. RBC count. B. D-dimer level. C. 13-(S)-HODE level. D. Combined model (RBC + D-dimer + 13-(S)-HODE). RBC, Red blood cell count; 13-(S)-HODE, 13-(s)-hydroxyoctadecadienoic acid.

of cancer diagnosis, which is consistent with the reported peak stroke risk within six months after cancer diagnosis [29, 30]. Furthermore, it is noteworthy that stroke can be the initial manifestation of an occult malignancy, highlighting the importance of cancer screening in cases of cryptogenic AIS [31]. However, for the purpose of this study, our CRIS cohort exclusively comprised patients with a preexisting cancer diagnosis to ensure the availability of precise oncological data.

Using rigorous PSM to adjust for potential baseline confounders, this study ensured comparability between the CRIS and NC-IS groups and identified RBC, D-dimer, and 13-(S)-HODE as factors independently associated with CRIS status.

Research on RBC differences between CRIS and NC-IS is relatively limited. Small-sample studies have reported decreased RBC and hemoglobin levels in lung cancer-associated AIS patients [32]. Numerous studies have focused on hemoglobin levels, consistently finding lower hemoglobin in CRIS patients than in NC-IS patients [33, 34]. One study proposed a hemoglobin cutoff of 128 g/L as a diagnostic threshold [35]. Our finding of significantly lower RBC in CRIS patients than in NC-IS patients aligns with previous research. Decreases in RBC and hemoglobin are consistent with the pathophysiology of malignancy: cancer cachexia reduces erythropoietin production and impairs hemoglobin synthesis; gastrointestinal bleeding, which is common in malignancies, contributes to blood loss. This is evidenced by the higher incidence of gastrointestinal cancers among patients with positive fecal occult blood tests compared to those with negative results [36].

D-dimer, a fibrin degradation product generated through plasmin-mediated fibrinolysis, is markedly elevated in hypercoagulable states. Elevated D-dimer levels have been documented in cancer patients [37] and are also commonly observed in several types of AIS [38]. In our study, D-dimer levels in the CRIS group were significantly elevated compared to those in the NC-IS group (after propensity score matching), the CNSP group (1:1 matched), and the NC group (1:1 matched), reflecting complex coagulation dysfunction resulting from the combined effects of cancer and stroke. These findings are consistent with the literature on CRIS. A meta-analysis indicated that among over 44 studies investigating D-dimer, 42 confirmed elevated D-dimer levels in CRIS patients relative to control groups [39]. Furthermore, one study directly compared D-dimer levels across the CRIS, NC-IS, CNSP, and NC groups, revealing that both the NC-IS and CNSP groups exhibited moderate increases in D-dimer levels compared with the NC group, while the CRIS group presented a markedly and persistently elevated D-dimer level relative to the other

Table 6. Discriminative potential of RBC, D-Dimer, 13-(s)-HODE and combined panel for CRIS vs. NC-IS in a propensity score-matched cohort

	RBC	D-Dimer	13-(s)-HODE	Combined
CRIS recognition rate	53.7%	65.9%	73.2%	70.7%
NC-IS recognition rate	80.5%	78.0%	73.2%	85.4%
Overall correct classification rate	67.1%	72.0%	73.2%	78.0%
Proportion of CRIS in test-positive cases	73.3%	75.0%	73.2%	82.9%
Proportion of NC-IS in test-negative cases	63.5%	69.6%	73.2%	74.5%

Abbreviations: CRIS, cancer related ischemic stroke; NC-IS, non-cancer ischemic stroke; RBC, Red blood cell count; 13-(s)-HODE, 13-(s)-hydroxyoctadecadienoic acid.

three groups [40]. Although D-dimer has been extensively studied as a potential biomarker in CRIS, it is not specific to cancer or stroke. Various factors - including mechanical thrombectomy, thrombolysis, anticoagulant therapy, advanced age, pregnancy, and active infection - can influence D-dimer levels. One study reported a positive correlation between D-dimer levels and the frequency of microembolic signals detected by transcranial Doppler (TCD) in CRIS patients, suggesting that elevated D-dimer may serve as an independent predictor of embolic activity [41]. We believe that the elevated D-dimer in the CRIS group in this study is largely attributable to active embolic events. In this study, blood sampling for D-dimer measurement was performed prior to any surgical or thrombolytic intervention, and pregnant patients were excluded to minimize potential confounders.

13-(S)-HODE, a linoleic acid metabolite generated by 15-lipoxygenase-1 (15-LOX-1) [42], was significantly lower in CRIS patients than in NC-IS controls. This finding aligns with previous reports in non-small cell lung cancer and oral squamous cell carcinoma [43, 44], supporting the notion that decreased 13-(S)-HODE may be a common feature in certain malignancies. The role of 13-(S)-HODE in cancer is context-dependent, as it has both tumor-suppressive and promoting effects through distinct pathways. As a tumor suppressor, 13-(S)-HODE acts as a PPARγ ligand, inducing anti-proliferative and pro-apoptotic responses in colorectal cancer cells [45-47]. In the MCF-7 breast cancer cell line, 13-(S)-HODE downregulates PPAR-δ expression, inhibiting its downstream proliferative signaling pathways and promoting apoptosis and growth suppression [48]. Studies have suggested that serum levels of 13-(S)-HODE are lower in patients with non-small cell lung cancer (NSCLC) than in healthy individuals. Further multiomics integration suggested that the reduced plasma levels of 13-(S)-HODE in NSCLC patients may be associated with increased linoleic acid metabolic flux, which activates the Akt pathway and promotes tumor cell proliferation [43]. 13-(S)-HODE also inhibits cancer-endothelial adhesion and counteracts prometastatic eicosanoids such as 12(S)-HETE [49]. Thus, its reduction in CRIS may indicate loss of these protective mechanisms. Conversely, 13-(S)-HODE can exhibit oncogenic properties by stimulating EGFR-MAPK signaling [50], activating IGF in prostate cancer, or promoting NF-κB-driven progression in endometrial cancer [51]. This functional duality depends on the cancer cell type and specific receptors activated. Moreover, the choice of control group is crucial for interpretation. Since 13-(S)-HODE is also enriched in atherosclerotic plaques, its levels may be elevated in NC-IS patients due to their atherogenic background and increased concentrations of blood lipid indicators [52]. Therefore, the lower levels in CRIS likely reflect both a cancer-specific reduction and a relatively elevated baseline in NC-IS controls. Unfortunately, the lack of serum from the CNSP and NC groups prevents definitive determination of whether this reduction is cancer-specific or exacerbated by stroke. Future studies measuring this metabolite across all four cohorts are essential. This study design, specifically the lack of 13-(S)-HODE measurements in CNSP and NC groups, prevents definitive determination of whether the observed reduction is specifically attributable to the coexistence of cancer and stroke or to cancer alone.

CRIS patients present with both cancer and stroke, involving complex mechanisms. There is currently no widely accepted, specific combined indicator for CRIS, and single indicators

are insufficient for distinguishing CRIS from NC-IS. The three indicators identified in this study - decreased RBC (reflecting chronic consumption/blood loss), elevated D-dimer (indicating hypercoagulability), and decreased 13-(S)-HODE (lipid metabolism) - correspond to the multifaceted pathological mechanisms of CRIS (nutritional depletion, hypercoagulability, metabolic dysregulation). However, similar changes in these indicators can occur in other conditions (e.g., decreased RBC in chronic kidney disease and elevated D-dimer in infection). To overcome the limitations of single indicators, we combined these three laboratory indicators. The combined model showed optimized performance for identifying CRIS, achieving an AUC of 0.819, which was superior to that of RBC, D-dimer, or 13-(S)-HODE alone.

All the serological indicators were measured after AIS onset, precluding direct assessment of their predictive value for CRIS. However, this study focused on distinguishing CRIS from NC-IS, not predicting AIS risk in known cancer patients.

Due to the limited incidence of CRIS and stringent inclusion/exclusion criteria, the relatively small sample size may affect the reliability of subgroup analyses (e.g., differences by cancer type or stage). Nevertheless, rigorous PSM (1:1 matching) and baseline balancing minimized confounding bias, and the core conclusion (diagnostic value of the triple-marker panel) demonstrated statistical robustness.

Owing to historical sample storage constraints, 13-(S)-HODE was only measured in the CRIS and NC-IS groups. The lack of available frozen serum for the CNSP and NC groups prevented the evaluation of the levels of this marker in “cancer-only” or “healthy” states. Therefore, we cannot conclusively determine whether the decreased 13-(S)-HODE level is a specific feature of the concurrent cancer and stroke state (CRIS) or is driven primarily by the presence of the cancer itself. Future studies including these control groups are necessary to elucidate the specific contribution of cancer versus stroke events to the observed alteration in 13-(S)-HODE metabolism.

In conclusion, this study, utilizing propensity score matching, found that RBC, D-dimer, 13-(S)-HODE, and their combination demonstrated value in distinguishing CRIS from NC-IS. However, their specificity is limited, and further validation in cohorts including cancer patients without stroke is required.

Disclosure of conflict of interest

None.

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Supplementary Table 1. Baseline characteristics of CRIS versus CNSP and CRIS versus NC

Characteristics	CRIS vs CNSP				CRIS vs NC			
	CRIS (40)	CNSP (40)	Δ (CRIS - CNSP)	*P* value	CRIS (41)	NC (41)	Δ (CRIS - NC)	*P* value
Age (year)	72 (63, 80)	71 (61, 77)	1 (-2.5, 3)	0.327	70.15 ± 11.5	70.15 ± 11.6	0 ± 1.8	1
Sex				1				1
Male	25 (62.5%)	24 (60.0%)			25 (61.0%)	25 (61.0%)		
Female	15 (37.5%)	16 (40.0%)			16 (39.0%)	16 (39.0%)		
DM	15 (37.5%)	14 (35.0%)		1	16 (39.0%)	14 (34.1%)		0.500
Hypertension	31 (77.5%)	28 (70.0%)		0.453	31 (75.6%)	31 (75.6%)		1
CHD	8 (20.0%)	6 (15.0%)		0.625	8 (19.5%)	7 (17.1%)		1
Smoking	11 (27.5%)	13 (32.5%)		0.625	11 (26.8%)	10 (24.4%)		1
Drinking	5 (12.5%)	5 (12.5%)		1	5 (12.2%)	5 (12.2%)		1
AF	7 (17.5%)	3 (7.5%)		0.125	7 (17.1%)	5 (12.2%)		0.625

Note: Continuous data: mean ± SD or median (IQR); categorical data: n (%). Abbreviations: CRIS, cancer related ischemic stroke; CNSP, cancer and no stroke patients; NC, normal control; DM, Diabetes mellitus; CHD, coronary heart disease; AF, atrial fibrillationl.

Supplementary Table 2. Laboratory data between CRIS group and NC-IS group after PSM

Laboratory data	CRIS (41)	NC-IS (41)	*P* value
WBC (10^9/L)	7.86 ± 3.44	7.90 ± 3.14	0.961
RBC (10^{12}/L)	4 (3, 5)	5 (4, 5)	0.027*
PLT (10^9/L)	187 (158, 236)	207 (183, 258)	0.087
D-Dimer (mg/L)	2.50 (0.79, 3.79)	0.50 (0.22, 1.30)	0.001*
Crea (μmol/L)	72 (60, 83)	73 (63, 94)	0.241
UA (μmol/L)	291 ± 106	324 ± 92	0.134
TG (mmol/L)	1.19 (0.97, 1.77)	1.62 (1.17, 2.25)	0.020*
HDL-C (mmol/L)	1.09 (0.90, 1.43)	1.16 (0.93, 1.75)	0.228
LDL-C (mmol/L)	2.31 (1.67, 3.07)	2.66 (1.76, 3.37)	0.525

Note: Continuous data: mean ± SD or median (IQR); categorical data: n (%); **P*-value < 0.05. Abbreviations: CRIS, cancer related ischemic stroke; NC-IS, non-cancer ischemic stroke; PSM, propensity score matching; WBC, White blood cell count; RBC, Red blood cell count; PLT, Platelet count; UA, Uric acid; TG, Triglycerides; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol.

Supplementary Table 3. Laboratory data of CRIS versus CNSP

Laboratory data	CRIS (40)	CNSP (40)	Δ (CRIS - CNSP)	*P* value
WBC (10^9/L)	7.19 (5.51, 9.27)	6.41 (5.56, 8.21)	0.78 (-1.07, 2.27)	0.136
RBC (10^{12}/L)	4.12 ± 0.74	4.30 ± 0.80	-0.19 ± 0.88	0.189
PLT (10^9/L)	195 ± 76	204 ± 58	-9 ± 92	0.554
D-Dimer (mg/L)	2.50 (0.79, 3.79)	0.52 (0.23, 0.85)	1.64 (0.07, 3.28)	0.001*
Crea (μmol/L)	74 ± 23	79 ± 23	-5 ± 31	0.297
UA (μmol/L)	72 (60, 83)	59 (73, 94)	-5 (-79, 44)	0.595
TG (mmol/L)	1.45 ± 0.79	1.31 ± 0.56	0.14 ± 1.03	0.505
HDL-C (mmol/L)	1.09 (0.90, 1.43)	1.21 (0.98, 1.40)	-0.05 (-0.27, 0.23)	0.737
LDL-C (mmol/L)	2.55 ± 1.08	2.62 ± 0.84	-0.07 ± 1.16	0.769
Metastasis of Cancer	11 (26.8%)	11 (26.8%)		1

Note: Continuous data: mean ± SD or median (IQR); categorical data: n (%); **P*-value < 0.05. Abbreviations: CRIS, cancer related ischemic stroke; CNSP, cancer and no stroke patients; WBC, White blood cell count; RBC, Red blood cell count; PLT, Platelet count; UA, Uric acid; TG, Triglycerides; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; 13-(S)-HODE, 13-(s)-hydroxyoctadecadienoic acid.

Supplementary Table 4. Laboratory data of CRIS versus NC

Laboratory data	CRIS (41)	NC (41)	Δ (CRIS - NC)	*P* value
WBC (10^9/L)	7.86 ± 3.44	6.72 ± 2.43	1.14 ± 3.81	0.062
RBC (10^{12}/L)	4.12 (3.48, 4.63)	4.47 (3.98, 4.84)	-0.58 (-0.76, -0.07)	0.001*
PLT (10^9/L)	195 ± 75	190 ± 60	5 ± 85	0.702
D-Dimer (mg/L)	2.50 (0.79, 3.79)	0.33 (0.20, 0.52)	2.17 (0.31, 3.53)	0.001*
Crea (μmol/L)	72 (60, 83)	77 (65, 93)	8 (-24, 9)	0.036*
UA (μmol/L)	291 ± 106	302 ± 111	-14 ± 152	0.552
TG (mmol/L)	1.19 (0.97, 1.77)	1.13 (0.87, 1.79)	-0.07 (-0.43, 0.33)	0.573
HDL-C (mmol/L)	1.09 (0.90, 1.43)	1.20 (0.93, 1.42)	0.03 (-0.36, 0.20)	0.534
LDL-C (mmol/L)	2.44 ± 1.01	2.43 ± 0.68	-0.12 ± 1.29	0.954

Note: Continuous data: mean ± SD or median (IQR); categorical data: n (%); **P*-value < 0.05. Abbreviations: CRIS, cancer related ischemic stroke; NC, normal control; WBC, White blood cell count; RBC, Red blood cell count; PLT, Platelet count; UA, Uric acid; TG, Triglycerides; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; 13-(S)-HODE, 13-(s)-hydroxyoctadecadienoic acid.