Tumor metastasis has a significant relationship with the development of acute ischemic stroke in Chinese cancer patients: a retrospective study

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Abstract

Objective: This study was designed to analyze the relationship between tumor metastasis and acute ischemic stroke (AIS) in Chinese cancer patients.

Methods: This retrospective study included 119 cancer patients with AIS and 152 cancer patients without AIS. Basic information was collected and tumor metastasis status was determined for all patients.

Results: The whole cohort had a median age of 59 (49–69) years with 150 men (55.4%). There were 98 patients (36.2%) with tumor metastasis. Patients with AIS had significantly more males, tumor metastasis, lung cancer, hypertension, diabetes mellitus, higher age, D-dimer, international normalized ratio, prothrombin time, prothrombin activity, and thrombin time, while they had significantly lower levels of hemoglobin, red blood cells, and hematocrit. In multivariate logistic regression analysis, AIS was significantly and positively associated with age, tumor metastasis, D-dimer, and thrombin time. In multivariate Cox regression analysis, tumor metastasis, AIS, D-dimer, thrombin time, and fibrinogen were significantly and positively associated with worse prognosis.

Conclusions: This study demonstrates that tumor metastasis was positively and independently associated with AIS in Chinese cancer patients, suggesting that tumor metastasis has a significant

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relationship with the development of AIS. Additionally, tumor metastasis and AIS had negative independent effects on the prognosis of patients.

Introduction

Based on a report from the World Health Organization, there was estimated to be 18.1 million new cancer cases and nearly 9.6 million deaths from cancer worldwide in 2018.[1] Although patients have had increased survival rates from improved treatments, cancer and stroke were still the second and third causes of death, respectively, across the globe.[2] Moreover, both of these epidemiologically growing diseases have a high impact on patients' daily activities and create an economic burden.[3–6] Compared with the general population, cryptogenic origin of stroke in cancer patients can reach up to 50%, suggesting that there is a potential pathogenesis of stroke closely related to cancer.[7–12]

As a very complicated and multifaceted disease, cancer is particularly dangerous because of one of its most feared features: tumor metastasis.[13] Although tumor metastasis can originate from any type of primary tumor, it frequently occurs in cancers like lung and breast.[14,15] A large proportion of lung and breast cancer patients have metastases present, which are generally associated with a grim prognosis.[16,17] Interestingly, cancer patients with tumor metastasis have a higher prevalence of stroke.[18] However, whether there is a definitive relationship between tumor metastasis and acute ischemic stroke (AIS) in cancer patients remains unclear, especially in Chinese cancer patients. To our knowledge, this relationship has not been fully evaluated and needs further investigation. Therefore, the present study was designed to analyze the relationship between tumor metastasis and AIS in Chinese cancer patients.

Methods

This retrospective study complies with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement. From January 2013 to February 2018, a computerized electronic database was designed to enroll 16,702 cancer patients with disease confirmed by the Pathology Department of Hainan Hospital of Chinese People's Liberation Army General Hospital. Patients who were less than 18 years old or had a history of acute hemorrhagic stroke were excluded. A total of 200 patients with AIS and 200 patients without AIS were randomly chosen from this database. After excluding patients with incomplete data, there were 119 patients with AIS and 152 patients without AIS included in the present study. AIS was confirmed by MRI and diagnosed by chief physicians from the Neurology Department of the same hospital. In this study, "tumor metastasis" refers to the presence of tumor cell growth at sites other than the primary site. Tumor metastasis was determined if imaging showed any lesion and was

confirmed by the Pathology Department. The study protocol was approved by the Ethics Committee of Hainan Hospital of Chinese People's Liberation Army General Hospital (Sanya, China, January 2018).

Data for the following variables were obtained from the patients or their relatives and confirmed by medical records at the time of consultation: age, sex, type of primary tumor, comorbid conditions, blood examination, and coagulation indicators. Hypertension was diagnosed based on the eight Joint National Committee criteria.[19] Diabetes mellitus was diagnosed based on the American Diabetes Association criteria.[20] The endpoint chosen for the present study was all-cause mortality over a follow-up period of 1 year. Follow-up data were obtained from medical records or telephone interviews. All patients were contacted during the follow-up period.

Statistical analysis

Based on $\alpha = 0.05$ and $\beta = 0.95$, we determined that the sample size must be more than 96 individuals for each group with at least 192 participants in the overall study. Data for continuous variables with normal distribution are presented as mean with standard deviation. Two groups were compared with a Student's t test. Data for continuous variables with skewed distribution are presented as median with interquartile range. Two groups were compared with a Mann–Whitney U test. Age, blood routine, and coagulation indicators were analyzed as continuous variables. Data for categorical variables are presented as number and percentage. Two groups were compared with a Chi-square test. Sex, type of primary tumor, and comorbid conditions were analyzed as categorical variables. Correlative analyses of AIS with all variables shown in Table 1 were determined by Pearson (continuous variables with normal distribution) or Spearman (continuous variables with skewed distribution) correlation coefficients. Multivariate logistic regression analysis was applied to determine the variables independently associated with AIS. Variables with $P < 0.05$ in either univariate analyses or correlative analyses were examined further with multivariate logistic regression analysis. A log-rank test was applied to compare the groups and a Kaplan–Meier curve was generated to present a survival rate comparison between patients with and without tumor metastasis or AIS. Multivariate Cox regression analysis was applied to evaluate independent effects of tumor metastasis and AIS on the survival of patients with adjustment of all variables shown in Table 1. To avoid selection bias, multivariate regression analyses were applied with adjustment of potential confounders, including age, sex, comorbidities, or other factors. All analyses were carried out with Statistic Package for Social Science (SPSS) software (SPSS, Chicago, IL, USA) and Power Analysis and Sample Size (PASS) software (NCSS, Kaysville, UT, USA). A P-value < 0.05 was regarded as statistically significant.

Results

The whole cohort had a median age of 59 (49–69) years, with 150 men (55.4%). There were 98 patients (36.2%) with tumor metastasis. As shown in Table 1, patients with AIS had significantly more men, tumor metastasis, lung cancer, hypertension, diabetes mellitus, higher levels of age, D-dimer, international normalized ratio, prothrombin time, prothrombin activity, and thrombin time ($P < 0.05$ for all). Additionally, patients with AIS had significantly lower levels of hemoglobin, red blood cell count, and hematocrit ($P < 0.05$ for all).

Correlative analyses showed that AIS was significantly related to age, sex, tumor metastasis, hypertension, diabetes mellitus,

Table 1. Characteristics of Chinese cancer patients with and without AIS.

Characteristic	Without AIS (n=152)	With AIS (n=119)	P-value
Age	53 (43–61)	67 (57–74)	<0.001
Male	67 (44.1%)	83 (69.7%)	<0.001
Tumor metastasis	31 (20.4%)	67 (56.3%)	<0.001
Type of primary tumor			<0.001
Lung cancer	72 (47.4%)	71 (59.7%)	
Breast cancer	42 (27.6%)	4 (3.4%)	
Other cancers	38 (25.0%)	33 (37.0%)	
Hypertension	23 (15.1%)	44 (37.0%)	<0.001
Diabetes mellitus	10 (6.6%)	29 (24.4%)	<0.001
Coronary artery disease	5 (3.3%)	10 (8.4%)	0.068
Atrial fibrillation	1 (0.7%)	5 (4.2%)	0.121
Hemoglobin	125 (110–137)	119 (101–135)	0.018
Red blood cell	4.3 (3.9–4.8)	4.1 (3.6–4.7)	0.043
Hematocrit	0.38 (0.34–0.42)	0.35 (0.31–0.41)	0.012
Mean corpuscular volume	89.4 (85.6–92.4)	88.1 (82.8–93.1)	0.318
Mean corpuscular hemoglobin	29.2 (28.0–30.7)	29.2 (27.4–31.0)	0.854
Mean corpuscular hemoglobin concentration	327 (319–335)	330 (319–338)	0.280
Platelet	223 (187–264)	208 (165–266)	0.126
D-dimer	222 (119–408)	515 (194–2803)	<0.001
International normalized ratio	1.02 (0.97–1.07)	1.06 (1.00–1.15)	<0.001
Prothrombin time	11.7 (10.8–12.7)	12.7 (11.8–14.3)	<0.001
Prothrombin activity	102 (92–111)	93 (82–105)	<0.001
Thrombin time	16 (15–20)	20 (15–22)	<0.001
Fibrinogen	3 (3–4)	3 (3–5)	0.154
Activated partial thromboplastin time	32 (29–34)	31 (29–36)	0.951

AIS, acute ischemic stroke.

atrial fibrillation, hemoglobin, red blood cell count, hematocrit, D-dimer, international normalized ratio, prothrombin time, prothrombin activity, and thrombin time ($P < 0.05$ for all; Table 2). In multivariate logistic regression analysis (Table 3), AIS was significantly and positively associated with age, tumor metastasis, D-dimer, and thrombin time ($P < 0.05$ for all).

The mortality rate was 38.7% (105 patients) during the follow-up period. Kaplan–Meier estimates of survival for these patients with and without tumor metastasis or AIS are shown in Figure 1. Log rank analyses suggested that patients with tumor metastasis or AIS had worse prognosis than those without tumor

metastasis or AIS ($P < 0.05$ for all). In multivariate Cox regression analysis (Table 4), tumor metastasis, AIS, D-dimer, thrombin time, and fibrinogen were significantly and positively associated with worse prognosis ($P < 0.05$ for all).

Discussion

Research on both cancer and stroke is growing in importance given the increased prevalence and strong coaction of these diseases.[7–10] An autopsy series demonstrated that 15% of cancer patients had different lesions that suggested a stroke had occurred.[21–24] Both cancer and stroke are extremely complex and have a poor

Table 2. Correlative analyses of Chinese cancer patient characteristics with AIS.

Characteristic	Correlation coefficient	P-value
Age	0.458	<0.001
Male	0.256	<0.001
Tumor metastasis	0.371	<0.001
Type of primary tumor	−0.028	0.650
Hypertension	0.251	<0.001
Diabetes mellitus	0.252	<0.001
Coronary artery disease	0.111	0.068
Atrial fibrillation	0.120	0.049
Hemoglobin	−0.144	0.018
Red blood cell	−0.123	0.042
Hematocrit	−0.153	0.012
Mean corpuscular volume	−0.061	0.318
Mean corpuscular hemoglobin	−0.011	0.855
Mean corpuscular hemoglobin concentration	0.066	0.281
Platelet	−0.093	0.126
D-dimer	0.323	<0.001
International normalized ratio	0.226	<0.001
Prothrombin time	0.344	<0.001
Prothrombin activity	−0.239	<0.001
Thrombin time	0.234	<0.001
Fibrinogen	0.087	0.154
Activated partial thromboplastin time	0.004	0.952

AIS, acute ischemic stroke.

Table 3. Multivariate logistics regression analyses of Chinese cancer patient characteristics with AIS.

Characteristic	OR	95% CI	P-value
Age	1.069	1.038–1.101	<0.001
Male	1.457	0.702–3.023	0.313
Tumor metastasis	2.552	1.206–5.402	0.014
Type of primary tumor	1.170	0.794–1.726	0.427
Hypertension	2.144	0.976–4.711	0.058
Diabetes mellitus	2.419	0.933–6.276	0.069
Atrial fibrillation	2.469	0.184–33.196	0.495
Hemoglobin	0.988	0.950–1.028	0.549
Red blood cell	1.040	0.576–1.881	0.896
Hematocrit	20.897	$0.000–2.285 \times 10^7$	0.668
D-dimer	1.000	1.000–1.001	0.007
International normalized ratio	0.009	0.000–27.716	0.251
Prothrombin time	1.205	0.784–1.853	0.395
Prothrombin activity	0.968	0.921–1.017	0.202
Thrombin time	1.130	1.015–1.259	0.026

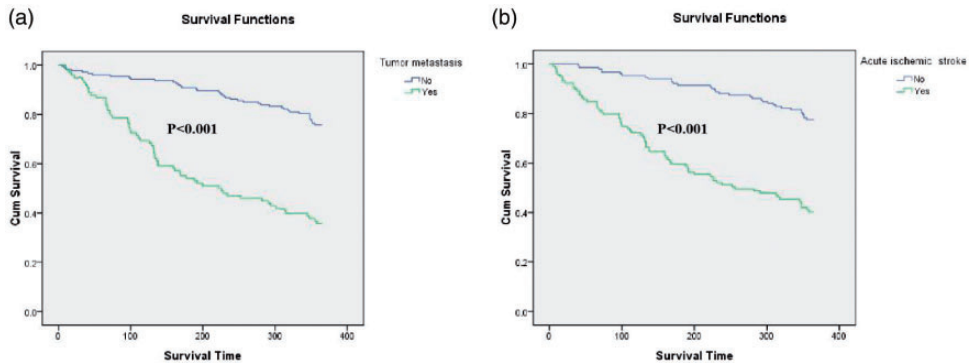AIS, acute ischemic stroke; OR, odds ratio; CI, confidence interval.

Figure 1. (a) Kaplan–Meier survival curve for Chinese cancer patients with and without tumor metastasis and (b) Kaplan–Meier survival curve for Chinese cancer patients with and without acute ischemic stroke.

Table 4. Multivariate Cox regression analyses of Chinese cancer patient characteristics with AIS.

Characteristic	OR	95% CI	*P*-value
Age	1.016	0.996–1.036	0.112
Male	1.133	0.699–1.837	0.612
AIS	1.837	1.050–3.211	0.033
Tumor metastasis	2.147	1.311–3.519	0.002
Type of primary tumor	0.973	0.760–1.245	0.827
Hypertension	0.701	0.421–1.168	0.173
Diabetes mellitus	1.163	0.664–2.034	0.598
Coronary artery disease	0.978	0.417–2.293	0.960
Atrial fibrillation	0.623	0.175–2.211	0.464
Hemoglobin	0.991	0.939–1.047	0.755
Red blood cell	1.089	0.276–4.294	0.903
Hematocrit	0.754	0.001–1087.903	0.939
Mean corpuscular volume	1.652	0.850–3.212	0.139
Mean corpuscular hemoglobin	0.211	0.026–1.703	0.144
Mean corpuscular hemoglobin concentration	1.148	0.963–1.367	0.123
Platelet	0.999	0.997–1.002	0.720
D-dimer	1.000	1.000–1.001	0.046
International normalized ratio	21.373	0.082–5541.037	0.280
Prothrombin time	0.787	0.589–1.052	0.106
Prothrombin activity	0.974	0.937–1.013	0.191
Thrombin time	1.087	1.014–1.166	0.019
Fibrinogen	1.207	1.026–1.420	0.023
Activated partial thromboplastin time	0.972	0.933–1.012	0.161

AIS, acute ischemic stroke; OR, odds ratio; CI, confidence interval.

prognosis for patients. However, stroke remains an understudied problem that seems difficult to address.[25–29] Moreover, tumor metastasis has been considered to be an important risk factor for a worse prognosis, but further studies are necessary to investigate this in more depth.

The present study confirms that tumor metastasis was positively and independently associated with AIS, suggesting that tumor

metastasis had a significant relationship with the development of AIS in these Chinese cancer patients. Tumor metastasis poses a significant risk of systemic embolization, making stroke a severe consequence of tumor metastasis.[30–32] Hematogenous metastasis of tumor cells not only affects the coagulation system, but can also form tumor thrombi. These events can all promote the development of systemic embolization and AIS. Systemic embolization has been found to have a high occurrence in cancer patients with tumor metastasis. The cerebral and retinal arteries are the most common sites of systemic embolization, although case reports of limb ischemia, pulmonary embolisms, and renal infarcts are also noted in the literature.[33,34]

A large amount of D-dimer is produced after the fibrinolytic system is activated and fibrous protein is degraded.[35] Thus, the D-dimer level is the most valuable indicator of a hypercoagulable state and secondary increased fibrinolytic activity in the human body.[36] The present study found that the D-dimer level was positively and independently associated with AIS and prognosis, suggesting that the coagulation system plays a significant role in the AIS development and survival status in Chinese cancer patients. A hypercoagulable state caused by cancer could be an important part of cryptogenic AIS-related pathogenesis.[37] Further studies are encouraged to illuminate the pathogenesis of AIS in Chinese cancer patients.

The present study had one main limitation: it is a retrospective study with a limited number of patients. Further studies with a larger number of patients should be performed to address this shortcoming.

Conclusion

Taken together, the present study demonstrates that tumor metastasis was positively and independently associated with AIS in a group of Chinese cancer patients, suggesting that tumor metastasis has a significant relationship with the development of AIS. Additionally, tumor metastasis and AIS showed independent effects leading to a worse prognosis for patients.

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