European Review for Medical and Pharmacological Sciences 2022; 26: 9365-9371

The association between white matter lesions and carotid plaque score: a retrospective study based on real-world populations

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Abstract. – OBJECTIVE: To date, more and more studies have focused on the occurrence and development of white matter lesions. Instead, we explored the association between the occurrence of white matter lesions and carotid plaque scores in different populations.

SUBJECTS AND METHODS: We studied patients who underwent head MRI and blood tests from April 1, 2016 to October 30, 2017 at Shin Takeo Hospital, Japan. We used multiple logistic regression analysis to analyze the relationship between the occurrence of white matter lesions and carotid plaque score and validated their relationship in three different models.

RESULTS: A total of 1,904 patients aged 20-85 years were included in this study. There were 860 patients in the non-white matter lesion group and 1,044 patients in the white matter lesion group. The mean age of patients in the non-white matter lesion group was 49.93±10.76 years, and in the white matter lesion group was 61.60±9.15 years. We established multiple regression analyses for white matter lesion and carotid plaque scores and found that the risk of white matter lesions increased with increasing carotid plaque score. (Model 1 (OR (95% CI): 1.360 (1.276, 1.450), Model 2 (OR (95% CI): 1.122 (1.048, 1.200), Model 3 [OR (95% CI): 1.106 (1.032, 1.186)].

CONCLUSIONS: Our study found that the incidence of white matter lesions tended to increase with increasing carotid plaque scores, a trend that was more pronounced in younger female patients but was not so pronounced in older male patients.

Key Words:
White matter lesions, Carotid plaque score, Real-world study, Dryad digital repository.

Introduction

Cerebral white matter lesions were a very common disease of brain tissue. It occurs in the elderly and can also occur in young patients, but in general, the incidence rate increases with age[1]. White matter lesions are usually diagnosed by magnetic resonance imaging (MRI) and may not be accompanied by any neurological symptoms[2]. White matter lesions usually appear hyperintense on fluid-attenuated inversion recovery (FLAIR) T2-weighted MRIs but isointense in T1-weighted MRIs. Carotid plaque is usually closely related to atherosclerosis, and some studies have shown that they are closely related to cerebral insufficiency, cerebrovascular lesions, and white matter lesions[3-7]. The carotid plaque score is a comprehensive score of the size, location and number of carotid plaques found by neck ultrasonography[5,8]. To date, most studies shown that age, history of heart disease or stroke, high blood pressure, and diabetes are the most important factors associated with white matter lesions[9]. The mechanism of white matter lesions has been explored by a small number of investigators who believe that vascular factors play an important role in the development of the disease, such as unstable carotid plaque (UCP) and atherosclerosis[10]. Hypertension is associated with cognitive impairment: a 20-year follow-up of 999 patients [11]. But so far, few studies have looked at the relationship between white matter lesions and carotid plaque scores. Through a retrospective study, we further explored the association between white matter lesions and carotid plaque scores. Therefore, it has made a certain contribution to the early diagnosis of white matter lesions and achieved the purpose of early diagnosis and early intervention.

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Subjects and Methods

Study Participants

This study included patients who underwent necessary examinations and randomized questionnaires at Shin Takeo Hospital[5], Japan, from April 1, 2016 to October 30, 2017. These data are uploaded to the Dryad Digital Repository database, an open public database (Patel, C. J. Dryad Digital Repository). These tests mainly include head MRI, hematology tests, cervical vascular ultrasound, and other tests. All patients included in the study received a questionnaire. The questionnaire included patients' eating habits: whether smoked or not, whether drinking or not, and so on.

Study Measures

We collected general information about patients, including gender, age, body mass index, blood pressure, body mass index, carotid plaque score (PS), patients' dietary habits, whether they smoked or drank alcohol, etc. We assessed the patient's general condition by carotid ultrasonography. The carotid plaque score was calculated as follows. The carotid artery is divided into 4 segments, each about 15 mm long: the central side of the carotid artery, the peripheral side of the carotid artery, the bifurcation of the carotid artery, and the central side of the internal carotid artery. Then, the sum of the maximum values of the intima-media thickness over 1.1 mm was calculated. The main contents of the research questionnaire include blood pressure drugs, use of hypoglycemic drugs, and drinking habits [every day, sometimes or infrequently (no alcohol)], alcohol consumption (<180 ml, 180-360 ml, 360-540 ml or >540 ml) etc.

Statistical Analysis

All statistical analyses were performed using EmpowerStats (http://www.empowerstats.net) and R version 4.1.1. We used multivariate logistic regression analysis to analyze the association between the occurrence of white matter lesions and carotid plaque scores and validated their association in three different models (unadjusted model, adjusted model 1, and adjusted model 2). In addition, we performed a stratified analysis by age, sex, and smoking habits to explore the relationship between white matter lesions and carotid plaques in different populations. Statistical analysis was performed using the *t*-test between continuous variables, while the Chi-square test was used for categorical variables. Statistical significance was considered if the *p*-value was lower than 0.05.

Results

A total of 1,904 patients aged 20-85 years were included in this study. According to the occurrence of white matter lesions, they were divided into two groups (Table I). There were 860 patients in the non-white matter lesion group and 1,044 patients in the white matter lesion group. The mean age of patients in the non-white matter lesion group was 49.93±10.76 years, and in the white matter lesion group was 61.60±9.15 years. Except for body mass index (BMI), triglyceride (TG), LH, low-density lipoprotein (LDL) and other characteristics, most of the baseline data were statistically different between the two groups. Compared with the non-white matter lesion group, the white matter group had more elderly patients, a higher proportion of women, and a higher proportion of smokers and drinkers.

Then, we established a multiple regression analysis for white matter lesion and carotid plaque scores, and the results are shown in Table II. In Model 1 (unadjusted model), the risk of white matter lesions increased with increasing carotid plaque score [OR (95% CI): 1.360 (1.276, 1.450)]. This trend remained unchanged after adjusting for confounders. In model 2, age, gender, and smoking were adjusted, and the results were consistent with the unadjusted model [OR (95% CI): 1.122(1.048, 1.200)]. In model 3, age, gender, smoking, HBA1C, BS, SBP, DBP, LDL, TG, BMI, RED_BP_MED, INSULIN, RED_CHO_MED, DRINK_QT, METABO, DRINK, LH were adjusted, this trend is still consistent with the previous [OR (95% CI): 1.106 (1.032,1.186)].

In the subgroup analysis, we performed subgroup analysis by gender, age, and smoking habits, as shown in Table II. It appears that higher carotid plaque scores were associated with higher risk of white matter lesions in patients younger than 60 years [OR (95% CI): 1.288 (1.151, 1.443)], female patients [OR (95% CI): 1.237 (1.065, 1.436)], smokers [OR (95% CI): 1.214 (1.028, 1.434)] and non-smokers [OR (95% CI): 1.214 (1.028, 1.434) OR (95% CI): 1.092 (1.008, 1.182)], but not in male [OR (95% CI): 1.064

Table I. Patient demographics.

	NWML	WML	*p*-value
Patients (n)	860 (45.17%)	1,044 (54.83%)	
AGE	49.93 ± 10.76	61.60 ± 9.15	**< 0.001**
PS	0.59 ± 1.32	1.49 ± 2.30	**< 0.001**
LDL	119.64 ± 31.56	121.88 ± 29.44	0.109
HDL	59.47 ± 14.74	62.49 ± 15.80	**< 0.001**
LH	2.14 ± 0.78	2.08 ± 0.74	0.064
TG	115.59 ± 124.38	108.71 ± 73.55	0.134
HBA1C	5.66 ± 0.57	5.86 ± 0.66	**< 0.001**
BS	102.41 ± 16.79	105.45 ± 19.22	**< 0.001**
SBP	119.96 ± 16.59	127.10 ± 19.26	**< 0.001**
DBP	72.43 ± 11.65	75.05 ± 12.49	**< 0.001**
N_PLAQUE	0.34 ± 0.72	0.84 ± 1.18	**< 0.001**
BMI	23.13 ± 3.41	23.17 ± 3.38	0.774
GENDER			**< 0.001**
Male	497 (57.79%)	491 (47.03%)	
Female	363 (42.21%)	553 (52.97%)	
SMOKING			**< 0.001**
No	663 (77.09%)	905 (86.69%)	
Yes	197 (22.91%)	139 (13.31%)	
RED_BP_MED			**< 0.001**
No	751 (87.33%)	691 (66.19%)	
Yes	109 (12.67%)	353 (33.81%)	
INSULIN			**< 0.001**
No	828 (96.28%)	937 (89.75%)	
Yes	32 (3.72%)	107 (10.25%)	
RED_CHO_MED			**< 0.001**
No	778 (90.47%)	811 (77.68%)	
Yes	82 (9.53%)	233 (22.32%)	
DRINK_QT			**< 0.001**
< 180 ml	504 (58.60%)	720 (68.97%)	
180-360 ml	237 (27.56%)	230 (22.03%)	
360-540 ml	89 (10.35%)	69 (6.61%)	
> 540 ml	30 (3.49%)	25 (2.39%)	
METABO			**< 0.001**
No	687 (79.88%)	742 (71.07%)	
Reserve	79 (9.19%)	117 (11.21%)	
Yes	94 (10.93%)	185 (17.72%)	
DRINK			0.029
Rarely	331 (38.49%)	465 (44.54%)	
Sometimes	269 (31.28%)	296 (28.35%)	
Everyday	260 (30.23%)	283 (27.11%)	

PS: plaque score, Drink_qt: amount of drinking per day, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, LH: LDL/HDL, TG: triglycerides, HbA1c: hemoglobin A1c, BS: blood glucose level, SBP: systolic blood pressure, DBP: diastolic blood pressure, N_plaque: plaque number, Red_bp_med : medication to reduce blood pressure, Red_cho_med: medication to reduce a level of cholesterol.

(0.982, 1.153)] and younger than 60 years patients [OR (95% CI): 1.077 (0.985, 1.176)]. Smooth curve fitting and generalized additive models were used to intuitively describe the relationship between the incidence of white matter lesions and PS in different populations (Figures 1-3). It can be seen from Figure 1 that in female patients with the increase of carotid plaque score, the incidence of white matter lesions increased significantly; when the carotid plaque score reached 5, white matter lesions occurred in almost 100% of female patients. There was also an increasing trend in male patients, but it was not statistically significant. In figure 2, the incidence of white matter lesions is significantly more likely in patients older than 60 years than in younger patients. In patients younger than 60 years, the incidence of white matter lesions increases linearly with the plaque score increased, but in patients older than 60 years their relationship became irregular. It can

Table II. The association between PS and white matter lesions.

	Model 1 OR (95% CI) *p*-value	Model 2 OR (95% CI) *p*-value	Model 3 OR (95% CI) *p*-value
PS	1.360 (1.276, 1.450) < 0.00001	1.122 (1.048, 1.200) 0.00089	1.106 (1.032, 1.186) 0.00458
Subgroup analysis stratified by Age			
< 60	1.339 (1.206, 1.487) < 0.00001	1.390 (1.248, 1.549) < 0.00001	1.288 (1.151, 1.443) 0.00001
> 60	1.077 (0.996, 1.165) 0.06310	1.095 (1.008, 1.189) 0.03149	1.077 (0.985, 1.176) 0.10233
Subgroup analysis stratified by Gender			
Male	1.383 (1.282, 1.491) < 0.00001	1.087 (1.006, 1.176) 0.03588	1.064 (0.982, 1.153) 0.13173
Female	1.528 (1.332, 1.754) < 0.00001	1.220 (1.060, 1.405) 0.00565	1.237 (1.065, 1.436) 0.00532
Subgroup analysis stratified by Smoking			
No	1.342 (1.248, 1.443) < 0.00001	1.112 (1.030, 1.202) 0.00680	1.092 (1.008, 1.182) 0.03050
Yes	1.483 (1.288, 1.709) 0.00001	1.159 (1.001, 1.341) 0.04783	1.214 (1.028, 1.434) 0.02264

Model 1: no covariates were adjusted. Model 2: Age, Gender, and Smoking were adjusted. Model 3: Age, Gender, Smoking, HBA1C, BS, SBP, DBP, LDL, TG, BMI, RED_BP_MED, INSULIN, RED_CHO_MED, DRINK_QT, METABO, DRINK, LH were adjusted. In the subgroup analysis stratified by age, gender and smoking.

be seen from Figure 3 that the incidence of white matter lesions in both smoking and non-smoking patients generally increased with the increase of the plaque score. The difference is that there is a linear positive relationship in smoking patients and a curvilinear positive relationship in non-smoking patients.

Discussion

Our study found a significant existential correlation between white matter lesions and carotid plaque scores. This conclusion is true whether in Model 1, Model 2, or Model 3. In subgroup analyses, we found a more robust relationship between

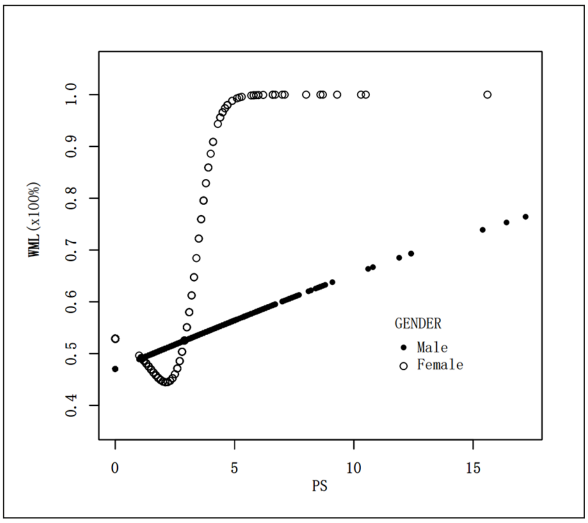

Figure 1. The association between WML and PS among male and female.

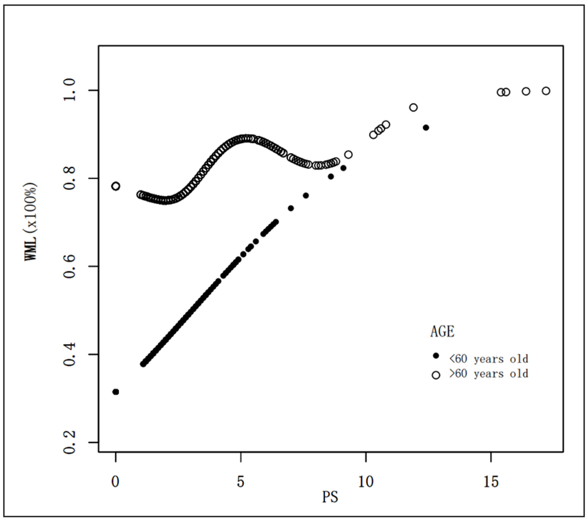

Figure 2. The association between WML and PS among patients older than 60 and younger than 60.

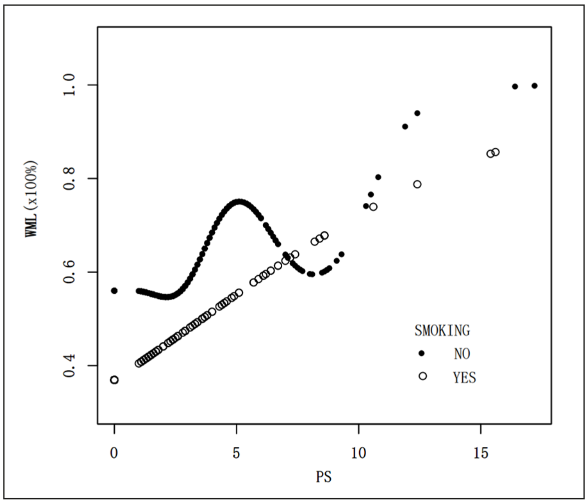

Figure 3. The association between WML and PS among smokers and non-smokers.

white matter lesions and carotid plaque scores in female patients and younger patients younger than 60 years of age. But in male patients and older patients, this relationship is not so obvious. Our study not only found the association between white matter lesions and carotid plaque scores, but also performed subgroup analyses to find the association in specific populations.

In recent years, with the development of medical technology, the detection rate of white matter lesions is getting higher and higher. It has attracted attention for its ability to predict dementia and stroke[12]. White matter lesions were considered a risk factor for dementia and stroke, and it presents with progressive exacerbations[12]. White matter lesions are mainly ischemic symptoms, usually accompanied by microvascular disease. The early symptoms are not typical, usually manifested as dizziness or memory loss, which is usually found by head MR examination during physical examination[13,14]. To date, there are few clinical studies[1,2] on white matter lesion, and the conclusions are controversial. Many studies[5,18] on the relationship between arteriosclerosis and vascular markers have found that aortic, carotid, and coronary, atherosclerosis was closely related to white matter lesions, cerebral microbleeds and cerebral infarction[1]. Carotid plaque score and carotid atherosclerosis are highly correlated. In our study, we found that with the increase of carotid plaque score, the incidence of white matter lesions increased by 1.1016 times. Therefore, our research and the above-mentioned research[5,13,14,18] conclusions are roughly similar. Shinkawa et al[5] found that with increasing age, the risk of white matter lesions increased by 1.1 times, this is consistent with the findings of Liu et al[19]. It is also shown in Table I that the incidence of white matter lesions is different between people of different ages. Overall, the possibility of white matter lesions in the elderly is higher than that in the young, and the difference is statistically significant. But our research also found that the incidence of white matter lesions is significantly more likely in patients older than 60 years than in younger patients. In younger patients younger than 60 years, the incidence of white matter lesions increases linearly with the plaque score increased, but in patients older than 60 their relationship became irregular. Studies have shown that the progression of white matter lesions is a risk factor for stroke and dementia. Therefore, early diagnosis and early intervention are of great significance for the prevention of stroke and dementia[14]. A study by Pantoni and Garcia[9] found that diabetes and hypertension were associated with white matter lesions. However, in our study, we found that the incidence of white matter lesions was different in smoking and non-smoking patients, also in hypertensive and normotensive patients. More interestingly, our study found that there is a linear positive relationship in smoking patients and a curvilinear positive relationship in non-smoking patients.

Limitations

However, our study still has many shortcomings. First, this study is a retrospective study, which has the general limitations of retrospective studies, and lack of randomness in the grouping, which affects the reliability of the results to a certain extent. Secondly, there were problems in the questionnaire, such as taking antihypertensive drugs, not providing the name and dosage of antihypertensive drugs. We also do not know if drug combinations are used to control blood pressure. In addition, there are many important research factors that cannot be obtained, including patients' hobbies, occupations, and whether they have the habit of staying up late. These factors also have a great influence on the occurrence of white matter lesions. Therefore, large-scale prospective studies are necessary to verify these conclusions.

Conclusions

Our study found a significant correlation between carotid plaque scores and white matter lesions. The incidence of white matter lesions increased with increasing carotid plaque score, a trend that was more pronounced in younger women and less in older men. In young and female patients, the incidence of white matter lesions increases linearly with the increase of carotid plaque score, but the relationship between carotid plaque scores and white matter lesions becomes irregular in older patients and male patients.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Ethics Approval

The data of this article comes from public databases and therefore, the Ethical Approval is not applicable.

Informed Consent

The patients in the public database have signed the relevant informed consent and can directly use the data to publish scientific research papers.

Availability of Data and Materials

All data in this study come from the Dryad public database. Patel, C. J. Dryad Digital Repository (available at: http://dx-.doi.org/10.5061/dry).

Funding

None.

Authors' Contribution

Xing Zhang made substantial contribution to the design of this study. Junjie Zeng carried out the analysis and interpreted the data. Xing Zhang and Jie Li made contributions to the drafting of the manuscript. All authors approved the final version of the manuscript.

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