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Original Article

Clinical features and prognosis of patients with malignant tumors complicated by cerebral infarction

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Abstract: Objectives: To investigate the clinical features and prognosis of patients with malignant tumor-associated acute cerebral infarction (MACI). Methods: This retrospective study compared 115 patients with MACI and 182 patients with simple acute cerebral infarction (ACI) admitted to the First Hospital of Zhangjiakou from January 2020 to December 2024. A comparison was made of the differences in demographic characteristics and prognosis survival rate between the two groups. Results: Non-small cell lung cancer (43.48%) was the most common malignant tumor in MACI patients. Compared with ACI patients, MACI patients had a higher prevalence of stroke history but a lower incidence of diabetes and hyperlipidemia. Imaging findings revealed a higher proportion of cortical/subcortical lesions and the typical diffusion-weighted imaging three-territory sign in the MACI group. Laboratory analyses demonstrated significantly elevated levels of D-dimer (D-D), fibrinogen (FIB), tissue factor (TF), plasminogen activator inhibitor-1 (PAI-1), and C-reactive protein in MACI patients. In the MACI group yielding an overall mortality rate of 62.61%, significantly higher than the 25.82% in the ACI group ($P < 0.001$). Multivariate Cox regression analysis identified TNM stage (*HR* = 2.127, 95% CI: 1.091-4.146), objective response rate (HR = 0.235, 95% CI: 0.088-0.621), D-D (HR = 2.320, 95% CI: 1.288-4.179), and National Institutes of Health Stroke Scale (NIHSS) score at admission (HR = 2.324, 95% CI: 1.215-4.444) as independent factors influencing overall survival in MACI patients. Conclusions: MACI has unique clinical and radiological characteristics. The presence of the three-territory sign and a hypercoagulable state are key factors increasing cumulative mortality from ACI.

Keywords: Malignancy, acute cerebral infarction, clinical features, prognosis

Introduction

Acute cerebral infarction (ACI) is one of the most serious diseases contributing to the global disease burden [1]. Its etiology is complex, with hypertension, diabetes, hyperlipidemia and long-term smoking considered as traditional risk factors. Studies have shown that malignant tumors significantly increase the risk of arterial thrombotic events [2]. As the most common form of ischemic stroke, cerebral infarction occurs 2-4 times more frequently in cancer patients than in the general population, and in some cases, it may even be the initial clinical manifestation of cancer [3]. The relationship between malignant tumors and cerebral infarction is bidirectional. Cerebral infarction reduces the quality of life of cancer patients, while cancer increases the risk of cerebral infarction [4]. Therefore, in-depth exploration of the relationship between the two is conducive to enhancing the quality of life of patients and prolong their survival time. Previous studies have elucidated the unique characteristics of cerebral infarction associated with malignant tumors. Its occurrence may stem from primary tumors of the central nervous system (such as gliomas) or stroke caused by tumor metastasis. Among systemic malignant tumors, solid tumor types are dominant, including lung cancer, colorectal cancer, prostate cancer, breast cancer and liver cancer [5]. Patients with acute ischemic stroke related to lung cancer often present with a hypercoagulable state, multiple or multi-vascular infarctions, severe neurological impairment, and complex etiologies [6]. In addition, there are significant differences in the characteristics of cerebral infarction among dif-

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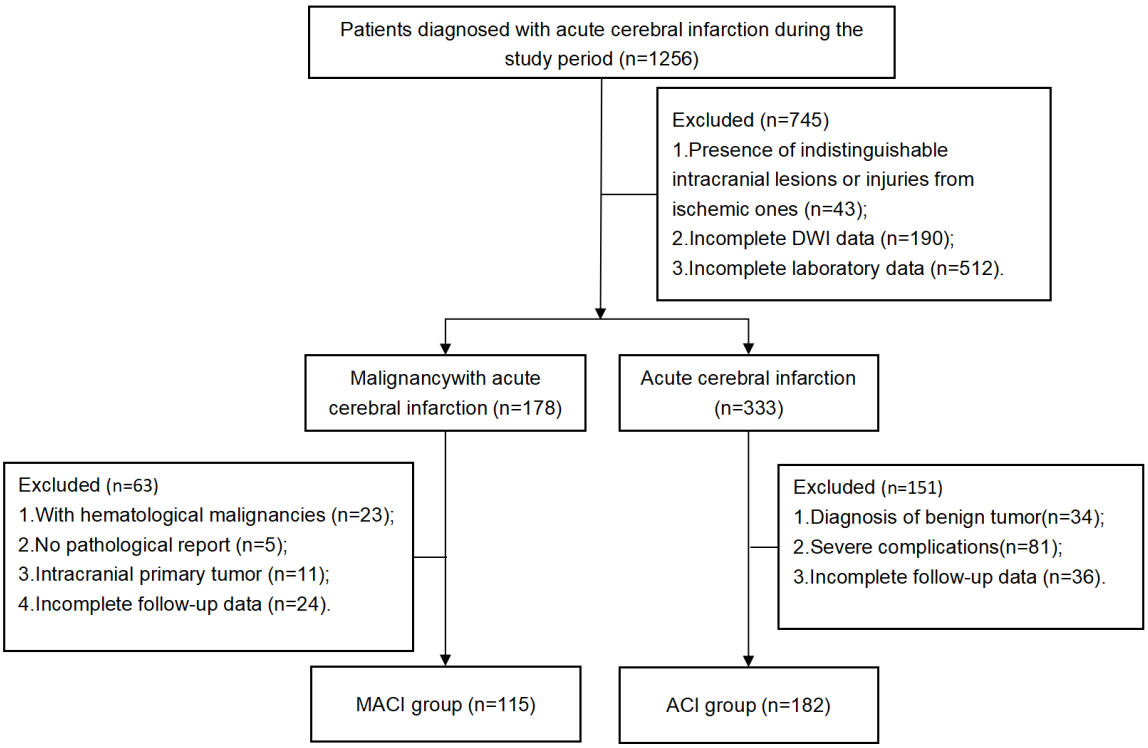

Figure 1. Study flow chart. Abbreviations: MACI, Malignancy with acute cerebral infarction; ACI, acute cerebral infarction.

ferent tumor types. The time interval from cancer diagnosis to cerebral infarction is the shortest in patients with colon cancer, while it is the longest in patients with nasopharyngeal carcinoma [7]. Currently, there is no clear consensus on the main factors for cerebral infarction in patients with malignant tumors. This study aims to comprehensively summarize the clinical characteristics and prognostic factors of patients with malignant tumors and cerebral infarction, and to provide a basis for developing clinical intervention strategies.

Materials and methods

Study subjects

Patients with malignant tumor-associated acute cerebral infarction (MACI, n = 115) admitted to the First Hospital of Zhangjiakou from January 2020 to December 2024 who met the inclusion criteria were retrospectively collected. Simultaneously, patients with simple ACI without any tumor form (n = 182) admitted during the same period were randomly selected (**Figure 1**).

MACI group inclusion criteria: (1) Age ≥ 18 years old; (2) First-time head MRI confirmed as ACI after tumor diagnosis, or first-time diagnosis of malignant tumor during hospitalization for ACI; (3) Enhanced CT/MRI showing typical malignant features conforming to RECIST 1.1 criteria [8], confirmed by biopsy or surgical specimens, and PET-CT was performed to assess metastasis if necessary. Exclusion criteria: (1) Comorbid primary or secondary central nervous system tumors; (2) Hematologic malignancies; (3) Serious complications such as myocardial infarction, cardiopulmonary, hepatic, and renal insufficiency, or mental disorders; (4) Incomplete clinical data.

ACI group inclusion criteria: (1) Age ≥ 18 years old; (2) Confirmed by cranial MRI as ACI; (3) Admitted at the same period as patients in the MACI group. Exclusion criteria: (1) Presence of other intracranial lesions or injuries that cannot be distinguished from ischemic lesions; (2) Enhanced CT/MRI showing typical malignant features in accordance with RECIST 1.1 criteria [8], confirmed by biopsy or surgical specimens; (3) Serious complications, such as myocardial

infarction, cardiopulmonary, hepatic and renal insufficiency or mental disorders; (4) Incomplete clinical data.

The sample size was estimated based on the difference in all-cause mortality between groups [9]. With $\alpha = 0.05$, a power of 80%, and a 1:1 allocation ratio, assuming a mortality rate of 60% in the MACI group and 20% in the ACI group, at least 46 participants were required per group. Considering a 20% dropout rate, the final requirement was 58 participants per group (116 in total). The study ultimately enrolled 115 participants in the MCI group and 182 participants in the ACI group, meeting the sample size requirement.

All cranial and tumor imaging data were independently reviewed by two physicians with over five years of diagnostic experience, who were unaware of the patient groupings and final diagnoses. In case of disagreement, a third attending physician made the final decision and recorded the consensus. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Medical Ethics Committee of the First Hospital of Zhangjiakou. Informed consent from patients was waived.

Definition of MACI

MACI is defined as an ACI occurring between one year before and two years after the diagnosis of a malignant tumor, encompassing all etiological mechanisms, including direct tumor effects, cancer-related coagulation disorders, and iatrogenic effects [10].

Research data

Clinical data of patients were collected through the hospital's electronic medical record system.

(1) General information: age, gender, and stroke risk factors, including smoking history, alcohol consumption history, stroke history, hypertension, diabetes, hyperlipidemia, coronary heart disease (CHD), and atrial fibrillation. Additionally, the time interval from the diagnosis of the malignant tumor to the occurrence of cerebral infarction was also included, tumor type, tumor pathological type, TNM stage, tumor metastasis, tumor treatment methods, clinical efficacy of tumor treatment, type of cerebral infarction (classified according to the TOAST classification), and the National Institutes of Health Stroke Scale (NIHSS) score at the time of infarction.

(2) Admission imaging: All patients were scanned using a 3.0-T Siemens Skyra scanner (Siemens AG, Munich, Germany), and comprehensive neuroradiological reports were generated. We carefully examined the diffusion-weighted imaging (DWI) features of each patient. Specifically, we recorded the vascular regions where new infarct lesions were located on DWI. Regarding imaging manifestations, we identified three distinct ischemic stroke patterns on MRI DWI in the MACI and ACI groups: 1. Single - Vascular - Territory Pattern: Infarction confined to the anterior or posterior cerebral circulation. 2. Dual - Vascular - Territory Pattern: Infarction involving both the anterior and posterior circulations simultaneously, or bilaterally in the anterior circulation. 3. Three - Vascular - Territory Pattern: Infarction involving both bilateral anterior and posterior circulations. In addition, cortical/subcortical lesions were evaluated.

(3) Laboratory test data upon admission: Hemoglobin (Hb), low-density lipoprotein (LDL-C), thrombin time (TT), prothrombin time (PT), activated partial thromboplastin time (APTT), D-dimer (D-D), fibrinogen (FIB), homocysteine (Hcy), tissue factor (TF), plasminogen activator inhibitor-1 (PAI-1), and C-reactive protein (CRP) were collected.

TOAST classification

According to the TOAST classification criteria, the etiology of ACI is divided into: large artery atherosclerosis (LAA), small artery occlusion (SAO, cardiogenic embolism (CE), the stroke of other determined etiology (SOE), and unknown etiology (SUE).

Follow-up

Patient survival and mortality information was obtained through outpatient visits, inpatient follow-ups, and telephone follow-ups. Based on patient survival status and cause of death, outcome events were categorized into three types: (1) Events of concern, i.e., deaths attributable to ACI, defined as deaths caused by ACI. (2) Competing events, i.e., events that prevent the

Table 1. Clinical characteristics of MACI group

Variables	n = 115, n (%)
Time from cancer diagnosis to ACI	28 (24.35)
Malignancy diagnosed during ACI hospitalization	
ACI occurred within < 3 months after malignancy diagnosis	30 (26.09)
ACI occurred between 3 months and 1 year after malignancy diagnosis	15 (13.04)
ACI occurred more than 1 year after malignancy diagnosis	42 (36.52)
The tumor types, n (%)	
Non-small cell lung cancer	50 (43.48)
Breast cancer	13 (11.30)
Hepatocellular carcinoma	12 (10.43)
Colorectal cancer	9 (7.83)
Gastric cancer	7 (6.09)
Prostate cancer	5 (4.35)
Cervical cancer	4 (3.48)
Bladder cancer	4 (3.48)
Thyroid cancer	3 (2.61)
Ovarian cancer	2 (1.74)
Endometrial carcinoma	2 (1.74)
Pancreatic cancer	2 (1.74)
Laryngeal cancer	1 (0.87)
Nasopharyngeal carcinoma	1 (0.87)
Pathological type	
Adenocarcinoma	76 (66.09)
Squamous cell carcinoma	9 (7.83)
Hepatocellular carcinoma	12 (10.43)
Ductal carcinoma	13 (11.30)
Urothelial carcinoma	4 (3.48)
Non-keratinizing carcinoma	1 (0.87)
TNM stage	
I	14 (12.17)
II	31 (26.96)
III	19 (16.52)
IV	51 (44.35)
Distant metastasis	51 (44.35)
Tumor treatment, n (%)	
ST	16 (13.91)
ST + CHT	28 (24.35)
ST + CHT + RT	22 (19.13)
ST + IT	18 (15.65)
ST + TT	31 (26.96)
Clinical efficacy of tumor treatment, n (%)	
CR	6 (5.22)
PR	29 (25.22)
SD	27 (23.48)
PD	53 (46.08)
ORR (CR + PR)	35 (30.43)

Note: Abbreviations: MACI, Malignancy with acute cerebral infarction; ACI, acute cerebral infarction; ST, surgical treatment; CHT, chemotherapy; IT, immunotherapy; RT, radiation therapy; TT, target therapy; CR, complete response; PR, partialresponse; SD, stable disease; PD, progressive disease; ORR, objective response rate.

Table 2. Comparison of clinical characteristics between the two groups

Variables	Total (n = 297)	MACI group (n = 115)	ACI group (n = 182)	Statistics	*P*
Male, n (%)	170 (57.24)	69 (60.00)	101 (55.49)	0.584	0.445
Age, year, Mean ± SD	66.90±10.35	66.35±10.20	67.25±10.46	0.729	0.467
BMI, kg/m^2, Mean ± SD	22.89±2.10	21.93±2.06	22.51±2.10	2.321	0.021
Smoking, n (%)	110 (37.04)	49 (42.61)	61 (33.52)	2.499	0.114
Drinking, n (%)	87 (29.29)	33 (28.70)	54 (29.67)	0.032	0.857
Previous stroke history, n (%)	50 (16.84)	28 (24.35)	22 (12.09)	7.565	0.006
Hypertension, n (%)	158 (53.20)	57 (49.57)	101 (55.49)	0.995	0.319
Diabetes, n (%)	80 (26.94)	23 (20.00)	57 (31.32)	4.587	0.032
Hyperlipidemia, n (%)	95 (31.99)	24 (20.87)	71 (39.01)	10.661	0.001
CHD, n (%)	42 (14.14)	13 (11.30)	29 (15.93)	1.244	0.265
Atrial fibrillation, n (%)	24 (8.08)	6 (5.22)	18 (9.89)	2.072	0.150
TOAST types, n (%)				163.112	< 0.001
Large artery atherosclerosis	139 (46.80)	17 (14.78)	122 (67.03)		
Cardioembolism	16 (5.39)	3 (2.61)	13 (7.14)		
Small artery occlusion	50 (16.84)	12 (10.48)	38 (20.88)		
Stroke of other determined etiology	10 (3.37)	4 (3.48)	6 (3.30)		
Stroke of undetermined etiology	82 (27.61)	79 (68.70)	3 (1.65)		
Three territory sign on MRI-DWI, n (%)	104 (35.02)	63 (54.78)	41 (22.53)	32.221	< 0.001
Cortical/subcortical lesions, n (%)	110 (37.04)	55 (47.83)	55 (30.22)	9.368	0.002
Hb, g/L, Mean ± SD	101.06±22.01	98.85±22.60	102.46±21.57	1.377	0.170
LDL-C, mmol/L, Mean ± SD	2.21±0.86	2.17±0.87	2.23±0.84	0.655	0.513
TT, s, Mean ± SD	13.27±1.79	13.20±1.79	13.31±1.80	0.546	0.586
PT, s, Mean ± SD	11.40±3.09	11.82±3.65	11.14±2.65	1.848	0.066
APTT, s, Mean ± SD	31.81±3.44	31.69±3.50	31.89±3.41	0.477	0.634
D-D, mg/L, Median (P_{15}, P_{75})	0.19 (0.14, 0.42)	0.42 (0.16, 1.20)	0.17 (0.13, 0.23)	7.330	< 0.001
FIB, g/L, Mean ± SD	3.88±1.44	4.47±1.76	3.50±1.03	5.985	< 0.001
Hcy, mmol/L, Mean ± SD	16.36±3.51	16.24±4.41	16.44±2.80	0.470	0.638
TF, pg/mL, Median (P_{15}, P_{75})	8.85 (7.14, 11.94)	12.56 (11.19, 14.02)	7.63 (6.42, 8.83)	12.593	< 0.001
PAI-1, ng/mL, Median (P_{15}, P_{75})	141.32 (83.85, 2166.34)	237.94 (178.78, 300.47)	94.52 (72.47, 135.19)	13.080	< 0.001
CRP, mg/L, Mean ± SD	9.17±2.30	10.20±2.20	8.45±2.06	6.963	< 0.001
NIHSS at admission, Mean ± SD	7.23±2.43	8.51±2.66	6.42±1.86	7.981	< 0.001
Mortality, n (%)	119 (40.07)	72 (62.61)	47 (25.82)	39.709	< 0.001

Note: Abbreviations: MACI, Malignancy with acute cerebral infarction; ACI, acute cerebral infarction; BMI, body mass index; CHD, coronary heart disease; Hb, hemoglobin; LDL-C, low - density lipoprotein; TT, thrombin time; PT, prothrombin time; APTT, activated partial thromboplastin time; D-D, D-dimer; FIB, fibrinogen; Hcy, homocysteine; TF, tissue factor; PAI-1, plasminogen activator inhibitor-1; CRP, C-reactive protein; NIHSS, National Institutes of Health Stroke Scale.

Table 3. The collinearity diagnosis of variables

Variables	Tolerance	VIF
BMI	0.943	1.060
Previous stroke history	0.958	1.044
Diabetes	0.941	1.062
Hyperlipidemia	0.921	1.085
TOAST types	0.638	1.568
Three territory sign	0.813	1.230
Cortical/subcortical lesions	0.971	1.030
D-D	0.715	1.399
FIB	0.829	1.207
TF	0.515	1.943
PAI-1	0.490	2.043
CRP	0.818	1.223

Note: Abbreviations: BMI, body mass index; D-D, D-dimer; FIB, fibrinogen; TF, tissue factor; PAI-1, plasminogen activator inhibitor-1; CRP, C-reactive protein.

occurrence of events of concern, defined as the process from the diagnosis of ACI to the patient's death due to cancer or other causes. (3) Censored events, i.e., patients still alive at the end of the follow-up period. Overall survival (OS) was defined as the time interval from the diagnosis of ACI to death from any cause or the end of the last follow-up. The follow-up cut-off date was June 30, 2025, and the follow-up period was calculated monthly.

Statistical analysis

SPSS Statistics 26.0 software was used for statistical analysis. To analyze the differences in laboratory and clinical indicators between the MACI group and the ACI group, t-tests, chi-square tests, and Mann-Whitney U tests were used. Normally distributed data were expressed as mean ± standard deviation (SD), and non-normally distributed data were expressed as median (P15, P75). Categorical variables were expressed as frequency and percentage. Binary logistic regression analysis was used to identify independent risk factors associated with the presence of MACI. In survival analysis, continuous variables were analyzed by dividing them into median groups. Kaplan-Meier survival curves were constructed using the Kaplan-Meier method, and overall survival was compared between the MACI group and the ACI group using the log-rank test. Multivariate Cox regression analysis was used to assess factors influencing overall survival in MACI patients. Based on the Fine-Gray competing risk model, prognostic factors for MACI were analyzed using univariate tests and multivariate analysis, and hazard ratio (HR) and 95% confidence interval (CI) were calculated. $P < 0.05$ was considered statistically significant.

Results

Clinical characteristics

During the study period, a total of 297 patients were recruited in accordance with the inclusion and exclusion criteria. The patients' ages ranged from 30 to 87 years, with an average age of 66.90±10.35 years, and 57.2% of them were male. A total of 115 patients with MACI. Among these MACI patients, 28 were diagnosed with malignant tumors during their ACI hospitalization. In contrast, 87 patients developed ACI after the diagnosis of malignant tumors (**Table 1**). Of the 115 MACI cases, 50 (43.5%) were lung cancers, all of which were non-small cell lung cancer (NSCLC). Five patients with stage I disease underwent surgical resection alone, while one patient with advanced disease received palliative surgery. Additionally, 23 patients with sensitising EGFR mutations received adjuvant osimertinib following surgery. Ten patients with negative driver genes received adjuvant PD-1/PD-L1 inhibitor immunotherapy for one year after surgery. The remaining patients were treated with various combined modalities. Nine adenocarcinoma patients received surgery plus chemotherapy (carboplatin plus pemetrexed), with or without radiotherapy. Three squamous cell carcinoma patients received surgery plus chemotherapy (carboplatin plus paclitaxel), one of whom also received radiotherapy.

Comparison of clinical characteristics between the two groups

The age and gender distribution of patients in the MACI and ACI groups were similar (**Table 2**). The MACI group had a higher incidence of stroke history, but lower incidences of diabetes and hyperlipidemia, and a lower body mass index (BMI) (both $P < 0.05$). MRI-DW assessment in the MACI group revealed a three-territory sign and a higher proportion of cortical/subcortical lesions (both $P < 0.05$). The BMI level in the MACI group was lower than that in the ACI group. Conversely, the levels of D-dimer,

Table 4. Analysis of influencing factors of malignancy with acute cerebral infarction

Variables	*β*	SE	Wald statistic	*P* value	*OR* (95% *CI*)
BMI	-0.289	0.267	1.175	0.278	0.749 (0.444-1.264)
Previous stroke history	0.631	1.187	0.283	0.595	1.879 (0.184-19.238)
Diabetes	-1.365	1.174	1.353	0.245	0.255 (0.026-2.549)
Hyperlipidemia	-0.100	1.111	0.008	0.928	0.905 (0.103-7.988)
TOAST types	1.102	0.326	11.414	0.001	3.010 (1.588-5.704)
Three territory sign	-0.433	1.073	0.163	0.687	0.649 (0.079-5.311)
Cortical/subcortical lesions	1.519	0.887	2.930	0.087	4.567 (0.802-26.001)
D-D	2.138	2.078	1.058	0.304	8.485 (0.144-498.593)
FIB	0.171	0.395	0.187	0.666	1.186 (0.547-2.571)
TF	0.794	0.244	10.622	0.001	2.211 (1.372-3.564)
PAI-1	0.037	0.011	12.205	< 0.001	1.037 (1.016-1.059)
CRP	0.119	0.241	0.245	0.621	1.127 (0.702-1.808)

Note: Previous stroke history no = 0, Diabetes no = 0, Hyperlipidemia no = 0, Three territory sign no = 0, Cortical/subcortical lesions no = 0. Abbreviations: BMI, body mass index; D-D, D-dimer; FIB, fibrinogen; TF, tissue factor; PAI-1, plasminogen activator inhibitor-1; CRP, C-reactive protein.

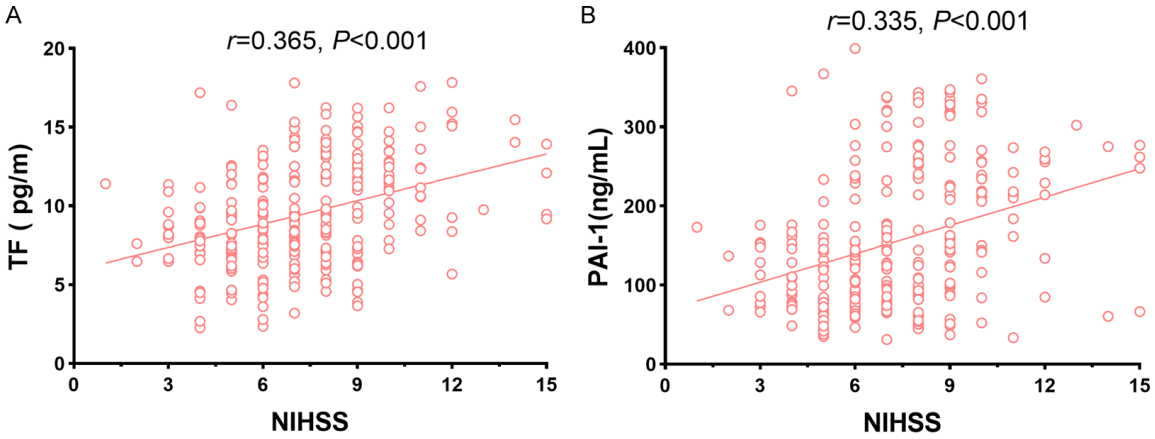

Figure 2. Correlation analysis of the NIHSS score with TF and PAI-1. Abbreviations: TF, tissue factor; PAI-1, plasminogen activator inhibitor-1.

fibrinogen, TF, PAI-1, and C-reactive protein were higher (all P < 0.05). Patients in the MACI group had higher NIHSS scores at admission (P < 0.05). During follow-up, the mortality rate in the MACI group was 62.61% (72/115), significantly higher than the 25.82% (47/182) in the ACI group (P < 0.05). Of the 115 patients in the MACI group, 30 (26.09%) died from ACI, event of interest), and 42 (35.62%) died from any other cause.

Multivariable regression analysis

BMI, history of stroke, diabetes mellitus, hyperlipidemia, TOAST classification, three-territory sign, cortical/subcortical lesions, D-D, FIB, TT, PAI-1, CRP were all considered influencing factors for MAI (**Table 3**). No collinearity was observed among these indicators. Multivariate analysis showed that TOAST classification, TF and PAI-1 were influencing factors for MACI (all *P* < 0.05), as detailed in **Table 4**. Spearman analysis showed that the expression levels of TF and PAI-1 were significantly positively correlated with NIHSS scores (r = 0.365, P < 0.001; r = 0.335, P < 0.001) as shown in **Figure 2**.

Prognostic analysis

The Kaplan-Meier method was used to assess and compare the survival outcomes of patients with MACI and those with ACI (**Figure 3A**).

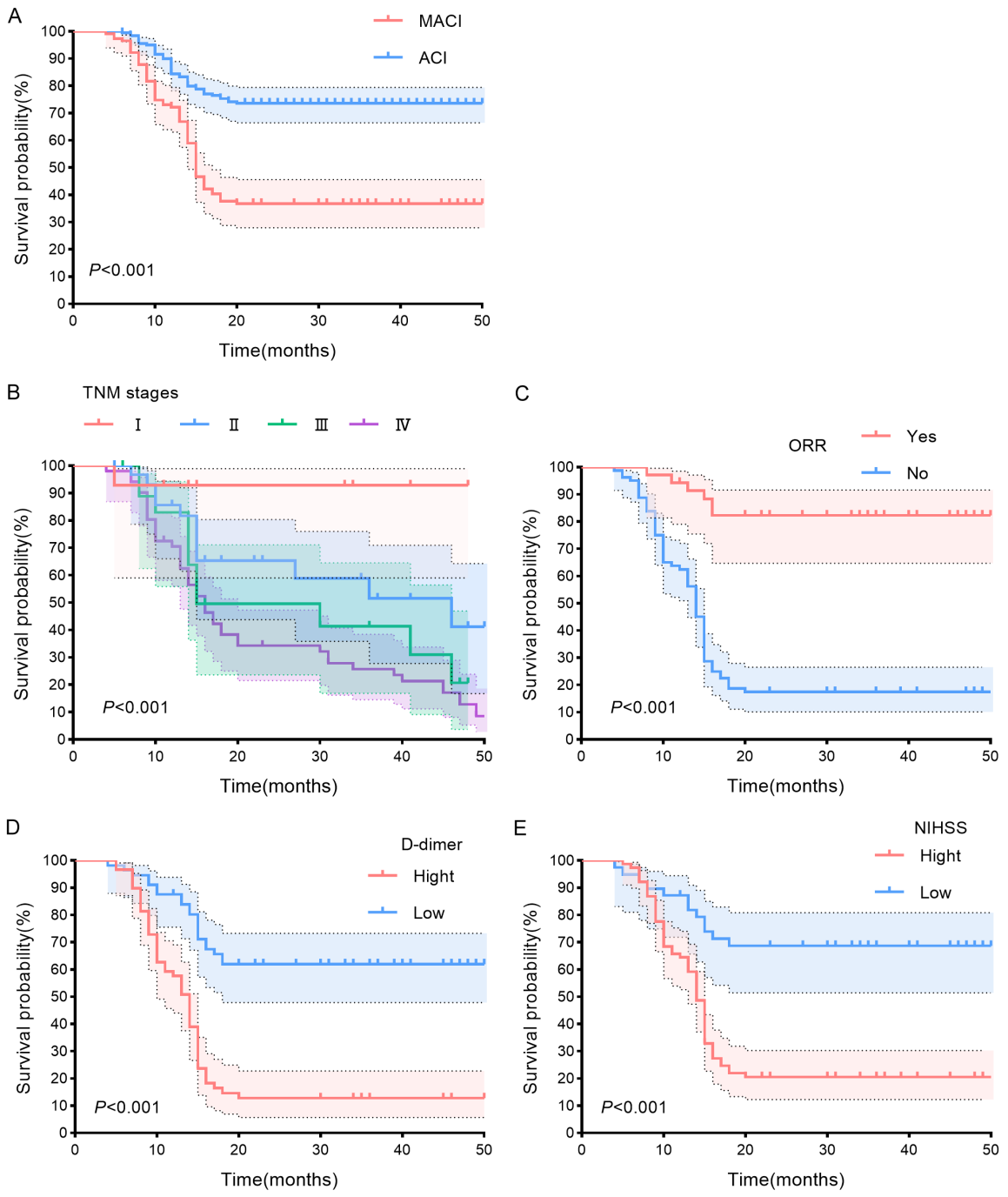

Figure 3. Analysis of total survival time. A: Comparison of survival probability between MACI and ACI; B: Comparison of survival rates of patients with different TNM stages of MACI; C: Comparison of survival rates of patients with different ORR of MACI; D: Comparison of survival rates of patients with different D-dimer of MACI (grouped by median: 0.42 mg/L); E: Comparison of survival rates of patients with different NIHSS of MACI (grouped by median: 8). Abbreviations: MACI, Malignancy with acute cerebral infarction; ACI, acute cerebral infarction.

Statistical analysis showed that the survival rate of the ACI group was significantly higher than that of the MACI group (χ^2 = 40.253, P < 0.001).

Subsequent prognostic analysis of MACI patients demonstrated a significant association between clinical characteristics and overall survival in patients with malignant tumors and

Table 5. COX regression analysis of malignancy with acute cerebral infarction

Variables	β value	Standard error	Single factor analysis		β value	Standard error	Multivariate analysis	
			HR (95% CI)	*P*			*HR* (95% CI)	*P*
Gender	0.076	0.229	1.079 (0.688-1.691)	0.741				
Age	1.108	0.257	3.028 (1.830-5.015)	< 0.001	0.492	0.272	1.636 (0.960-2.786)	0.070
BMI	-0.169	0.237	0.844 (0.531-1.343)	0.474				
Smoking	0.120	0.237	1.128 (0.709-1.796)	0.612				
Drinking	0.121	0.256	1.129 (0.684-1.864)	0.636				
Previous stroke history	0.006	0.272	1.006 (0.590-1.715)	0.983				
Hypertension	0.296	0.237	1.345 (0.845-2.139)	0.211				
Diabetes	-0.240	0.307	0.787 (0.431-1.435)	0.787				
Hyperlipidemia	-0.377	0.307	0.686 (0.376-1.251)	0.219				
CHD	0.150	0.356	1.162 (0.578-2.337)	0.673				
Atrial fibrillation	0.774	0.465	2.168 (0.872-5.392)	0.096				
TOAST types	0.051	0.083	1.052 (0.894-1.238)	0.539				
Three territory sign	0.740	0.254	2.095 (1.274-3.445)	0.001	-0.336	0.91	0.714 (0.404-1.264)	0.248
Cortical/subcortical lesions	0.021	0.237	1.021 (0.642-1.624	0.929				
Types of tumors	0.009	0.035	1.009 (0.943-1.079)	0.805				
Pathological type	-0.020	0.107	0.980 (0.795-1.209)	0.853				
TNM stage	0.774	0.142	2.169 (1.643-2.863)	< 0.001	0.755	0.341	2.127 (1.091-4.146)	0.027
Distant metastasis	1.354	0.258	3.458 (2.102-5.687)	< 0.001	-0.795	0.609	0.451 (0.137-1.490)	0.192
Time from cancer diagnosis to acute cerebral infarction	-0.096	0.094	0.909 (0.755-1.093)	0.310				
Tumor treatment	0.085	0.082	1.088 (0.927-1.277)	0.300				
ORR	-2.015	0.429	0.133 (0.057-0.309)	< 0.001	-1.448	0.496	0.235 (0.088-0.621)	0.003
Hb	-0.343	0.238	0.710 (0.445-1.131)	0.149				
LDL-C	-0.175	0.236	0.839 (0.529-1.333)	0.458				
TT	0.660	0.242	1.935 (1.203-3.113)	0.006	0.160	0.260	1.174 (0.706-1.953)	0.536
PT	0.133	0.237	1.143 (0.719-1.817)	0.573				
APTT	-0.269	0.236	0.764 (0.481-1.215)	0.256				
D-D	1.353	0.265	3.870 (2.304-6.499)	< 0.001	0.842	0.300	2.320 (1.288-4.179)	0.005
FIB	0.147	0.236	1.158 (0.729-1.839)	0.534				
Hcy	-0.040	0.236	0.961 (0.605-1.525)	0.865				
TF	1.175	0.259	3.238 (1.948-5.384)	< 0.001	0.316	0.295	1.372 (0.769-2.448)	0.285
PAI-1	0.663	0.243	1.942 (1.207-3.124)	0.006	0.147	0.253	1.158 (0.707-1.886)	0.566
CRP	0.159	0.240	1.680 (1.049-2.689)	0.031	0.144	0.250	1.154 (0.707-1.886)	0.566
NIHSS at admission	1.296	0.319	3.654 (1.956-6.827)	< 0.001	0.843	0.331	2.324 (1.215-4.444)	0.011

Note: Age (grouped by median: 67 years), BMI (grouped by median: 22 kg/m^2), Hb (grouped by median: 98 g/L), LDL-C (grouped by median: 2.15 mmol/L), TT (grouped by median: 13.24 s), PT (grouped by median: 11.72 s), APTT (grouped by median: 31.44 s), D-D (grouped by median: 0.42 mg/L), FIB (grouped by median: 4.53 g/L), Hcy (grouped by median: 15.37 mmol/L), TF (grouped by median: 12.56 pg/mL), PAI-1 (grouped by median: 237.94 ng/mL), CRP (grouped by median: 9.82 mg/L), Admission NIHSS (grouped by median: 8). Abbreviations: BMI, body mass index; CHD, coronary heart disease; ORR, objective response rate; Hb, hemoglobin; LDL-C, low - density lipoprotein; TT, thrombin time; PT, prothrombin time; APTT, activated partial thromboplastin time; D-D, D-dimer; FIB, fibrinogen; Hcy, homocysteine; TF, tissue factor; PAI-1, plasminogen activator inhibitor-1; CRP, C-reactive protein; NIHSS, National Institutes of Health Stroke Scale.

Table 6. The collinearity diagnosis of variables

Variables	Tolerance	VIF
Age	0.854	1.171
Three territory sign	0.852	1.173
TNM stage	0.206	4.846
Distant metastasis	0.223	4.477
ORR	0.698	1.432
TT	0.908	1.101
D-D	0.811	1.234
TF	0.770	1.300
PAI-1	0.875	1.142
CRP	0.885	1.130
NIHSS at admission	0.836	1.196

Note: Abbreviations: ORR, objective response rate; TT, thrombin time; D-D, D-dimer; TF, tissue factor; PAI-1, plasminogen activator inhibitor-1; CRP, C-reactive protein; NIHSS, National Institutes of Health Stroke Scale.

cerebral infarction (**Table 5**). In univariate analysis, age, three territory sign, TNM stage, distant metastasis, objective response rate (ORR), TT, D-D, TF, PAI-1, CRP, and the NIHSS score at admission were all associated with overall survival. No collinearity was observed among these indicators (**Table 6**). Multivariate analysis showed that TNM stage, ORR, D-D, and the NIHSS score at admission were the main factors affecting overall survival in MACI patients. Patients with elevated D-D and NIHSS levels had lower survival rates, while those achieving ORR through tumor treatment had higher survival rates. Additionally, higher tumor stages were associated with lower survival rates (**Figure 3B-E**). Univariate analysis using the Fine-Gray competing risk model showed that the three territory sign, TNM stage, distant metastasis, ORR, TT, D-D, TF, PAI-1, and NIHSS significantly affected the cumulative mortality rate of ACI in patients with MACI (**Table 7**). No collinearity was observed among these indicators (**Table 8**). Multivariate analysis using the Fine-Gray competing risk model showed that the three territory sign and elevated levels of D-D, TF, and PAI-1 were associated with increased cumulative mortality of ACI in MACI patients (**Figure 4**). Spearman analysis showed that the expression levels of D-D and TF were significantly positively correlated with TNM stage ($r = 0.341$, $P < 0.001$; $r = 0.369$, $P < 0.001$) as shown in **Figure 5**.

Discussions

A clinical analysis of 115 MACI patients revealed that lung cancer (43.48%) was the most common malignant tumor in this cohort, with non-small cell lung cancer being the predominant type. This distribution is consistent with previous studies, namely that lung cancer is a clear risk factor for cancer-associated ischemic stroke [11]. According to global cancer statistics, the incidence of lung cancer has consistently been high among all types of malignant tumors [12]. Considering the relatively high prevalence of lung cancer in the overall cancer population, its high proportion among malignant tumors in patients with recurrent cerebral infarction is reasonable. This suggests that the high prevalence of lung cancer may explain its high proportion in MACI.

This study compared the clinical data of two groups of patients. The results showed no significant differences between the two groups in terms of traditional stroke risk factors such as smoking, alcohol consumption, and hypertension. These common lifestyle and underlying disease factors may have similar effects on the occurrence of ACI and are not key factors for differentiating MACI from ACI. However, the incidence of diseases such as diabetes and hyperlipidemia was relatively low in the MACI group, which is consistent with previous reports [13]. In existing studies, most reports indicate that there is no difference in common risk factors for ischemic stroke between cancer patients and non - cancer patients [14, 15]. Nevertheless, some studies have found that the incidence of hyperlipidemia is lower in cancer patients with ischemic stroke compared with the non-cancer group [16]. It is worth noting that during the study, it was also found that, according to the TOAST classification, 68.7% of patients in the MACI group had cryptogenic stroke. This implies that the stroke in patients with malignant tumors is different from that in ordinary patients, with fewer traditional risk factors, and may involve tumor-related risk factors. In addition, in terms of imaging features, ACI with malignant tumors often presents with three-vessel signs and cortical/subcortical lesions, which is consistent with previous reports [17, 18].

Table 7. Analysis of competitive risk model of malignant tumor complicated with cerebral infarction

Variables	β value	Standard error	Single factor analysis		β value	Standard error	Multivariate analysis	
			HR (95% CI)	*P*			*HR* (95% CI)	*P*
Gender	-0.133	0.374	0.875 (0.420-1.824)	0.720				
Age	0.600	0.371	1.823 (0.881-3.773)	0.110				
BMI	-0.736	0.383	0.497 (0.226-1.015)	0.055				
Smoking	-0.120	0.367	0.887 (0.432-1.818)	0.740				
Drinking	-0.117	0.407	0.889 (0.400-1.977)	0.770				
Previous stroke history	-0.321	0.443	0.725 (0.305-1.727)	0.470				
Hypertension	0.342	0.361	1.408 (0.694-2.855)	0.340				
Diabetes	-0.573	0.520	0.564 (0.204-1.563)	0.270				
Hyperlipidemia	-0.123	0.432	0.884 (0.379-2.062)	0.780				
CHD	0.161	0.507	1.175 (0.435-3.175)	0.750				
Atrial fibrillation	0.255	0.686	1.290 (0.336-4.950)	0.710				
TOAST types	0.170	0.138	1.185 (0.905-1.552)	0.220				
Three territory sign	1.810	0.546	6.112 (2.097-17.813)	0.001	1.430	0.727	4.200 (1.010-17.500)	0.049
Cortical/subcortical lesions	-0.175	0.362	0.839 (0.413-1.705)	0.630				
Types of tumors	0.055	0.048	1.057 (0.962-1.161)	0.250				
Pathological type	-0.204	0.136	0.816 (0.625-1.065)	0.130				
TNM staging	0.805	0.206	2.237 (1.493-3.352)	< 0.001	1.040	0.535	2.820 (0.990-8.050)	0.052
Distant metastasis	1.182	0.396	3.260 (1.499-7.086)	0.003	-1.200	0.994	0.300 (0.040-2.120)	0.230
Time from cancer diagnosis to acute cerebral infarction	-0.057	0.143	0.945 (0.714-1.250)	0.690				
Tumor treatment	0.126	0.129	1.135 (0.881-1.462)	0.333				
ORR	-1.912	0.750	1.148 (0.034-0.643)	0.011	-0.538	1.310	0.580 (0.040-7.610)	0.680
Hb	0.238	0.362	1.269 (0.624-2.578)	0.510				
LDL-C	-0.481	0.365	0.618 (0.302-1.265)	0.190				
TT	1.320	0.428	3.742 (1.619-8.652)	0.002	0.660	0.359	1.940 (0.960-3.910)	0.066
PT	-0.653	0.373	0.521 (0.251-1.081)	0.088				
APTT	-0.011	0.358	0.989 (0.490-1.995)	0.980				
D-D	2.346	0.617	10.449 (3.115-35.049)	< 0.001	1.860	0.688	6.410 (1.660-24.600)	0.007
FIB	0.329	0.360	1.390 (0.686-2.816)	0.360				
Hcy	-0.215	0.358	0.806 (0.400-1.626)	0.550				
TF	1.768	0.488	5.861 (2.252-15.255)	< 0.001	1.210	0.488	3.370 (1.300-8.760)	0.013
PAI-1	1.332	0.424	3.787 (1.649-8.697)	0.002	1.080	0.379	2.940 (1.400-6.180)	0.005
CRP	0.283	0.361	1.327 (0.654-2.692)	0.430				
NIHSS at admission	1.018	0.491	2.769 (1.058-7.247)	0.038	0.397	0.451	1.490 (0.620-3.600)	0.380

Note: Abbreviations: BMI, body mass index; CHD, coronary heart disease; ORR, objective response rate; Hb, hemoglobin; LDL-C, low - density lipoprotein; TT, thrombin time; PT, prothrombin time; APTT, activated partial thromboplastin time; D-D, D-dimer; FIB, fibrinogen; Hcy, homocysteine; TF, tissue factor; PAI-1, plasminogen activator inhibitor-1; CRP, C-reactive protein; NIHSS, National Institutes of Health Stroke Scale.

Table 8. The collinearity diagnosis of variables

Variables	Tolerance	VIF
Three territory sign	0.862	1.161
TNM stage	0.208	4.801
Distant metastasis	0.228	4.394
ORR	0.708	1.413
TT	0.912	1.096
D-D	0.840	1.191
TF	0.796	1.256
PAI-1	0.890	1.123
NIHSS at admission	0.843	1.187

Note: Abbreviations: ORR, objective response rate; TT, thrombin time; D-D, D-dimer; TF, tissue factor; PAI-1, plasminogen activator inhibitor-1; NIHSS, National Institutes of Health Stroke Scale.

Clearly, the pathogenesis of ischemic stroke in patients with malignant tumors may differ from that of ischemic stroke alone. Numerous studies have demonstrated that direct infiltration or compression of cerebral blood vessels by malignant tumors, tumor-induced coagulation abnormalities, infection, and secondary effects of radiotherapy or chemotherapy are all associated with the occurrence of ischemic stroke [19, 20]. Malignant tumors can invade cerebral circulation, directly promoting emboli formation and thus triggering acute stroke. The manifestation of the three territory sign may be related to the metastatic characteristics of malignant tumors. Tumor cells can be transported to different parts of the brain via the bloodstream, leading to multiple regional infarctions [21]. Cortical/subcortical lesions suggest that these lesions may be related to the direct invasion or indirect influence of tumor cells on cerebral blood vessels and nerve tissue. The cortical and subcortical regions are rich in nerve cells and blood vessels, and tumor invasion may impair local perfusion and neurological function.

The proportion of patients with a history of cerebral infarction in the MACI group was significantly higher than that in the ACI group. These results suggest that a history of cerebral infarction may be a key factor in the occurrence of ACI in patients with malignant tumors. A history of cerebral infarction implies a pathological basis for cerebrovascular disease, manifested as poor vascular elasticity and lumen condition. In addition, patients with malignant tumors are inherently more vulnerable. This poor vascular basis further increases the risk of ACI. In addition, hypercoagulable state is another potential cause of cerebral infarction [20]. The pathophysiological mechanism of cancer-related hypercoagulability is complex, involving multiple factors related to procoagulant factors, inflammatory cytokines, and cancer pathology and histology [22]. Tumor cells possess procoagulant properties and can directly produce a variety of coagulation factors. Their surface tissue factors can also adhere to and mediate the activation of a variety of coagulation factors, leading to endothelial cell damage and promoting thrombus formation [23]. This study revealed that the serum D-D and FIB levels in patients in the MACI group were significantly higher than those in the ACI group. Numerous studies have shown that elevated D-D levels are an important indicator of tumor - associated hypercoagulability and are associated with the incidence and survival of ischemic stroke [9, 24]. Guo et al. [25] used a D-dimer cutoff value ≥ 0.55 mg/L combined with multi-regional infarction as a diagnostic criterion for cancer-associated stroke, reporting a specificity of 99.7% and a positive predictive value of 92.9%. Routine examinations, such as measuring D-dimer levels and fibrinogen concentrations, are the basis for assessing hypercoagulable states. In patients with malignant tumors, FIB levels are usually abnormally elevated. This is because during the growth and spread of malignant tumors, a large number of procoagulant factors are released, stimulating the liver to synthesize more FIB to participate in the coagulation reaction [26]. Consequently, this leads to a tendency for excessive blood coagulation in the body. In a persistent hypercoagulable state, fibrin is continuously generated and degraded, resulting in a significant increase in D-dimer levels [27]. This procoagulant state increases the risk of intravascular thrombosis. Once microthrombi break off and enter cerebral blood vessels, they may cause cerebral infarction. In addition to elevated D-D and FIB levels, CRP levels are also closely related to the occurrence of ACI in patients with malignant tumors [28]. This study further found that the serum CRP level in the MACI group was significantly higher than that in the ACI group, which is consistent with previous studies [29]. Therefore, in clinical practice, physicians should pay close attention to the history of cerebral infarction, coagulation

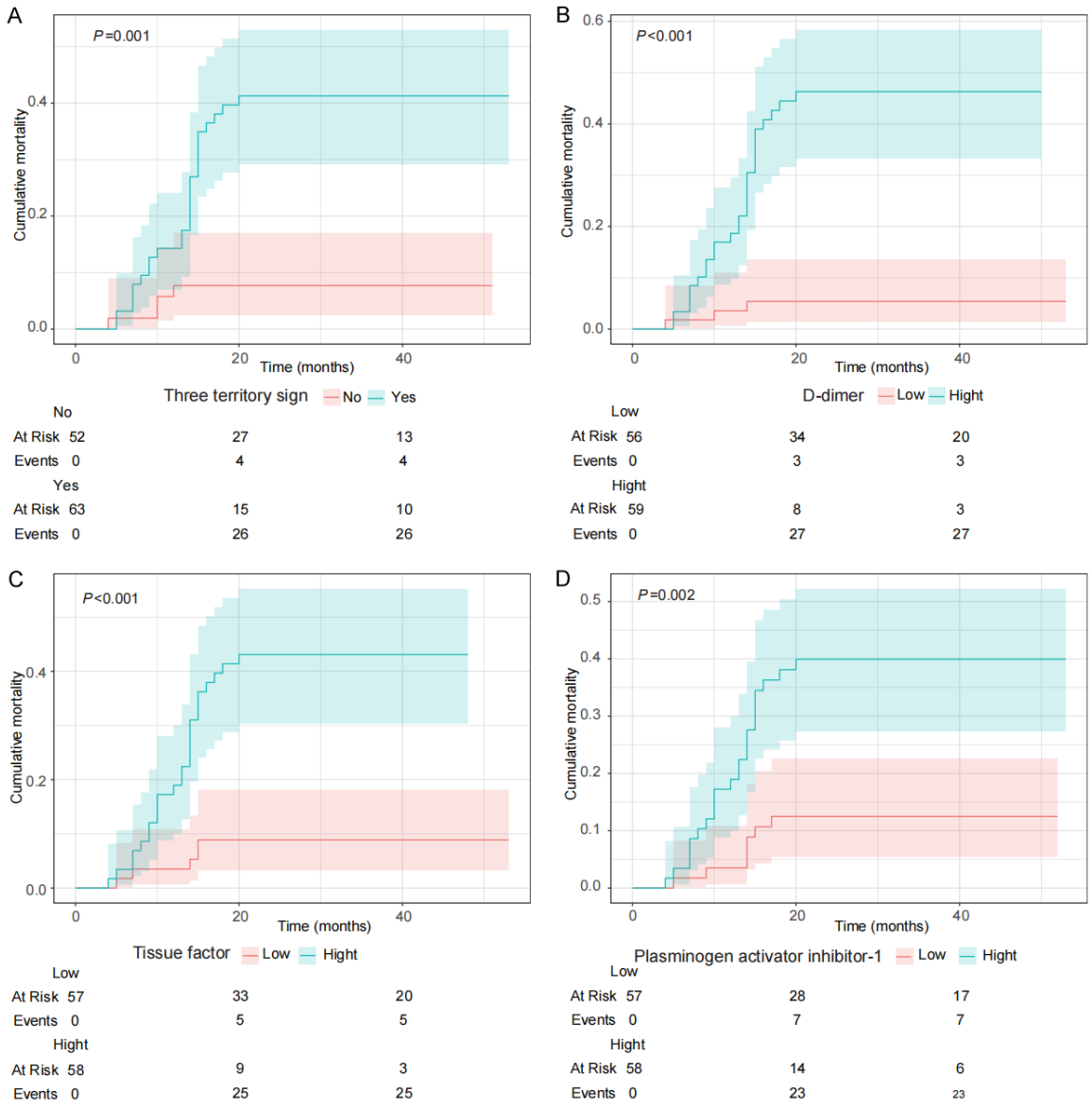

Figure 4. The effect of three territory sign, D-D, TF and PAI-1 on the cumulative mortality of acute cerebral infarction in patients with MACI. A: Three territory sign; B: D-dimer (grouped by median: 0.42 mg/L); C: Tissue factor (grouped by median: 12.56 pg/mL); D: Plasminogen activator inhibitor-1 (grouped by median: 237.94 ng/mL). Abbreviations: MACI, Malignancy with acute cerebral infarction.

indices, and CRP levels in patients with malignant tumors. Timely evaluation and intervention should be carried out to reduce the risk of ACI.

Our study showed that in cancer patients with ACI, the levels of TF and PAI-1 were significantly elevated, and their levels were closely associated with poor functional outcomes. Furthermore, we found a positive correlation between TF expression and tumor stage. This suggests that TF not only reflects a hypercoagulable state but also reflects tumor burden and invasiveness. These findings imply that TF expression can serve as a reliable prognostic indicator for risk stratification in this population.

Tissue factor, as the most well-defined coagulation initiator, plays a crucial role in the development and progression of tumor-related coagulation abnormalities. Tumor cells possess unique biological characteristics. TF can be stably expressed on the surface of tumor

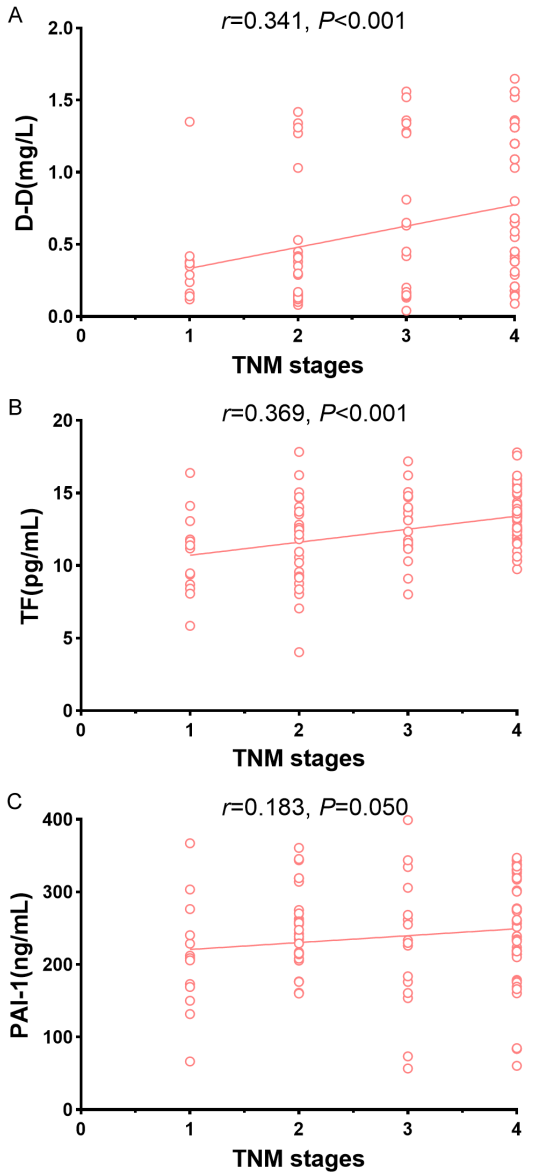

Figure 5. Correlation analysis of the TNM stages with DD, TF and PAI-1. Abbreviations: D-D, D-dimer; TF, tissue factor; PAI-1, plasminogen activator inhibitor-1.

cells and actively released into the bloodstream, initiating a coagulation cascade reaction by activating the extrinsic coagulation pathway [30]. TF binds to coagulation factor VII or activated coagulation factor VIIa in the blood, forming the TF-FVIIa complex. This complex has strong procoagulant activity, which can further activate coagulation factor X (FX) and coagulation factor IX (FIX), promote thrombin generation, and ultimately lead to fibrin formation and thrombus formation [31]. In addition, some tumor cells can ectopically synthesize factor VII and directly release the TF-VIIa complex [32].

Yoo et al. [33] conducted an in-depth study on patients undergoing endovascular thrombectomy. Their results showed that the TF level in thrombi of cancer patients was significantly higher than that of non-cancer patients. This finding provides important evidence for a more comprehensive understanding of the pathogenesis of ACI in cancer patients.

Fibrinolytic inhibitors may synergize with procoagulant factors and tissue factors, thereby promoting thrombus formation. Tumor cells can express fibrinolytic regulators on their cell surface, which can not only promote tumor growth and spread but also induce vascular complications [21]. As a key regulator of the fibrinolytic system, plasminogen activator inhibitor-1 can inhibit the activity of plasminogen activator, thereby hindering the fibrinolytic process [34]. Under normal physiological conditions, the fibrinolytic and coagulation systems maintain a dynamic balance to ensure normal blood flow within blood vessels. However, in cancer patients, PAI-1 levels are significantly elevated, disrupting this balance. Studies have confirmed that PAI-1 expression is associated with the risk of venous thromboembolism, particularly in pancreatic cancer patients [35]. Furthermore, changes in PAI-1 levels may be closely related to patient prognosis. Elevated PAI-1 levels may indicate impaired fibrinolytic function and decreased thrombus clearance capacity, thereby affecting the recovery of neurological function and overall prognosis.

Therefore, combined assessment of TF and PAI-1 may have additional clinical value. This can help identify high-risk patients, guide anticoagulation therapy, and improve prognostic assessment of cancer-related ischemic stroke.

Whether cancer worsens the prognosis of stroke remains controversial. Some studies have shown no difference between the two groups in terms of in-hospital mortality, short-term and long-term prognosis [28]. Conversely, other studies have shown a higher risk of death in cancer patients [36]. This study supports the view that patients diagnosed with cancer face a higher risk of death compared to stroke patients without cancer. This study confirms the role of elevated D-dimer as a known prog-

nostic risk factor [37, 38]. The study also found that TNM stage, objective response rate, D-D, and NIHSS scores were independent predictors of overall survival in patients with MACI. In addition, the Fine-Gray competing risk model further showed that high expression of D-dimer, TF, and PAI-1 was significantly associated with a specific risk of death from ACI, providing a new reference indicator for predicting the prognosis of cancer-associated stroke patients.

Limitations

This study has several limitations that need to be considered. First, as a retrospective study with a relatively small sample size, the findings may be subject to selection bias. Second, the biological behavior and treatment regimens of different cancers vary significantly, and this tumor heterogeneity may affect prognosis. Furthermore, the use of anti-angiogenic drugs was not systematically recorded, and we did not assess their potential impact on the risk of MACI. We also could not completely rule out other potential causes of elevated plasma D-dimer levels, such as infection, inflammation, or recent surgery. Moreover, the potential prognostic impact of dynamic changes in D-dimer and other laboratory indicators is unknown. Future large-scale, multicenter prospective studies, combined with comprehensive laboratory and imaging evaluations are needed to further elucidate the characteristics and outcomes of MACI.

Conclusions

MACI mainly occurs in lung cancer patients, with some patients experiencing ACI shortly after cancer diagnosis. ACI complicated by malignant tumors has unique clinical features in terms of medical history and imaging indicators, including elevated levels of D-D, TF, PAI-1, and mortality. Prognostic analysis indicates that three territory sign and hypercoagulable state are key factors contributing to the increased cumulative mortality of ACI.

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Disclosure of conflict of interest

None.

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