A Clinical Differential Study on Symptomatic Lacunar Infarction between Smoking and Non-smoking Male Patients

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Research Article

Keywords: Lacunar infarction, Smoking, Stroke, Symptomatic, Risk factor

Posted Date: February 7th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1283950/v1

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Abstract

**Objective:** Lacunar infarction (LI) has a high prevalence and recurrence rates. Smoking is a risk factor for stroke and has a large population. At present, there are no studies on the clinical differences of symptomatic LI between patients with smoking and non-smoking. This study aimed to reveal the relationship between smoking and LI and help the treatment and primary and secondary prevention of LI.

**Methods:** We performed a retrospective study of symptomatic LI in male patients. These patients were divided into the smoking group (SG) and non-smoking group (NSG). The variables with \( P<0.1 \) in univariate analysis were used as correction factors in multivariate logistic regression analysis.

**Results:** We enrolled 202 smoking and 162 non-smoking male patients with symptomatic LI. Multivariate logistic regression analysis showed that the differences of SG age of onset<65Y (OR 2.461, 95% CI 1.524-3.973, \( P<0.001 \)), hyperlipidemia (OR 0.543, 95% CI 0.332-0.887, \( P<0.05 \)), drinking rate (OR 1.865, 95% CI 1.153-3.017, \( P<0.05 \)), leukoaraiosis (OR 0.503, 95% CI 0.27-0.939, \( P<0.05 \)), asymptomatic cerebral infarction (OR 0.484, 95% CI 0.276-0.846, \( P<0.05 \)) and recurrence rate within 3 months of stroke (OR 2.792, 95% CI 1.014-7.691, \( P<0.05 \)) were statistically significant.

**Conclusions:** Smoking could lead to the onset age of symptomatic LI male patients significantly earlier, the prevalence of hyperlipidemia increased, accompanied by a higher drinking rate, with a higher incidence of leukoaraiosis and asymptomatic cerebral infarction. Smoking is a significant risk factor for LI. This study suggests that quitting smoking plays a vital role in the treatment and the primary and secondary prevention of LI.

1. Introduction

Lacunar infarction (LI) is a small subcortical infarction caused by intracranial perforating artery occlusion. The diameters of infarction lesions are mostly 2 to 20mm. LI is an important type of ischemic stroke, accounting for about one-quarter of all stroke cases [1]. LI has a high incidence. Studies have shown that the prevalence rate of asymptomatic cerebral infarction is five times that of symptomatic cerebral infarction [2]. The incidence in a community population can reach 10.7% [3]. Most of the asymptomatic cerebral infarctions are LI [4].

China is the world’s largest tobacco producer and consumer. The number of smokers accounts for about 28% of the world, and nearly half (47.2%) of the men are smoking, while only 2.7% of women smoke [5, 6]. Smoking has been identified as a clear risk factor for cerebral stroke [7–9]. Although patients with LI have a relatively good prognosis in the near future, their prevalence and recurrence rates are higher, and their prognoses in the mid-long term are poorer [10]. At present, there are no studies on the clinical differences of symptomatic LI between patients with smoking and patients with non-smoking. The clinical differential study between smoking and Non-smoking symptomatic LI in male Patients, reveals the relationship between smoking and LI, and better understands the impact of smoking on LI, so as to help the treatment and primary and secondary prevention of LI.
2. Methods

2.1 Research objects

A retrospective analysis of 1582 patients with symptomatic ischemic stroke treated in the Department of Neurology of the First Affiliated Hospital of Guangdong Pharmaceutical University from August 1, 2014, to December 31, 2019, was performed.

2.2 Inclusion criteria

(1) Patients who meet the latest definition of ischemic stroke proposed by the Chinese guidelines for the diagnosis and treatment of acute ischemic stroke [11]. (2) Patients who're the first stroke and first hospital are the First Affiliated Hospital of Guangdong Pharmaceutical University and whose time from onset to admission is ≤ 7 days. (3) For brain magnetic resonance scan, the longest diameter of the maximum cross-section of high signal in magnetic resonance (MR) diffusion-weighted imaging (DWI) sequence is ≤20mm. (4) Patients without a significant functional disability before the onset of disease, Modified Rankin Scale (MRS) score ≤ 2 points. (5) Patients with complete follow-up information.

2.3 Exclusion criteria

(1) Exclude patients with cerebral infarction whose longest diameter of the maximum cross-section of high signal in the DWI sequence for craniocerebral magnetic resonance scans is greater than 20mm. (2) Exclude patients with cerebral infarction accompanied by atrial fibrillation, mural thrombosis, valvular disease, and the patients with severe stenosis of intracranial aorta and vertebrobasilar artery (≥50%). (3) Exclude patients with arthritis, congenital vascular disease, hypercoagulability, drug-derived and hematological abnormalities. (4) Patients with incomplete clinical data.

2.4 Collection and processing of data

The enrolled patients were divided into the smoking group(SG) and non-smoking group(NSG), and a uniformly designed research form was used to collect and record baseline information of all subjects: Age, gender, hypertension, diabetes, hyperlipidemia, atrial fibrillation/atrial flutter, body mass index (BMI), history of previous transient ischemic attacks (TIA) or stroke, smoking and drinking, family history of stroke, etc. [the relevant definitions of the China National Stroke Registry (CNSR) were used] [12]. Information on an antithrombotic, lipid-lowering, anticoagulant, antihypertensive, hypoglycemic, and other related medications before admission and during hospitalization; The score of National Institutes of Health Stroke Scale (NIHSS) at the visit. All patients underwent craniocerebral magnetic resonance examination (3.0T GE Silent MR Scanner) after admission, including MR plain scan + angiography + diffusion-weighted imaging. Two imaging physicians read the MRI of patients by an independent blind method. If they disagree with the results of image evaluation, they finally reach an agreement through discussion.

2.5 Follow-up and prognostic evaluation
Follow-up observations were performed 90 days after the onset of the disease, and the data on stroke recurrence and MRS evaluations were collected. Poor prognosis was defined as MRS > 2 points; Stroke recurrence was defined as patients who had a recurrence of initial neurological symptoms or who in complete remission had recurring neurological symptoms, including a diagnosis of ischemic stroke, cerebral hemorrhage, or subarachnoid hemorrhage.

2.6 Statistical analysis

SPSS17.0 software was used for statistical analysis. The categorical variable is expressed as a percentage; if the continuous variable conforms to the normal distribution, it is represented by (X ± s). Categorical variables were compared using Pearson’s chi-squared test. Comparisons between two groups of continuous variables were performed using the Mann-Whitney U test. The variables with P < 0.1 in univariate analysis were used as correction factors in multivariate logistic regression analysis. Taking NSG as the control, the odds ratio (or) and 95% confidence interval (CI) of each outcome variable of NG was calculated, and the difference was statistically significant (P < 0.05).

The principles of the Declaration of Helsinki were followed. This study was approved by the ethics committee of the First Affiliated Hospital, Guangdong Pharmaceutical University, and all participants gave written informed consent.

3. Results

A total of 1582 patients with symptomatic ischemic stroke were collected, including 364 male patients with symptomatic LI meeting the inclusion and exclusion criteria, 202 patients with smoking, and 162 patients with non-smoking. Besides, there were 175 women who met the diagnosis of symptomatic LI, accounting for 32.5% of all patients with symptomatic LI, but only 3 had a history of smoking.

There were 202 smoking male patients with symptomatic LI, with an average age of 63.09±10.32 years old, and there were 162 non-smoking male patients, with an average age of 69.6±11.81 years old. The age of onset of the SG was significantly lower than that of the NSG (p<0.001). In terms of age composition (Fig. 1), the number of patients under the age of 65 in the SG was higher, accounting for 62.87% of the total number of patients in the group; and in the NSG only accounted for 35.19%, the difference was statistically significant (p<0.001). The differences in the prevalence of hyperlipidemia (p<0.001), drinking rate (p<0.001), and BMI Index(p<0.01) were statistically significant. The incidence of asymptomatic cerebral infarction and leukoaraiosis in the SG was higher than that in the NSG (p<0.001). The NIHSS score that reflects the severity of stroke at the visit was lower in the SG (p<0.001). There was no significant difference in the prevalence of homocysteine and diabetes between the two groups (Table 1).
Table 1
Baseline data, clinical risk factors and prognosis of smoking group and non-smoking group.

| Variables                              | SG (n=202)  | NSG (n=162) | P value |
|----------------------------------------|-------------|-------------|---------|
| Age(Y)                                 | 63.09±10.32 | 69.6±11.81  | 0.000   |
| ≤65Y,%                                 | 127(62.87)  | 57(35.19)   | 0.000   |
| Hypertension,%                         | 176(87.1)   | 128(79.01)  | 0.038   |
| Diabetes,%                             | 77(38.3)    | 74(45.7)    | 0.146   |
| Hyperlipidemia, %                      | 112(55.6)   | 49(30.0)    | 0.000   |
| HCY                                    | 15.47±3.63  | 15.08±2.91  | 0.255   |
| Drinking rate, %                       | 70(34.65)   | 11(6.79)    | 0.000   |
| BMI index                              | 24.97±3.17  | 24.0±2.91   | 0.002   |
| Leukoaraiosis,%                        | 166(82.18)  | 106(65.43)  | 0.000   |
| Asymptomatic cerebral infarction,%     | 133(65.8)   | 61(37.6)    | 0.000   |
| NIHSS score at visit                   | 3.11±2.08   | 3.79±2.37   | 0.004   |
| MRS score after 3 months≥2,%           | 8(3.96)     | 15(9.26)    | 0.039   |
| Recurrence rate of stroke after 3 months,% | 7(3.47)     | 14(8.54)    | 0.035   |

Abbreviations and definitions: HCY= Homocysteine, BMI index= Body mass index, NIHSS= National Institutes of Health Stroke Scale, MRS= Modified Rankin Scale.

All patients were followed up for 3 months, and no deaths occurred. A total of 21 (5.77%) stroke patients recurred, including 7 patients in the SG and 12 patients in the NSG. The difference was statistically significant (p<0.05). Among the 7 recurrent patients in the SG, after the first onset, 6 patients did not quit smoking, and 1 patient quit smoking immediately. Among the patients with recurrent stroke, there were two (0.55%) cases of a cerebral hemorrhage, all of which were in NSG. During the 3 months of follow-up, the number of patients with MRS score>2 points was 8 (3.96%) in the SG and 15 (9.26%) in the NSG, the difference was statistically significant (p<0.05) (Table 1).

Multivariate logistic regression analysis: Compared with NSG patients after adjusting age and other factors. SG patients were younger, age of onset <65Y(OR 2.461, 95%CI 1.524-3.973, P<0.001); The prevalence of hyperlipidemia (OR 0.543, 95%CI 0.332-0.887, P < 0.05) was higher; With a higher drinking rate (OR 1.865, 95%CI 1.153-3.017, P < 0.05); The prevalence of leukoaraiosis (OR 0.503, 95%CI 0.27-0.939, P < 0.05) and asymptomatic cerebral infarction was higher (OR 0.484, 95% CI0.276-0.846, P < 0.05); But the recurrence rate within 3 months of stroke (or 2.792, 95%CI 1.014-7.691, P < 0.05) was lower (Table 2).
Table 2
Multivariate logistic regression analysis (with NSG as reference)

| Variable                          | OR(ExpB) | 95%CI         | P value |
|-----------------------------------|----------|---------------|---------|
| Age(≥65Y)                         | 2.461    | 1.524~3.973   | 0.000   |
| Hypertension,%                    | 1.156    | 0.593~2.255   | 0.670   |
| Hyperlipidemia ,%                 | 0.543    | 0.332~0.887   | 0.015   |
| Drinking rate ,%                  | 1.865    | 1.153~3.017   | 0.011   |
| BMI index                         | 0.654    | 0.412~1.037   | 0.071   |
| leukoaraiosis,%                   | 0.503    | 0.270~0.939   | 0.031   |
| Asymptomatic cerebral infarction,%| 0.484    | 0.276~0.846   | 0.011   |
| NIHSS score at visit              | 1.532    | 0.963~2.435   | 0.071   |
| MRS score after 3 months₂,%       | 2.575    | 0.957~6.933   | 0.061   |
| Recurrence rate of stroke after 3 months,% | 2.792 | 1.014~7.691 | 0.047   |

Adjusted by age, hypertension, diabetes and other factors.

4. Discussion

Lacunar infarction (LI) is a small subcortical infarction caused by intracranial perforating artery occlusion. The lesion is usually located in the deep part of the cerebral hemisphere or brain stem, such as basal ganglia, thalamus, internal capsule, brain stem, white matter in the center of semioval [13]. The prevalence of LI is high, and the number of patients is large. The early symptoms of this disease are not obvious, and the clinical manifestations are lack specificity. Many LI patients could not be diagnosed, treated, and effectively prevented in time. With the development of the disease, there is gradually recurrent stroke or cognitive impairment leading to disability, which seriously affects the daily work and life of patients, with great harm [10].

Common risk factors for ischemic stroke are age, gender, racial inheritance, smoking, obesity, arteriosclerosis, hypertension, diabetes, coronary heart disease, etc [12]. The effects of these risk factors are somewhat different in different ischemic stroke subtypes [14–17]. Smoking is an important and controllable pathogenic factor of cerebrovascular disease and is one of the independent risk factors for the occurrence and death of cerebrovascular disease [18]. Wang et al. reported in Lancet that the overall incidence rate of smoking in China in 2013 was 25.2%, the incidence rate of men was 47.2%, and that of women was 2.7% [6]. The base number of patients with smoking in China is large. At present, there are no studies on the clinical differences of symptomatic LI between patients with smoking and patients with non-smoking. The smoking prevalence rate of men in China is higher, while that of women is very low, so the research on smoking men is more representative. This study selected smoking and non-smoking
patients with symptomatic LI to conduct a retrospective study to evaluate their clinical characteristics, so that it could let us better understand the impact of smoking on LI, in the hope that it can help the treatment and primary and secondary prevention of stroke and LI.

Age is a significant independent risk factor for stroke, the older the age, the higher the incidence [19]. In this study, the average age of SG was 63.04 ± 10.57 years old. The average age of NSG was 69.42 ± 12.53 years old. In univariate analysis, the average age of SG was significantly lower than that of NSG. Multivariate analysis showed that the age of onset(65Y) in SG was younger than that in NSG, suggesting that smoking was a vital factor in the early onset of LI.

O'Donnell et al. confirmed through a large sample study that hypertension is the primary factor in the risk factors that can be intervened for stroke [19]. Univariate analysis showed that the prevalence of hypertension of the SG was higher than that of the NSG (p<0.05). However, multivariate analysis showed that there was no significant difference in the prevalence of hypertension between the two groups. However, both SG and NSG had a very high prevalence of hypertension, suggesting that hypertension played a vital role in the pathogenesis of LI.

The prevalence rate of hyperlipidemia, drinking rate, and BMI in the SG was significantly different from that in the NSG, according to univariate analysis. Multivariate analysis showed that hyperlipidemia and drinking rate were significantly different between the two groups, suggesting that the SG had a higher drinking rate, more prone to hyperlipidemia.

Wiszniewska et al. found that leukoaraiosis is closely related to LI in patients with ischemic stroke [20]. Studies have shown that the destruction of the blood-brain barrier and the decrease of cerebral blood flow is the common initiating factors of LI and leukoaraiosis [21, 22]. Smoking can cause endothelial dysfunction of cerebral blood vessels, leading to dysfunction of the blood-brain barrier. The destruction of the blood-brain barrier can lead to leakage of toxic substances outside the blood vessels, and secondary damage to neurons and glial cells around the blood vessels [23]. Smoking can also lead to reduced cerebral blood flow and lowered cerebral perfusion [24–25]. Smoking leads to the destruction of the blood-brain barrier and the decrease of cerebral blood flow, which promotes the occurrence of leukoaraiosis and LI. In this study, univariate analysis showed that the leukoaraiosis and asymptomatic cerebral infarction in SG were higher than those in NSG (P < 0.001). Multivariate analysis indicated that there were significant differences between the two groups, suggesting that patients in the SG were more likely to suffer from leukoaraiosis and asymptomatic cerebral infarction.

In terms of stroke severity and prognosis, univariate analysis showed NIHSS score, 90-day MRS score, and recurrence rate of the SG were lower than those of NSG. However, there was no significant difference in NIHSS score and 90-day MRS score while there was a significant difference in the recurrence rate of the SG according to multivariate analysis. In this study, most smoking patients can actively control smoking after the onset of LI, and they can actively control blood pressure by insisting on oral clopidogrel or antiplatelet aspirin treatment for 90 days after the onset of the disease, as the patients in the NSG. The
reason for a lower recurrence rate of patients with smoking may be related to the fact that they control the risk factors of smoking after the onset.

Previously, the pathology and pathogenesis of LI were thought to be hyalinosis of perforating arteries, fibrinoid necrosis, embolism, atherosclerosis, and other causes [1]. However, in recent years, studies have showed that the lesions of both small arteries and large arteries could lead to LI [26–28]. The pathogenesis and etiology of LI are still worthy of our further research. Due to the limitation of conditions, there are still some shortcomings in this study: (1) The sample size is small: The study population is mainly adult smoking patients, and it cannot accurately reveal all the characteristics of LI in smoking and non-smoking patients in the whole population; (2) All patients come from the same hospital, and single-center data may be biased; (3) Due to the limitation of follow-up time, this study did not focus on long-term prognosis. Therefore, the differential analysis of smoking and non-smoking patients may not be comprehensive enough.

5. Conclusion

Our study showed significant differences between smoking and non-smoking patients with symptomatic LI. Smoking can lead to the onset age of symptomatic LI male patients significantly earlier, the prevalence of hyperlipidemia increased, accompanied by a higher drinking rate, with a higher incidence of leukoaraiosis and asymptomatic cerebral infarction. Smoking is a significant risk factor for LI. This study also suggests that quitting smoking plays a vital role in the treatment and the primary and secondary prevention of LI.

Abbreviations

LI: lacunar infarction; MRI: magnetic resonance; DWI: diffusion weighted imaging; TIA: transient ischemic attacks; NIHSS: National Institutes of Health Stroke Scale; OR: odds ratio; CI: confidence interval

Declarations

Acknowledgements

We would like to acknowledge the subject who participated in this study.

Author’s contributions

MF H contributed to the conception of the study. ZH Z and QY Y contributed significantly to analysis and manuscript preparation. SP D and AQ L performed the data analyses and wrote the manuscript. ZX P helped perform the analysis with constructive discussions.
Funding

Not applicable.

Availability of Data and Materials

The datasets generated and/or analysed during the current study are not publicly available due to privacy or ethical restrictions. But are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the First Affiliated Hospital, Guangdong Pharmaceutical University. All enrolled patients provided written, informed consent to be included in the study. All methods were performed in accordance with the relevant guidelines and regulations.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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**Figures**

**Figure 1**

Comparison of the age of symptomatic lacunar infarction between the smoking group and non-smoking group.