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# Sex differences of ischemic stroke in young adults—A single-center Chinese cohort study

Mingyu Tang, MS, Ming Yao, MD, Yicheng Zhu, MD, Bin Peng, MD,  
Lixin Zhou, MD, and Jun Ni, MD

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**Background and Objective:** Stroke at a young age is a societal challenge with a rising incidence. Our aim was to investigate sex differences in risk factors, etiology, and diagnostic process of ischemic stroke in Chinese young adults. **Methods:** We retrospectively recruited 411 consecutive patients with first-ever ischemic stroke who were 18 to 50 years of age (mean age,  $38.2 \pm 8.1$  years, women 31.4%), admitted to Peking Union Medical College Hospital from 2007 to 2018. Sex differences in demographics, risk factors, etiology, and diagnostic testing were analyzed. **Results:** Females were significantly younger than males (36.9 versus 38.7 years,  $P < 0.05$ ). Hypertension (43.0%), smoking (41.1%), hyperlipidemia (37.2%), and hyperhomocysteinemia (27.9%) were common risk factors, statistically higher among males than females ( $P < 0.05$ ). Stroke etiology showed a significant sex difference that large-artery atherosclerosis and small-vessel diseases were more common among males than females (48.6% versus 19.4%,  $P < 0.001$ ; 9.9% versus 3.1%,  $P < 0.05$ , respectively). Stroke of other determined etiology was more common among females (50.4% versus 19.1%,  $P < 0.001$ ). Relevant abnormality rates were higher among females on screening for autoimmune diseases and thrombophilia (23.3% versus 11.1%,  $P < 0.05$  and 50.0% versus 16.7%,  $P < 0.001$ , respectively). **Conclusions:** A high rate of the traditional stroke risk factors and etiological subtype of large artery atherosclerosis in males were found, as well as prominent sex differences in relevant diagnostic testing abnormality rates, providing useful information for developing sex-specific strategies in stroke evaluation and prevention in young adults.

**Keywords:** Stroke in young adults—Sex differences—Risk factors—Etiology  
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## Introduction

Ischemic stroke in young adults (usually defined as 18-50 years) is a serious event that can cause death, lifelong disability, and decreased quality of life. Worldwide, more than two million young adults suffer from ischemic stroke every year,<sup>1,2</sup> and the incidence of ischemic stroke in young adults has considerably increased in recent decades,<sup>3-5</sup>

especially in low and middle-income countries.<sup>6</sup> Stroke in young adults has major social and economic impacts because of high healthcare costs and loss of labor productivity.<sup>2,7</sup> Thus, stroke prevention and improvement of outcomes are particularly important in this group. Notably, compared with stroke in older patients, many different, often rare, causes and risk factors are associated with stroke at a young age. Investigations into the cause of ischemic stroke at a young age often pose challenges. With the intention not to miss rare causes, etiologic work-up is frequently extensive and complicated.

In the last decade, sex differences in stroke epidemiology, risk factors, management, and outcome have been increasingly investigated, and there is now ample evidence that the pathophysiology of stroke is sex specific.<sup>8,9</sup> However, there is a paucity of studies on sex differences of stroke in young adults, especially in China. Considering the fact that most of the unique risk factors such as

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From the Department of Neurology, Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, No 1, Shuaifuyuan, Dongdan Dongcheng District, Beijing 100730, China.

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Corresponding authors. E-mails: [zhoulixin\\_pumch@163.com](mailto:zhoulixin_pumch@163.com), [pumchnijun@163.com](mailto:pumchnijun@163.com).

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pregnancy and preeclampsia occur before the age of 50, the development of strategies for stroke evaluation and prevention in young adults must consider sex as an important factor. Furthermore, the rising incidence of stroke in young adults has been accompanied by an increase in traditional risk factors<sup>10</sup> and might impact the distribution of etiologies and risk factors. Thus, in order to gather more generalizable and usable information for etiologic workup and stroke prevention, research on sex-specific differences in ischemic stroke in young adults is essential.

The optimal management focused on young adult patients with stroke remains unknown, and it's imperative to establish prevention and treatment guidelines specifically on this population. Thus, the aims of this study were to thoroughly investigate the risk factors, etiologies, and diagnostic workup of ischemic stroke in Chinese young adults, but also to assess the sex differences in this group.

## Methods

### *Patients*

We retrospectively reviewed the data of young adults with ischemic stroke consecutively admitted to the Peking Union Medical College Hospital (PUMCH) from 2007 to 2018. This study was approved by the ethical authority of the PUMCH. The inclusion criterion was young adults diagnosed with first-ever ischemic stroke who fulfill the following criteria: (1) age 18 to 50 years, (2) computed tomography or magnetic resonance imaging proven cerebral infarction. Patients were excluded according to the following criteria: (1) venous infarction; (2) stroke due to head trauma; (3) iatrogenic stroke such as stroke because of carotid endarterectomy, angiography procedure, or major surgery. A total of 411 patients met the inclusion criterion and were recruited in our study. All medical and laboratory records, as well as brain imaging studies, were reviewed by a team of stroke neurologists. We extracted data on patient demographics, National Institutes of Health Stroke Scale (NIHSS) score at admission, traditional stroke risk factors (including hypertension, diabetes mellitus, hyperlipidemia, smoking, atrial fibrillation, and family history) and other risk factors (including hyperhomocysteinemia, migraine and oral contraceptive use), etiologies, and diagnostic workup.

### *Diagnostic Workup*

The diagnostic workup data specified for stroke etiologies in young adults were collected. All patients were investigated using a standard protocol including blood tests (determination of red and white blood cell and platelet counts, glucose, cholesterol, electrolytes, transaminases, creatinine, urea, homocysteine, prothrombin time, activated partial thromboplastin time), cranial computed tomography (CT) and/or conventional magnetic resonance imaging (MRI), 12-lead electrocardiography, carotid artery

ultrasound, and transcranial Doppler (TCD). The following additional investigations were carried out at the discretion of the treating physician: serological tests consisting of screening for thrombophilia (protein C and S, antithrombin), antiphospholipid antibodies (anticardiolipin, anti- $\beta$ 2 glycoprotein 1 antibody, and lupus anticoagulant), and screening for autoimmune diseases or vasculitis, including antinuclear antibody, anti-extractable nuclear antigen antibody, and antineutrophil cytoplasmic antibodies, cervicocerebral vascular imaging including digital subtraction angiography (DSA), computed tomography angiography (CTA) or magnetic resonance angiography (MRA), and 24-hour Holter monitoring. At our center, a bubble-TCD, specific and sensitive for the screening of patent foramen ovale (PFO),<sup>11</sup> is often combined with transthoracic echocardiography (TTE). Transesophageal echocardiography (TEE) is then performed for confirmation when a cardiac right-to-left shunt is detected.

### *Stroke Classification*

Stroke subtype of each patient was classified by two experienced clinical neurologists according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria:<sup>12</sup> (1) large artery atherosclerosis, (2) cardioembolism, (3) small-artery occlusion, (4) stroke of other determined etiology, (5) stroke of undetermined etiology. The subtype of ischemic stroke was confirmed by our stroke team in case of discrepancy.

### *Statistical Analysis*

Pearson's chi-squared and Fisher's exact tests were used to compare categorical variables. Student's t-test was used to compare the means of quantitative data. The Wilcoxon rank-sum test was used to compare medians of quantitative data. Two-sided values of  $P < 0.05$  were considered statistically significant. SPSS version 17.0 for Windows was used for statistical analysis.

## Results

### *Demographics*

Of 411 patients, there were 282 men and 129 women, with an overall male preponderance (male: female ratio, 2.19:1) both in the 18-35 years group (62.3% were men) and the 36-50 years group (72.1% were men). The mean age of onset was  $38.2 \pm 8.1$  years. Women were significantly younger than men (36.9 years versus 38.7 years,  $P < 0.05$ ). The median time from onset to admission to our hospital was 7 days (interquartile range: 2-30), and there was a significant difference between sex groups (5 days in men versus 15 days in women,  $P < 0.001$ ). The median NIHSS score on admission was 3 (interquartile range: 1-6) (Table 1). NIHSS score on admission did not show any significant difference between the sex groups.

**Table 1.** Demographics, risk factors and etiologies

	N (%)						P value
	All (n = 411)		Male (n = 282)		Female (n = 129)		
<b>Demographics</b>							
Age, mean (SD), y	38.2	(8.1)	38.7	(8.2)	36.9	(7.8)	0.039*
Time from onset to admission (day)	7	(2,30)	5	(2,20)	15	(3,43)	0.000*
NIHSS <sup>#</sup> severity at admission	3	(1,6)	3	(1,6)	2	(1,6.5)	0.319
<b>Risk factors<sup>##</sup></b>							
≥ 1 risk factor	317	(77.5)	248	(88.3)	69	(53.9)	0.000*
<b>Traditional Risk Factors</b>							
Hypertension	176	(43)	142	(50.5)	34	(26.6)	0.000*
Diabetes mellitus	70	(17.1)	58	(20.6)	12	(9.4)	0.005*
Hyperlipidemia	152	(37.2)	123	(43.8)	29	(22.7)	0.000*
Smoking	168	(41.1)	162	(57.7)	6	(4.7)	0.000*
Family history	35	(8.6)	27	(9.6)	8	(6.3)	0.176
Atrial fibrillation	5	(1.2)	4	(1.4)	1	(0.8)	0.79
<b>Other risk factors</b>							
Hyperhomocysteinemia	114	(27.9)	100	(35.6)	14	(10.9)	0.000*
Oral contraceptive	3	(0.7)	0	(0)	3	(2.3)	0.030*
Migraine	12	(2.9)	7	(2.5)	5	(3.9)	0.638
<b>Etiology</b>							
Large artery atherosclerosis	162	(39.4)	137	(48.6)	25	(19.4)	0.000*
Cardioembolism	28	(6.8)	18	(6.4)	10	(7.8)	0.609
Small artery occlusion	32	(7.8)	28	(9.9)	4	(3.1)	0.017*
Other determined etiology	119	(29)	54	(19.1)	65	(50.4)	0.000*
Undetermined etiology	70	(17)	45	(16)	25	(19.4)	0.392

<sup>#</sup>NIHSS: National Institutes of Health Stroke Scale.

<sup>##</sup>One patient's data was missed in both sexes.

#### Risk factors, etiologies, and sex differences

The distribution of risk factors is presented in Table 1. Three hundred and seventeen patients (77.5%) had at least one traditional risk factor for stroke. Hypertension, smoking, and hyperlipidemia were detected in 43%, 41.1%, and 37.2% of cases, respectively, while diabetes mellitus and atrial fibrillation were uncommon (17.1% and 1.2%, respectively). In our study, 88.3% of male patients had at least one risk factor and was significantly higher than females (53.9%,  $P < 0.001$ ). The prevalence of hypertension, smoking, hyperlipidemia, hyperhomocysteinemia, and diabetes mellitus was significantly higher among males than females ( $P = 0.005$  for diabetes mellitus,  $P < 0.001$  for other risk factors).

Stroke etiology according to the TOAST criteria was summarized in Table 1. Large-artery atherosclerosis was the most common (39.4%), whereas cardiac embolism (6.8%) and small vessel disease (7.8%) were relatively uncommon in this cohort. In total, 119 (29.0%) cases were classified as 'other identified etiologies', including autoimmune diseases (7.5%), Moyamoya disease (6.6%), cervicocerebral arterial dissection (3.9%), antiphospholipid syndrome (3.2%), hereditary or acquired thrombophilia (0.7%), and other rare etiologies (7.1%). The etiology remained undetermined in only 17.0% despite a thorough diagnostic workup. Stroke etiology showed a

significant sex difference, in that large-artery atherosclerosis and small-vessel diseases were more common among males (48.6% versus 19.4%,  $P < 0.001$ ; 9.9% versus 3.1%,  $P < 0.05$ , respectively), and females were more commonly classified as 'other identified etiology' (50.4% versus 19.1%,  $P < 0.001$ ).

#### Diagnostic Tests and sex differences

The frequency and yield of all diagnostic testing were described in Table 2. Patients in our study were more frequently evaluated by cervicocerebral angiography (88.6%), and transthoracic or transesophageal echocardiography (65.5%). However, only 13.9% of patients performed a 24-h Holter monitor. Relevant abnormalities were revealed on cervicocerebral angiography in 279 of 364 patients (76.6%), on antiphospholipid antibodies in 21 of 156 (13.5%), on screening for autoimmune diseases in 25 of 164 (15.2%), on thrombophilia panels in 29 of 106 (27.4%), on cardiac ultrasonography in 20 of 269 (7.4%), and on Holter monitoring in 3 of 57 (5.3%). The relevant abnormality rates of the screening for autoimmune diseases as well as that of the screening for thrombophilia were significantly higher in females than in males (23.3% versus 11.1%,  $P < 0.05$  and 50.0% versus 16.7%,  $P < 0.001$ , respectively) (Table 2).

**Table 2.** *Diagnostic Workup*

	Frequency of diagnostic tests N (%)	Abnormality rate N (%)	No. (%)		P value
			Male	Female	
<b>Cervicocerebral vascular imaging</b>	364(88.6)	279(76.6)	192 (76.2)	87 (77.7)	0.757
<b>Antiphospholipid antibodies</b>	156(38.0)	21(13.5)	10 (10.3)	11 (18.6)	0.109
<b>Tests for autoimmune diseases</b>	164(39.9)	25(15.2)	12 (11.1)	13 (23.2)	0.041*
<b>Thrombophilia</b>	106(25.8)	29(27.4)	12 (16.7)	17 (50)	0.000*
<b>TTE and/or TEE<sup>#</sup></b>	269(65.5)	20(7.4)	13 (7.3)	7 (7.8)	0.879
<b>Holter</b>	57(13.9)	3(5.3)	3 (7.7)	0 (0)	0.206

<sup>#</sup>TTE: transthoracic echocardiography. TEE: transesophageal echocardiography.

## Discussion

Studies on ischemic stroke in young adults allowing representation of populations with diverse ethnic and geographical backgrounds are necessary. Our study provides a retrospective profile of ischemic stroke in Chinese young adults in recent decades. Traditional risk factors for stroke were frequent in this patient population, especially in males. In our series, large-artery atherosclerosis was the most common cause of ischemic stroke in young adults, which is quite different from the usual reports of US and European populations.<sup>13–15</sup> Significant sex differences in demographics, risk factors and etiologies of ischemic stroke in Chinese young adults were identified, which might support the development of sex-specific strategies to improve evaluation, management, and prevention of stroke in young adults and reduce their excess burden of disability.

In previous series of ischemic stroke in young adults from Europe and the US, males have commonly predominated, but females usually outnumber males among patients under 30. In our cohort, a global male predominance was found, which is consistent with previous reports in China.<sup>16,17</sup> Another important finding of our study is that females are more likely to delay admission after the onset of stroke, which might result in poorer outcomes. This is consistent with the findings of previous studies.<sup>18,19</sup> The fact that women arrive later than men might indicate that women present with more non-conventional stroke symptoms<sup>20</sup> or have lower stroke awareness. Today, the average age of first-time stroke patients continues to decrease. However, stroke awareness among young patients remains poor. Providing targeted stroke education to improve stroke awareness in young individuals is crucial.

Our study indicated that the traditional risk factors were prominent among young patients, especially in males. Compared with previously reported epidemiological investigations, the frequencies of some traditional risk factors were higher in our cohort. The prevalence of hypertension among general population aged 18–44 years in a large Chinese study was 17.5%, with 20.6% in men and 14.3% in women.<sup>21</sup> The rate in our study is 43%, with 50.5% in men and 26.6% in women. In a large-scale cross-sectional

research, dyslipidemia was observed in 27.5% of Chinese young adults aged 18–49 years, with 38.3% in men and 19.6% in women.<sup>22</sup> In our study, the number is 37.2%, with 43.8% in men and 22.7% in women. According to Ng's research, the smoking prevalence rates among young men aged 20–49 in developing countries were between 30–50%.<sup>23</sup> However, this percentage increased to 57.5% in our study. The high frequencies of traditional modifiable risk factors in our research indicate a need for aggressive primary and secondary prevention strategies for stroke in young adults. Unlike in previous studies in developed countries, we noted that hypertension, rather than hyperlipidemia, was the most prevalent risk factor in our patients, which is consistent with the results of studies carried out earlier in China.<sup>17</sup> This might be due to large amounts of salt in the Chinese diet as well as poor recognition and control of hypertension. Moreover, illicit drug use in our study was extremely rare compared with other studies in western countries, which may be attributed to the sociocultural differences and discrepancy in lifestyles. Additionally, although more common in children, infection is a relatively rare cause of stroke in young adults, which is consistent with our research as well. However, as the spread of Coronavirus disease 2019 (COVID-19) pandemic, more and more cases of COVID-19-related stroke have been reported, which included stroke in young adults.<sup>24</sup> Therefore, the cerebrovascular complication of infection, especially viral infection like COVID-19, should be put more emphasis on in further research.

Significant sex-specific distribution of risk factors was found in our series. For traditional risk factors including hypertension, hyperlipidemia, smoking, and diabetes mellitus, the risk was greater in males than in females. A more conspicuous tendency to smoke in men and the effect of estrogen may explain a relatively higher prevalence of the modifiable risk factors among males than females. However, the use of oral contraceptives and pregnancy-related effects have been proven to be the sex-specific risk factors for women.<sup>20,25</sup> The sex differences in risk factors should be taken into account when planning specific strategies of etiologic diagnostic evaluation and primary and secondary prevention of ischemic stroke in young adults.



The most common etiological subtype of ischemic stroke in our cohort was large artery atherosclerosis (39.4%), which is in line with the results of previous studies in China.<sup>17,26</sup> In contrast to those reported from US and European populations, the proportion of cardiac embolism is conspicuously much lower,<sup>13–15</sup> which may result mainly from ethnicity. To some extent, a relatively lower rate of TTE/TEE evaluation might be responsible for the lower percentage of cardioembolism as well. Considering the fact that young adults with stroke due to large artery atherosclerosis are at higher risk of recurrence than other subtypes,<sup>27,28</sup> it is necessary to emphasize lifestyle changes in primary and secondary prevention among these patients. Meanwhile, we found a relatively low rate of undetermined stroke etiology compared with other studies in China,<sup>17</sup> which might be explained by an extensive battery of tests and modern imaging techniques that were routinely performed at our center. We also noted the prominent sex-specific etiologic distribution of ischemic stroke in Chinese young adults. Large artery atherosclerosis and small-vessel occlusion were more common in men, which may be attributed to the higher incidence of traditional risk factors in males than in females. On the other hand, other determined etiologies were more prevalent among females, consistent with the results of some previous studies.<sup>15</sup> Women at a young age could benefit from the protective effects of estrogen, which may attenuate the risk of atherosclerosis,<sup>20</sup> but more are vulnerable to systemic autoimmune diseases,<sup>29</sup> as well as the patent impact of pregnancy and oral contraceptives. Our findings suggested that a sex-specific diagnostic process to detect the underlying causes of ischemic stroke in young adults should be established.

Young adults with ischemic stroke typically undergo a wide spectrum of diagnostic tests, but there is little knowledge about the diagnostic yields of these tests. We found a high diagnostic yield for brain and vascular imaging which provided insights into the pathophysiology of stroke and should be evaluated initially by all young stroke patients. Sex differences in the yields of some other investigations were observed in our study. The number of positive results of screening for thrombophilia and autoimmune diseases was higher in females than males. In Ji's research of stroke and TIA in young adults, the abnormal result of functional protein S was more common in females than in males.<sup>13</sup> An elevated risk of ischemic stroke related to a prothrombotic state in young women was found in a previous study.<sup>30</sup> Considering the susceptibility of certain systemic autoimmune diseases like systemic lupus erythematosus and antiphospholipid syndrome in females,<sup>29</sup> the importance of selected diagnostic workup algorithms in different sexes should be considered in further studies and clinical practice. What's more, although rarely seen in our research, infection, especially viral infection like coronavirus disease 2019 (COVID-19), which may become more prevalent in the

etiologies of ischemic stroke in young adults in the future, need to be put more emphasis on in further researches.

Our study is an over-ten-year research with a relatively large number of patients and well-documented data. However, it has some limitations. First, because our study was hospital-based, the results might be susceptible to hospital referral selection bias. Second, because of its retrospective nature, some permanent or transient risk factors were missing in the medical records. Third, the diagnostic workup was not fully standardized and might vary during the long period of this retrospective study. For example, TTE/TEE was performed in nearly half of the patients, leading to a potential lower frequent detection of cardiac sources of emboli.

In conclusion, our findings contribute to the understanding of the spectrum of risk factors, etiology, and diagnostic workup; and the sex differences of stroke in young adults in a tertiary hospital in China. The traditional risk factors and etiologic subtype of large artery atherosclerosis are frequently seen in ischemic stroke in Chinese young adults, especially men. Sex differences in risk factors and etiologies in our study provided useful information for developing sex-specific strategies for stroke evaluation and prevention in Chinese young adults. Our findings are warranted to be confirmed in a prospective study setting with a standardized methodology.

### Declaration of Competing Interest

The authors declare no conflicts of interest.

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