RESEARCH ARTICLE

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In Patients with Acute Ischemic Stroke and Cancer: The Shorter Interval, the Higher D-Dimer

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Abstract

Objectives: Acute ischemic stroke in cancer patients is uncommon. The study was aimed to identify the relationship of patients' characteristics and the interval time between the diagnosis of stroke and cancer. **Methods:** The clinical features of acute ischemic stroke patients with cancer were retrospectively analyzed from May, 2016 to April, 2021. Categorical data was compared between groups using chi-square test. Hematological biomarkers were compared using Mann-Whitney U test. **Results:** A total of 70 acute ischemic stroke patients with cancer were identified. The median interval time between the diagnosis of acute ischemic stroke and cancer was 53.0 months. Patients with interval < 53.0 months and > 53.0 months were regarded the short interval group and the long interval group, respectively. Between the short and long interval groups, there was no significant differences in respect to sex, age, chemotherapy, hypertension, diabetes, smoking, atrial fibrillation and dyslipidemia. The medians of homocysteine, high-sensitivity C-reactive protein and fibrinogen were also not significantly different between the two different interval groups. D-dimer in the short interval group was higher than that in the long interval group (216 vs. 142 ng/mL, p = 0.037). The long interval group had more surgery for cancer than the short interval group (94.3% vs. 57.1%, p = 0.000). **Conclusion:** In conclusion, in patients with ischemic stroke and cancer, patients with short interval time between the diagnosis of ischemic stroke and cancer had higher D-dimer than patients with long interval time.

Keywords: Interval time- acute ischemic stroke- cancer- D-dimer

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Introduction

With the aging of the population, increasing people will suffer from ischemic stroke and cancer in their lifetime(Kato et al., 2016; Navi and Iadecola, 2018; Dardiotis et al., 2019). Cancer patients with acute ischemia stroke were reported to have significantly older age, more tumor metastasis, higher D-dimer and thrombin time than cancer only patients(Wu et al., 2021). In a prospective study, patients with stroke and cancer have higher markers of coagulation, endothelial dysfunction [ICAM-1 (intercellular adhesion molecule-1),VCAM-1 (vascular cell adhesion molecule-1)], and more circulating microemboli than stroke-only patients, or cancer-only patients(Navi et al., 2021).

Ischemic stroke patients with active cancer patients had poor outcome than those with non-active caner (in-hospital mortality, 21.9% vs. 6.2%)(Kneihsl et al., 2016). As regards the long-term outcome, stroke patients with active cancer were associated with higher 12-month mortality (hazard ratio 5.56, p < 0.001), when compared with non-active cancer patients(Nezu et al., 2022). Cancer cells have been reported to contribute hypercoagulability by activating factor VIII/X to set off coagulation cascade, and releasing mucins to active endothelial cells(Yeh and Chang, 2017). In addition, various anti-neoplastic treatments, such as chemotherapy, targeted therapy and radiotherapy, can also cause hypercoagulability by releasing microparticles, or injuring vessels(Li et al., 2006; Seet et al., 2011; Hung et al., 2014). Therefore, it might be speculated that the interval time between the diagnosis of stroke and cancer would affect coagulation markers and clinical outcomes.

However, the relationship of patients' characteristics and the interval time between the diagnosis of stroke and cancer is not clear. In this study, we retrospectively analyzed the clinical features of ischemic stroke patients with cancer, in order to identify the factors which may be associated the interval time between stroke and cancer.

Materials and Methods

Patients

The consecutive patients with acute ischemic stroke

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were searched in our hospital from May, 2016 to April, 2021. The diagnosis of acute ischemic stroke should have neurological deficit symptoms and corresponding abnormal high DWI signal on the MRI examination. Among the patients with ischemic stroke, those who had cancer were further identified. Cancer should be diagnosed pathologically and hematological malignancies are excluded. The demographic characteristics, the history of hypertension, diabetes, atrial fibrillation and dyslipidemia, and the treatment of cancer were collected after reviewing electronic medical record system. Some laboratory testing items were also recorded, including homocysteine, high-sensitivity C-reactive protein (hs-CRP), fibrinogen and D-dimer.

Statistics

Continuous data were calculated as median value. Categorical data were calculated as n and percent. The comparison of quantitative data was performed by t test or Mann-Whitney U test. Chi-square test was used to compare the qualitative data. All the statistics are performed by SPSS version 22. A $p < 0.05$ was considered statistically significant.

Results

From May, 2016 to April, 2021, a total of 869 patients with acute ischemia stroke are found in our hospital. After further review, 70 patients (8.1%, 70/869) are identified with ischemia stroke and cancer. The median interval time between ischemic stroke and cancer is 53.0 months (range, 0.1-363.0 months). The median age is 76.5 years (range, 39-91 years). Forty-five (64.3%) patients are male. With regard to the treatment for cancer, surgery and chemotherapy are performed in 53 (75.7%) patients and 23 (32.9%) patients, respectively. The history of hypertension, diabetes, smoking, atrial fibrillation and dyslipidemia are found in 49 (70.0%), 32 (45.7%), 18 (25.7%), 9 (12.9%) and 20 (28.6%) patients, respectively (shown in Table 1). The three most common types of cancer are lung cancer (13 cases, 18.6%), colon cancer (9 cases, 12.9%) and prostate cancer (8 cases, 11.4%) (shown in Table 2).

According to the median interval time between ischemic stroke and cancer, all patients are divided into two groups, the short interval group (< 53.0 months) and the long interval group (> 53.0 months). Between the different interval groups, there was no significant differences in respect to sex, age, chemotherapy, hypertension, diabetes, smoke, atrial fibrillation and dyslipidemia. The long interval group had more surgery for cancer than the short interval group (94.3% vs. 57.1%, $p = 0.000$) (shown in Table 3).

The comparisons of laboratory results were further performed between the short and long interval groups. The medians of homocysteine, hs-CRP and fibrinogen were not significantly different between the two different interval groups. D-dimer in the short interval group was higher than that in the long interval group (216 vs. 142 ng/mL, $p = 0.037$) (shown in Table 4).

Table 1. Patients' Characteristics

Total patients, n	70
Interval time between ischemic stroke and cancer, median (range), months	53.0 (0.1-363.0)
Male, n (%)	45 (64.3)
Age, mean (range), years	76.5 (39-91)
Surgery for cancer, n (%)	53 (75.7)
Chemotherapy for cancer, n (%)	23 (32.9)
Hypertension, n (%)	49 (70.0)
Diabetes, n (%)	32 (45.7%)
Smoking, n (%)	18 (25.7%)
Atrial fibrillation, n (%)	9 (12.9)
Dyslipidemia, n (%)	20 (28.6%)
Homocysteine, median (range), μmol/L	12.57 (2.16-54.69)
hs-CRP, median (range), mg/L	4.1 (0.3-165.9)
Fibrinogen, median (range), g/L	3.21 (1.28-6.90)
D-dimer, median (range), ng/ml	193 (36-5000)

hs-CRP, high-sensitivity C-reactive protein

Discussion

In the present study, 8.1% (70/869) of acute ischemic stroke patients are identified with the diagnosis of cancer. Half of the patients with short interval time between ischemic stroke and cancer had higher D-dimer than another half patients with long interval time.

In a retrospective study of consecutive 799 patients with ischemic stroke(Jiang et al., 2021), 53 (6.63%) patients were found to have active cancer, which was

Table 2. Types of Cancer in Patients with Ischemic Stroke and Cancer

Types of cancer	Total n=70 (%)	Short interval group n = 35	Long interval group n = 35
Lung cancer	13 (18.6)	8	5
Colon cancer	9 (12.9)	5	4
Prostate cancer	8 (11.4)	4	4
Breast cancer,	7 (10.0)	3	4
Gastric cancer	7 (10.0)	4	3
Cervical cancer	4 (5.7)	3	1
Rectal cancer	4 (5.7)	0	4
Esophageal cancer	3 (4.3)	0	3
Thyroid cancer	3 (4.3)	0	3
Bladder cancer	3 (4.3)	2	1
Soft tissue sarcoma	2 (2.9)	1	1
Endometrial cancer	2 (2.9)	1	1
Pancreatic cancer	2 (2.9)	2	0
Ovarian cancer	1 (1.4)	0	1
Tongue cancer	1 (1.4)	1	0
Liver cancer	1 (1.4)	1	0

Table 3. Demographic and Clinical Characteristics between Different Interval Group

	Short interval group n = 35	Long interval group n = 35	p value
Male, n (%)	22 (62.9)	23 (65.7)	0.803
Age, median, years	72	80	0.178
Surgery for cancer, n (%)	20 (57.1)	33 (94.3)	0.000
Chemotherapy for cancer, n (%)	13 (37.1)	10 (28.6)	0.445
Hypertension, n (%)	22 (62.9)	27 (77.1)	0.192
Diabetes, n (%)	18 (51.4)	14 (40.0)	0.337
Smoking, n (%)	9 (25.7)	9 (25.7)	1.000
Atrial fibrillation, n (%)	5 (14.3)	4 (11.4)	0.721
Dyslipidemia, n (%)	10 (28.6)	10 (28.6)	1.000

defined as the diagnosis or treatment of cancer in the past 6 months, or the metastasis or recurrence of known cancers. In our study, 8.1 percent of ischemic stroke were found to have cancer, regardless of the interval time. Obviously, less patients would have active cancer.

The cancer with the highest incidence in the world is breast cancer, followed by lung cancer, colorectal cancer and prostate cancer (Zaorsky et al., 2019; Sung et al., 2021). The results about the most common types of cancer in our study basically reflect the trend, except for breast cancer, which may be due to the less women (25 cases, 35.7%).

The history of hypertension, diabetes, smoking, atrial fibrillation and dyslipidemia are generally recognized as risk factors of ischemia stroke (Kneihsl et al., 2016; Grazioli et al., 2018). Though less dyslipidemia was found in ischemic stroke patients with active cancer when compared with patients with only ischemic stroke (Jiang et al., 2021). These factors were found to have no association with the interval time between ischemia and cancer. More surgery for cancer was observed in long interval group (94.3% vs. 57.1%, p = 0.000). In ischemic stroke patients with long-interval cancer, cancers were nearly cured. The main cure for solid malignancies is surgery. Besides, ischemic stroke patients with short-interval cancer might suffer from the metastasis or recurrence of cancer that were not suitable for surgery, and might not tolerate surgery due to the contraindication of concurrent ischemia stroke.

In the study of M. Abdelsalam, C-reactive protein, fibrinogen and D-dimer were highly elevated in 78 ischemic stroke patients with cancer than in 78 patients with only ischemic stroke(Abdelsalam et al., 2020). In the present study, there were no significant differences of homocysteine, hs-CRP and fibrinogen between the short and long interval groups. Despite the different interval time, patients with both stroke and cancer may have similar laboratory changes in some items.

In several reports, D-dimer levels were significantly

Table 4. Hematological Biomarkers between Different Interval Group

	Short interval group n = 35	Long interval group n = 35	p value
Homocysteine, median, μmol/L	12.85	11.92	0.557
hs-CRP, median, mg/L	4.3	3.4	0.672
Fibrinogen, median, g/L	3.22	3.18	0.643
D-dimer, median, ng/ml	216	142	0.037

increased in patients with stroke and cancer than in patients with stroke only(Kim and Lee, 2014; Kataoka et al., 2021; Lee et al., 2021).However, the role of D-dimer in ischemic stroke and cancer patients with different interval time is not clear. We divided 70 stroke and cancer patients into two interval groups according to the median 53.0-month interval, and found that D-dimer was significantly elevated in the short interval group (216 vs. 142 ng/mL, p = 0037). The varied therapies of cancer and cancer itself have some impact on blood coagulation function. As the interval time between stroke and cancer increases, the impact may become smaller.

In conclusion, in patients with ischemic stroke and cancer, the medians of homocysteine, high-sensitivity C-reactive protein and fibrinogen were not significantly different between the short and long interval groups. Patients with short interval time between the diagnosis of ischemic stroke and cancer had higher D-dimer than patients with long interval time.

Author Contribution Statement

Wang XK collected the data, and drafted the work; Zhou MH performed the design of the work, analyzed the data and revised the work. All authors read and approved the final manuscript.

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It was not approved by any scientific body; it is not part of an approved student thesis.

This study protocol was reviewed and approved by the institutional review board of Chinese PLA General Hospital. The study was retrospective and the data were anonymous, so written informed consent was not required.

Data Availability

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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