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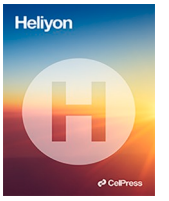

Research article

Disparity in risk factors of ischemic stroke in four coastal-area hospitals in China

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ABSTRACT

Background: Currently, ischemic stroke is the leading cause of death in China. To compare regional differences of ischemic stroke, we analyzed the clinical characteristics of patients with ischemic stroke in four regionally representative hospitals in China.

Methods: We conducted a retrospective study at four tertiary hospitals in east China, with regionally representative patients. The associated factors include hypertension, diabetes mellitus, coronary heart disease, hyperlipidemia and a combination of these factors. The standardized ratio (SR), estimated as the observed number divided by the expected number, computed as the sum of predicted probabilities from a multivariable logistic regression model derived using data from all other cities, was used to compare to average levels.

Results: A total of 34,707 patients were included. The number of patients increased with age in all four hospitals and patients were predominantly male. The number of ischemic stroke cases with related factors increased with age, except for hyperlipidemia. There was no significant gender difference when multiple related factors existed simultaneously. Coronary heart disease had a more significant impact on ischemic stroke in Qingdao Municipal Hospital and the First Hospital of Qinhuangdao, while hyperlipidemia had a significant influence on ischemic stroke in the First Hospital of Qinhuangdao.

Conclusions: At four hospitals in east China, with the increase of age, the risk factors associated with ischemic stroke increased, and the distribution of ischemic stroke-related factors showed regional differences.

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1. Introduction

Ischemic stroke can cause severe central nervous system injury and dysfunction. It has been reported that globally about 15 million people suffer from acute ischemic stroke annually, and approximately two-thirds of patients have obvious sequelae or die [1]. In China, there are about 1.5 million new-onset ischemic stroke cases each year [2], and the total number of patients is increasing at an annual rate of 8.7 % [3]. Ischemic stroke is the leading cause of death in China [4].

The main risk factors for ischemic stroke are hypertension, diabetes mellitus, coronary artery disease, and hyperlipidemia, and effective control of these factors greatly reduces the risk of ischemic stroke. Several previous studies on ischemic stroke revealed that the distribution of risk factors had significant regional, gender, race, and age differences [5–7].

China is a vast country with great differences in living habits, climatic conditions and geographical environment. Therefore, we speculate that there are regional differences in the risk factors and clinical features of ischemic stroke. The analysis of these differences will help us to control and reduce the occurrence of cerebral infarction more effectively in different regions. Therefore, the objective of this study is to analyze regional differences in ischemic stroke risk factors in China. To study the differences in factors related to ischemic stroke in coastal areas of China, we selected four large regionally representative tertiary hospitals on the east coast of China and collected the clinical data of ischemic stroke patients hospitalized in these hospitals. The four hospitals we selected have regional and population representation, which can effectively represent the clinical characteristics of ischemic stroke in these regions. We compared the regional differences in risk factors for ischemic stroke, in order to lay a foundation for regional prevention and treatment of stroke risk factors in China.

2. Materials and methods

2.1. Study design and study population

We conducted a retrospective analysis of acute ischemic stroke patients from four large tertiary hospitals in eastern coastal cities in China. Under the current Chinese health care system, patients in these hospitals come from different social groups, including people living in the rural areas surrounding the cities. So, the four hospitals we selected have regional and population representation. The four hospitals were the First Hospital of Qinhuangdao, Hebei Province (data collection from 2010 to 2016), Qingdao Municipal Hospital, Shandong Province (data collection from 2004 to 2016), the First Affiliated Hospital of Nanjing Medical University, Jiangsu Province (data collection from 2005 to 2016), and the First Affiliated Hospital of Sun Yat-sen University, Guangdong Province (data collection from 2004 to 2015). All patients met the diagnostic criteria from the *International Classification of Diseases* 10th edition (ICD-10) for acute ischemic stroke, including rapid onset of local symptoms or signs, such as hemiplegia, hemi-paresthesia, dysarthria, dysphagia, vertigo, and sometimes whole brain symptoms. All symptoms lasted more than 24 h, and diagnosis was confirmed by non-enhanced head CT or MRI [8]. Those without identify risk factors patients were excluded. The clinical data were obtained from medical records, and this retrospective analysis was approved by the Institutional Review Board of the Second Hospital of Hebei Medical University (Ethical approval no. 2018-R105). All procedures were performed in accordance with the principles of the Declaration of Helsinki, and individual consent for this retrospective analysis was waived.

2.2. Definition of factors related to ischemic stroke

All the related factors met the ICD-10 diagnostic criteria. Hypertension was defined as (i) systolic blood pressure $\geq$140 mmHg and/or diastolic blood pressure $\geq$90 mmHg as measured at least three times on different days, (ii) current use of oral antihypertensive drugs, and/or (iii) patients were told by doctors that they had hypertension at least twice [9]. Diabetes mellitus was defined as (i) fasting blood glucose $\geq$7.0 mM as measured at least twice, (ii) blood glucose $\geq$11.1 mM at 2 h after oral administration of 75-g glucose, and/or (iii) current use of oral glucose-lowering drugs [8]. Coronary artery disease was defined as (i) a coronary artery stenosis rate of $\geq$50 % and/or (ii) current use of oral medication for coronary artery disease [10]. Hyperlipidemia was defined as (i) total cholesterol $\geq$6.2 mM, (ii) low-density lipoprotein–cholesterol $\geq$4.2 mM, (iii) triglyceride $\geq$2.3 mM, and/or (iv) current use of oral lipid-lowering drugs [11].

2.3. Statistical analysis

Categorical variables are expressed as percentages and were compared using the χ^2 test or Fisher's exact test. The standardized ratio (SR) was calculated as the observed number of patients having a risk factor divided by the number of patients expected to have that risk factor, computed as the sum of predicted probabilities from a multivariable logistic regression model derived using data from all other cities with adjustment for age and sex. As the SR estimate was calculated in relation to all cities combined, it was not directly comparable between contributors. SR $>$ 1 indicates that the observed rate in a specific city was higher than average, and vice versa. All analyses were based on non-missing values of covariates and outcomes. *P*-values $<$0.05 were considered statistically significant. Due to data collection from different hospitals covered different data ranges, sensitivity analysis based on the data collected 2010 onward was conducted. Analyses were completed using SAS statistical software version 9.4 (SAS Institute Inc., Cary, NC).

3. Results

3.1. Demographic characteristics of patients

A total of 34,707 patients with acute ischemic stroke were enrolled, including 8122 from the First Hospital of Qinhuangdao, 9601 from Qingdao Municipal Hospital, 10,016 from the First Affiliated Hospital of Nanjing Medical University, and 6968 from the First Affiliated Hospital of Sun Yat-sen University. The number of patients increased with age in these four hospitals. The First Affiliated Hospital of Sun Yat-sen University had the largest proportion of ischemic stroke patients under 40 years old, accounting for 3.9 % (274/6968). The proportion of ischemic stroke patients under 40 years old in Qingdao Municipal Hospital and the First Affiliated Hospital of Nanjing Medical University was 1.3 % (124/9601) and 1.4 % (144/10016), respectively; however, more than 50 % of ischemic stroke patients in the two hospitals were over 70 years old (Table 1). The number of male patients was higher than female patients in the four hospitals (Table 1).

3.2. Age and gender differences in ischemic stroke risk factors

The number of patients with a single risk factor increased with age; however, the number of patients with hyperlipidemia decreased over the age of 70. Overall, the number of patients with multiple risk factors increased with age; however, the number of patients with hyperlipidemia decreased, remained the same, or increased a little after 70 years old (Table 2). We found that more male patients had a single risk factor; however, as the number of risk factors increased, the gender difference was narrowing. There was no significant gender difference in patients with four risk factors (Table 2). To assess the impact of time and their prevalence over time, all hospitals from 2010 onwards be rechecked for a sensitivity analysis, which showed no significant difference in the conclusions compared data covered 2004 to 2016, as detailed in Attachment 1.

3.3. Regional distribution of risk factors

A comparison of estimated SRs of related factors in each city relative to one another is presented in Table 3. There was a disparity in risk factors of ischemic stroke across regions. The First Hospital of Qinhuangdao had the fewest patients with hypertension. Stroke patients in the First Hospital of Qinhuangdao and Qingdao Municipal Hospital had higher rates of coronary artery disease than stroke patients in the First Affiliated Hospital of Nanjing Medical University and the First Affiliated Hospital of Sun Yat-sen University. The First Hospital of Qinhuangdao had the highest proportion of hyperlipidemia patients. Similarly, a sensitivity analysis has been done and we didn't find significant difference, as detailed in Attachment 2.

4. Discussion

Risk factors determine the pathophysiological characteristics of ischemic stroke. Age is an important and unchangeable risk factor [12]. Rothwell et al. found that the risk of ischemic stroke more than doubled every 10 years after the age of 55 [13]. Lloyd-Jones et al. pointed that more than 70 % of ischemic stroke cases occurred in patients over 65 years old and that the risk of ischemic stroke continued to increase with age [14]. Gentil et al. observed that the risk of ischemic stroke was approximately 100-fold higher in people aged over 80 years than in people aged 40–80 years [15]. Our study confirmed that ischemic stroke mainly occurs in older people. Several mechanisms could account for this phenomenon. Primarily, aging could cause metabolic disorders, increase the secretion of pro-inflammatory factors, damage the anti-inflammatory system, disrupt the energy balance of the central nervous system, and destroy the integrity of the neuro-vascular system [16,17]. Second, aging changes the cerebrovascular structure, damages arterial endothelial cells, and disrupts the cerebrovascular self-regulation function [12,18]. With the rapidly aging population in China, the number of ischemic stroke patients will continue to increase; therefore, we should pay more attention to the prevention of ischemic stroke in the elderly. Ischemic stroke under the age of 40 is defined as young stroke, which accounts for approximately 10%–14 % of new-onset ischemic stroke cases annually [5]. Marcel et al. observed that young stroke patients often had non-traditional risk factors, such as

Table 1
Age and gender distribution of ischemic stroke in four hospitals.

	FHQHD (n = 8122)	QDMH (n = 9601)	FAHNJMU (n = 10,016)	FAHSYSU (n = 6968)	P-value
Age (y), n (%)					<0.001
≤40	163 (2.0)	124 (1.3)	144 (1.4)	274 (3.9)	
40–50	701 (8.6)	467 (4.9)	542 (5.4)	643 (9.2)	
50–60	1792 (22.1)	1462 (15.2)	1490 (14.9)	1228 (17.6)	
60–70	2453 (30.2)	2204 (23.0)	2641 (26.4)	1711 (24.6)	
≥70	3013 (37.1)	5344 (55.7)	5199 (51.9)	3112 (44.7)	
Sex, n (%)					<0.001
Male	5170 (63.7)	5656 (58.9)	6109 (61.0)	4395 (63.1)	
Female	2952 (36.4)	3945 (41.1)	3907 (39.0)	2573 (36.9)	

Abbreviations: FAHNJMU: the First Affiliated Hospital of Nanjing Medical University; FHQHD: the First Hospital of Qinhuangdao; FAHSYSU: the First Affiliated Hospital of Sun Yat-sen University; QDMH: Qingdao Municipal Hospital.

Table 2
Age and gender distribution of major risk factors for ischemic stroke.

	NRF	HP	DM	CVD	HL	HP/DM	DM/CVD	CVD/HL	HP/CVD	DM/HL	HP/HL	HP/DM/CVD	HP/DM/HL	DM/CVD/HL	HP/CVD/HL	HP/DM/CVD/HL	*P*-value
Age (y), *n* (%)																	<0.001
≤40	335 (5.7)	151 (1.4)	15 (1.0)	12 (1.1)	40 (5.9)	39 (0.7)	2 (0.5)	1 (1.1)	26 (0.7)	3 (1.2)	46 (3.3)	20 (0.9)	13 (1.5)	1 (3.1)	0 (0.0)	1 (0.4)	
40–50	545 (9.3)	756 (6.8)	129 (8.9)	35 (3.3)	121 (17.9)	245 (4.7)	14 (3.7)	6 (6.8)	105 (3.0)	37 (14.9)	159 (11.5)	95 (4.3)	79 (9.2)	0 (0.0)	18 (6.3)	9 (4.0)	
50–60	1074 (18.3)	1870 (16.8)	282 (19.3)	113 (10.7)	173 (25.6)	920 (17.5)	42 (11.0)	18 (20.5)	443 (12.5)	71 (28.5)	381 (27.4)	272 (12.2)	228 (26.7)	9 (28.1)	38 (13.4)	38 (16.7)	
60–70	1426 (24.4)	2897 (26.0)	394 (27.0)	213 (20.2)	205 (30.3)	1522 (29.0)	97 (25.5)	26 (29.6)	786 (22.2)	77 (30.9)	390 (28.1)	535 (24)	269 (31.5)	11 (34.4)	95 (33.5)	66 (29.1)	
≥70	2476 (42.3)	5469 (49.1)	638 (43.8)	682 (64.6)	138 (20.4)	2518 (48.0)	226 (59.3)	37 (42.1)	2175 (61.5)	61 (24.5)	413 (29.7)	1312 (58.7)	266 (31.1)	11 (34.4)	133 (46.8)	113 (49.8)	
Sex, *n* (%)																	<0.001
Male	3707 (63.3)	7226 64.9)	970 (66.5)	635 (60.2)	446 (65.9)	3126 (59.6)	241 (63.3)	48 (54.6)	1998 (56.5)	149 (59.8)	854 (61.5)	1173 (52.5)	478 (55.9)	20 (62.5)	147 (51.8)	112 (49.3)	
Female	2149 (36.7)	3917 (35.2)	488 (33.5)	420 (39.8)	231 (34.1)	2118 (40.4)	140 (36.8)	40 (45.5)	1537 (43.5)	100 (40.2)	535 (38.5)	1061 (47.5)	377 (44.1)	12 (37.5)	137 (48.2)	115 (50.7)	

Abbreviations: CVD: coronary heart disease; DM: diabetes mellitus; HL: hyperlipidemia; HP: hypertension; NRF: no risk factor.

Table 3
Crude rate, adjusted rate, and standardized ratios of risk factors in ischemic stroke patients in four hospitals.

	Crude rate, *n* (%)				Adjusted rate[a]				SR[b] (95 % CI)			
	FHQHD	QDMH	FAHNJMU	FAHSYSU	FHQHD	QDMH	FAHNJMU	FAHSYSU	FHQHD	QDMH	FAHNJMU	FAHSYSU
NRF	1109 (13.7)	1332 (13.9)	1906 (19.0)	1509 (21.7)	18.4	17.5	15.8	16.1	0.74 (0.70, 0.79)	0.79 (0.75, 0.84)	1.21 (1.15, 1.26)	1.34 (1.28, 1.41)
HP	1988 (24.5)	2465 (25.7)	4368 (43.6)	2322 (33.3)	34.7	34.4	27.3	32.1	0.7 (0.67, 0.74)	0.75 (0.72, 0.78)	1.6 (1.55, 1.64)	1.04 (1, 1.08)
DM	328 (4.0)	322 (3.4)	503 (5.0)	305 (4.4)	4.2	4.5	3.9	4.1	0.96 (0.86, 1.07)	0.74 (0.66, 0.82)	1.3 (1.19, 1.42)	1.06 (0.94, 1.18)
CVD	275 (3.4)	483 (5.0)	189 (1.9)	108 (1.6)	2.9	2.3	3.5	3.4	1.16 (1.03, 1.31)	2.2 (2.01, 2.4)	0.54 (0.46, 0.62)	0.46 (0.37, 0.55)
HL	393 (4.8)	33 (0.3)	47 (0.5)	204 (2.9)	1.1	2.6	2.6	1.7	4.57 (4.13, 5.04)	0.13 (0.09, 0.19)	0.18 (0.13, 0.24)	1.73 (1.50, 1.98)
HP/DM	869 (10.7)	1231 (12.8)	1964 (19.6)	1180 (16.9)	16.3	16.2	13.4	14.5	0.66 (0.62, 0.7)	0.79 (0.75, 0.84)	1.47 (1.40, 1.53)	1.17 (1.10, 1.24)
DM/CVD	105 (1.3)	160 (1.7)	76 (0.8)	40 (0.6)	1.0	0.9	1.2	1.2	1.27 (1.04, 1.53)	1.87 (1.59, 2.18)	0.61 (0.48, 0.76)	0.47 (0.34, 0.64)
CVD/HL	68 (0.8)	8 (0.1)	3 (0.0)	9 (0.1)	0.1	0.3	0.3	0.3	11.33 (8.80, 14.37)	0.26 (0.11, 0.51)	0.09 (0.02, 0.25)	0.46 (0.21, 0.87)
HP/CVD	627 (7.7)	2016 (21.0)	582 (5.8)	310 (4.5)	10.7	6.1	12.0	11.4	0.72 (0.67, 0.78)	3.43 (3.28, 3.58)	0.48 (0.44, 0.52)	0.39 (0.35, 0.44)
DM/HL	170 (2.1)	10 (0.1)	8 (0.1)	61 (0.9)	0.3	1.0	1.0	0.7	7.24 (6.19, 8.42)	0.11 (0.05, 0.20)	0.08 (0.04, 0.16)	1.32 (1.01, 1.69)
HP/HL	904 (11.1)	32 (0.3)	61 (0.6)	392 (5.6)	1.8	5.5	5.4	3.5	6.27 (5.87, 6.69)	0.06 (0.04, 0.09)	0.11 (0.09, 0.14)	1.6 (1.44, 1.76)
HP/DM/CVD	369 (4.5)	1399 (14.6)	265 (2.7)	201 (2.9)	6.8	3.4	8.1	7.2	0.67 (0.60, 0.74)	4.29 (4.07, 4.52)	0.33 (0.29, 0.37)	0.4 (0.35, 0.46)
HP/DM/HL	526 (6.5)	32 (0.3)	37 (0.4)	260 (3.7)	1.2	3.3	3.4	2.1	5.4 (4.95, 5.88)	0.1 (0.07, 0.14)	0.11 (0.08, 0.15)	1.78 (1.57, 2.01)
DM/CVD/HL	26 (0.3)	0 (0.0)	0 (0.0)	6 (0.1)	0.0	0.1	0.1	0.1	14.63 (9.56, 21.43)	NA	NA	0.94 (0.34, 2.05)
HP/CVD/HL	205 (2.5)	37 (0.4)	7 (0.1)	35 (0.5)	0.3	1.0	1.1	0.9	8.76 (7.60, 10.05)	0.38 (0.27, 0.53)	0.06 (0.02, 0.13)	0.57 (0.40, 0.80)
HP/DM/CVD/HL	160 (1.9)	41 (0.4)	0 (0.0)	26 (0.4)	0.2	0.8	0.9	0.7	8.06 (6.86, 9.41)	0.56 (0.40, 0.77)	NA	0.53 (0.34, 0.77)

Abbreviations: CVD: coronary heart disease; DM: diabetes mellitus; FAHNJMU: the First Affiliated Hospital of Nanjing Medical University; FAHSYSU: the First Affiliated Hospital of Sun Yat-sen University; FHQHD: the First Hospital of Qinhuangdao; HL: hyperlipidemia; HP: hypertension; NA: Not available; NRF: no risk factor; QDMH: Qingdao Municipal Hospital; SR: Standardized ratio. Example: HP/DM represents the patients with both hypertension and diabetes mellitus.

[a] Adjusted for age and sex.

[b] The standardized ratio (SR) was calculated as the observed number of patients having a risk factor divided by the number of patients expected to have the same risk factor, computed as the sum of predicted probabilities from a multivariable logistic regression model derived using data from all other provinces with adjustment for age and sex. The SR estimate is calculated in relation to all provinces combined.

smoking, alcoholism, and mental stress [19]. Deng et al. found that the behavioral risk factors were more common in young ischemic stroke patients than in the control group [4]. Our research showed that the proportion of young ischemic stroke patients was highest in the First Affiliated Hospital of Sun Yat-sen University. We hypothesize that the pace of life is faster and the mental pressure is greater in southeast coastal areas of China, and these non-traditional risk factors increase the risk of young ischemic stroke.

Gender is also an important risk factor for ischemic stroke. We found that ischemic stroke was more common in males. We speculate that this may be related to genetic factors. Touze et al. found that male stroke patients were more likely to have a stroke family history [20]. Liu et al. revealed that male-derived cultured mouse hippocampal neurons were more sensitive to ischemic injury than female-derived cells [21]. Second, estrogen may reduce the risk of ischemic stroke. Alonso et al. discovered that estrogen could reduce the risk of ischemic stroke, especially non-cardiogenic ischemic stroke [22]. Third, the atherosclerotic cardiovascular disease risk factors also have gender differences. Fang et al. showed that blood pressure was significantly higher in males [23]. Ischemic heart disease, peripheral arterial disease, hyperlipidemia, diabetes mellitus, smoking, and alcoholism were also more common in males, all of which increase the risk of ischemic stroke [24].

Our study also demonstrated that there were regional differences in the distribution of risk factors, which may be related to dietary habits, the level of economic development, the level of education, climate conditions, and income level among different regions. A number of studies found that lower average temperature or larger temperature differences was an independent risk factor for coronary artery disease [25–27]. In our study, we found that coronary artery disease had a greater effect on ischemic stroke in the First Hospital of Qinhuangdao and Qingdao Municipal Hospital, which may be related to the lower average temperature and the larger temperature differences in Qinhuangdao and Qingdao. In addition, we observed that more patients with ischemic stroke had hyperlipidemia in the First Hospital of Qinhuangdao. We hypothesize that this is because Qinhuangdao is close to northeast China, where more fatty meat is consumed [28]. We also demonstrated that the incidence of hypertension, diabetes mellitus, and coronary artery disease, but not hyperlipidemia, increased with age. Several observational studies found that in people younger than 65 years old, the risk of hyperlipidemia increased with age, peaked between 60 and 65 years, and gradually decreased thereafter, which may be related to the fact that the elderly undergo physical examination more regularly [29,30]. Therefore, we suggest that the intervention of ischemic stroke risk factors should be based on regional differences.

The advantages of this study is the inclusion of more patients, which makes the conclusion more convincing. At the same time, compared with similar studies, we analyzed the differences in the combination of risk factors between different regions, which is helpful for us to take regional prevention and control measures. There are also some limitations in our research. First, as is common to retrospective studies, the collection of data related to ischemic stroke risk factors was incomplete and the time span of data collection varied among the four hospitals. Second, although the hospitals included in our study were regionally representative, they were all located in urban areas. Third, we did not include outpatients with ischemic stroke. Finally, due to the limited data, we did not analyze the differences in etiological classification and severity of ischemic stroke.

5. Conclusions

In four coastal cities in eastern China, ischemic stroke mainly occurs in men, and advanced age is the risk factor. Owing to regional differences in major risk factors, coronary heart disease should be paid more attention in northern coastal China ischemic stroke patients, and hyperlipidemia should be strictly controlled in Qinhuangdao.

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Compliance with ethical standards

This study was reviewed and approved by the institutional review board of the Second Hospital of Hebei Medical University, with the approval number 2018-R105. All procedures performed in studies involving human participants were in accordance with the principles of the Declaration of Helsinki, and individual consent for this retrospective analysis was waived.

Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Luji Liu: Writing – original draft, Formal analysis, Data curation. **Yuhua Fan:** Resources, Investigation, Data curation. **Zhaolu Wang:** Resources, Investigation, Data curation. **Fei Liu:** Resources, Data curation. **Xin Wang:** Resources, Data curation. **Jinsheng Fu:** Investigation, Formal analysis. **Zhenzhong Li:** Investigation. **Huilian Sun:** Software, Methodology, Formal analysis. **Yuanyuan Du:** Investigation. **Jie Yang:** Software, Methodology, Formal analysis. **Xiaoyan Fan:** Investigation. **Bo Liu:** Investigation. **Lihong Zhang:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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