Nomograms for predicting the incidence of white matter lesions: a real-world study based on elderly patients

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Abstract. – OBJECTIVE: Nowadays, there are still some doubts about the etiology, development, and preventive measures of white matter lesions. This research collected patient information in the Dryad Digital Repository database to identify predictors of patients with white matter lesions.

PATIENTS AND METHODS: We studied patients who underwent head MRI and blood tests during comprehensive physical examinations at Shin Takeo Hospital, Japan, between April 1, 2016, and October 30, 2017. We screened patients over the age of 60 and investigated white risk factors in material lesions in older patients and, randomly assigning patients to training and validation groups, we built nomograms on the basis of the training group and used other group data to verify its accuracy and consistency.

RESULTS: A total of 854 patients were included in this study. Multivariate analysis was performed according to the data before randomization, and the results showed that the age of patients (OR=2.81, 95% CI: 1.74-4.54), high-density lipoprotein (OR=1.31, 95% CI: 1.02-1.68), diastolic blood pressure (OR=1.47, 95% CI: 1.04-2.08).

Taking antihypertensive drugs (OR=1.78, 95% CI: 1.21-2.66) was significantly associated with white matter lesions. The area under the curve value (AUC) was 0.625 for the training group and 0.729 for the validation group. The clinical impact curve and calibration curve show that the model has good accuracy and clinical application value.

CONCLUSIONS: Age, high-density lipoprotein (HDL), diastolic blood pressure (DBP), and the use of antihypertensive drugs are closely related to white matter lesions. Furthermore, our model may be a useful tool for predicting the incidence of white matter lesions.

Key Words:
White matter lesions, Nomogram, Real-world study, Dryad digital repository.

Introduction

Cerebral white matter lesions are a relatively common neurological disease, mainly in the elderly, but it can also occur in young patients, and the incidence increases with age[1]. Brain magnetic resonance imaging (MRI), visible white matter lesions (WML) exhibit hyperintensity during t2-weighted or fluid-attenuated inversion recovery (FLAIR) acquisitions in healthy older adults[2,3]. Little is known about the pathogenesis of WML. To date, most studies have shown that age, hypertension, diabetes, and a history of stroke or heart disease are the most important factors associated with the presence of white matter lesions[4]. The mechanisms of white matter degeneration have been discussed by some scholars[5-7], who believe that vascular factors play a role in the development and progression of the disease have positive effects such as atherosclerosis and unstable carotid plaques. Many researchers[1,8,9] have found that hypertension is a major risk factor for cerebral small vessel ischemic disease, especially the development of white matter lesions. Other researchers[10,11] have found that white matter lesions are an independent risk factor for cognitive decline and are closely related to the development of stroke.

To date, no studies have focused on establishing clinical prognostic models of white matter lesions. Through research on real-world populations, we have established a clinical prognostic model of white matter lesions for the first time, aiming at early detection of high-risk groups of white matter lesions, in order to achieve early detection, early intervention, and early treatment. This has important clinical implications for patients with white matter lesions.

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Patients and Methods

Study Participants

The data we researched from Shin Takeo Hospital in Japan who underwent head MRI and blood tests during a comprehensive medical examination from April 1, 2016, to October 30, 2017 (Figure 1). We selected patients older than 60 years to investigate risk factors for white matter lesions in elderly patients. All patients underwent head MRI examination at Shin Takeo Hospital; information on blood biochemical examination and basic living habits, such as smoking and drinking, were collected.

Study Measures

We recorded general information on patients, including gender, age, body mass index, diastolic blood pressure, systolic blood pressure, carotid plaque score (PS). The blood biochemical examination mainly included high-density lipoprotein cholesterol, low-density lipoprotein Cholesterol, LH ratio (quotient of LDL and HDL), hemoglobin A1c (HbA1c), Triglyceride (TG), and blood glucose level (BS). Basic questions were: the frequency of smoking and drinking, the use of antihypertensive drugs, hypoglycemic drugs, and lipid-lowering drugs. All patients underwent head MRI examinations in Shin Takeo Hospital. According to the results of MRI, the patients were divided into white matter lesion group and non-white matter lesion group, and the two groups of patients were studied whether the above factors were statistically different.

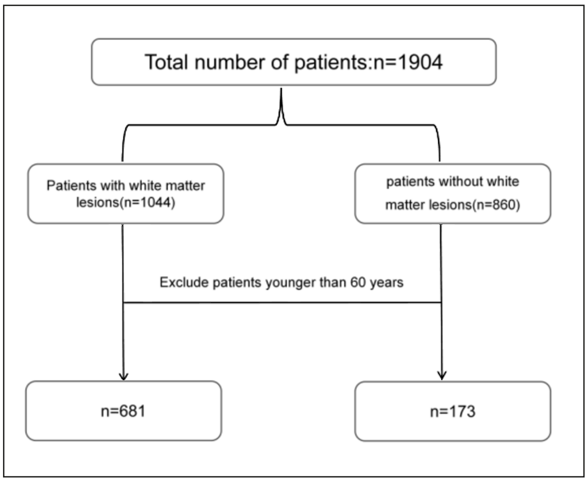

Figure 1. Flowchart of patients' selection.

Statistical Analysis

All statistical analyses were performed with version R4.1.0. Comparisons between continuous variables were performed using the *t*-test, while categorical variables were performed using the Chi-square test. *p*-values lower than 0.05 were considered statistically significant. In the univariate analysis, the meaningful variables are selected and used to establish the logistic regression model. Finally, the clinical accuracy and clinical practical value of the model were evaluated.

Results

Basic information for the study population (n=854, years older than 60) is presented in Table I. The average age of patients was 65.67 years in non-white matter lesions patients and 67.27 in white matter lesions patients; 44.8% (n=383) of the participants were male, while 55.2% (n=471) were female. In the questionnaire, 89.7% (n=766) of patients have the habit of smoking, among these people 152 in non-white matter lesions group, 614 in white matter lesions group. In terms of drinking, most people drink less than 180 ml (n=639), which accounts for 74.8% of the total. In the specific health of examination questionnaire, medications to reduce blood pressure showed significant differences in the two groups, but in insulin injection, medication to reduce a level of cholesterol and in metabolic syndrome aspects, the differences were not significant. In the blood biochemical examination, there were significant differences in high-density lipoprotein cholesterol (HDL), triglyceride (TG). But the differences were not significant in low-density lipoprotein cholesterol (LDL), LH (quotient of LDL and HDL), and HbA1c (hemoglobin A1c). It was surprising that although the average value of carotid artery plaque score (PS) and the number of plaque (N_plaque) in the white matter lesion group was greater than that in the non-white matter lesion group, but the difference was not statistically significant.

We used univariate analysis to select statistically significant study factors: Age, HDL, TG, SBP, DBP, Red_bp_med, PS, N_plaque. Multivariate analysis was then used to remove the effect of confounding factors. Finally, four meaningful factors (Table II) were screened out and included in our clinical prediction mod-

Table I. Patients' demographics.

	Total number (%)	NWML 173	WML 681	*p*
Age		65.67 ± 3.81	67.27 ± 3.99	< 0.001
Gender				0.62
Male	383 (44.8%)	81 (46.8%)	302 (44.3%)	
Female	471 (55.2%)	92 (53.2%)	379 (55.7%)	
Smoking				0.45
No	766 (89.7%)	152 (87.9%)	614 (90.2%)	
Yes	88 (10.3%)	21 (12.1%)	67 (9.8%)	
Drink_qt				0.80
< 180 ml	639 (74.8%)	127 (73.4%)	512 (75.2%)	
180-360 ml	160 (18.7%)	32 (18.5%)	128 (18.8%)	
360-540 ml	44 (5.2%)	11 (6.4%)	33 (4.8%)	
> 540 ml	11 (1.3%)	3 (1.7%)	8 (1.2%)	
Drink habit				0.28
Rarely	431 (50.4%)	93 (53.7%)	338 (49.6%)	
Sometimes	202 (23.7%)	33 (19.1%)	169 (24.8%)	
Everyday	221 (25.9%)	47 (27.2%)	174 (25.6%)	
LDL		123.05 ± 31.65	188.46 ± 29.72	0.47
HDL		59.90 ± 13.28	62.89 ± 15.48	0.020
LH		2.15 ± 0.71	2.04 ± 0.69	0.052
TG		112.94 ± 69.43	102.44 ± 57.56	0.041
HbA1c		5.89 ± 0.55	5.92 ± 0.59	0.65
BS		105.97 ± 18.02	106.08 ± 17.88	0.94
SBP		125.50 ± 11.83	129.25 ± 19.31	0.022
DBP		71.77 ± 11.83	74.17 ± 11.66	0.016
PS		1.44 ± 1.93	1.82 ± 2.50	0.062
N_plaque		0.82 ± 1.02	1.02 ± 1.26	0.054
BMI		23.11 ± 3.11	22.98 ± 3.29	0.63
Red_bp_med				0.001
No	527 (61.7%)	126 (72.8%)	401 (58.9%)	
Yes	327 (38.3%)	47 (27.2%)	280 (41.1%)	
Insulin				0.16
No	751 (87.9%)	158 (91.3%)	593 (87.1%)	
Yes	103 (12.1%)	15 (8.7%)	88 (12.9%)	
Red_cho_med				0.070
No	638 (74.7%)	139 (80.3%)	499 (73.3%)	
Yes	216 (25.3%)	34 (19.7%)	182 (26.7%)	
Metabolic				0.41
No	613 (71.8%)	131 (75.7%)	482 (70.8%)	
Reserve	86 (10.1%)	14 (8.1%)	72 (10.6%)	
Yes	155 (18.1%)	28 (16.2%)	127 (18.6%)	

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.

Table II. Multivariate analysis.

Variables	OR (95% CI)	*p*
Age	2.81 (1.74, 4.54)	< 0.001
HDL	1.31 (1.02, 1.68)	0.036
TG	0.91 (0.78, 1.05)	0.19
SBP	0.89 (0.65, 1.23)	0.49
DBP	1.47 (1.04, 2.08)	0.027
Red_bp_med	1.78 (1.21, 2.66)	0.0076
PS	0.98 (0.49, 1.97)	0.97
N_plaque	1.23 (0.48. 3.17)	0.67

el: age (OR=2.81, 95% CI: 1.74-4.54), HDL (OR=1.31, 95% CI:1.02-1.68), DBP (OR=1.47, 95% CI: 1.04-2.08) and Red_bp_med (OR=1.78, 95% CI: 1.21-2.66).

Construction of Clinical Prediction Model

Patients in this research were randomly divided into a validation group (n=173) and a training group (n=681), as shown in Table III. There was no significant difference between the basic characteristics data of the training group and the

Table III. Training and validation of patients.

Characteristics	Training group	Validation group	*p*
Age	66.84 ± 3.98	67.20 ± 4.05	0.24
Gender			0.56
Male	273 (45.50%)	110 (43.31%)	
Female	327 (54.50%)	144 (56.69%	)
Smoking			0.13
No	532 (88.67%)	234 (92.13%)	
Yes	68 (11.33%)	20 (7.87%)	
Drink_qt			0.09
< 180 ml	439 (73.17%)	200 (78.74%)	
180-360 ml	117 (19.50%)	43 (16.93%)	
360-540 ml	38 (6.33%)	6 (2.36%)	
> 540 ml	6 (1.00%)	5 (1.97%)	
Drink habit			0.06
Rarely	295 (49.17%)	136 (53.54%)	
Sometimes	136 (22.67%)	66 (25.98%)	
Everyday	169 (28.16%)	52 (20.47%)	
LDL	121.17 ± 30.69	122.48 ± 28.73	0.56
HDL	62.65 ± 15.38	61.41 ± 14.42	0.27
LH	2.05 ± 0.70	2.10 ± 0.68	0.30
TG	103.32 ± 53.40	107.52 ± 74.04	0.35
HbA1c	5.901 ± 0.59	5.92 ± 0.55	0.81
BS	106.12± 19.00	105.92 ± 15.01	0.88
SBP	128.46 ± 19.05	128.57 ± 19.65	0.93
DBP	73.64 ± 11.67	73.79 ± 11.89	0.86
PS	1.734 ± 2.40	1.76 ± 2.41	0.89
N_plaque	1.00 ± 1.25	0.94 ± 1.14	0.54
BMI	23.023 ± 3.27	22.96 ± 3.22	0.80
Red_bp_med			0.79
No	372 (62.00%)	155 (61.02%)	
Yes	228 (38.00%)	99 (38.98%)	
Insulin			0.13
No	521 (86.83%)	230 (90.55%)	
Yes	79 (13.17%)	24 (9.45%)	
Red_cho_med			0.46
No	444 (74.00%)	194 (76.38%)	
Yes	156 (26.00%)	60 (23.62%)	
Metabolic			0.73
No	431 (71.83%)	182 (71.65%)	
Reserve	63 (10.50%)	23 (9.06%)	
Yes	106 (17.67%)	49 (19.29%)	
WML			0.40
No	117 (19.50%)	56 (22.05%)	
Yes	483 (80.50%)	198 (77.95%)	

validation group. We use the RMS package in R 4.1.0 to build a nomogram prediction model based on the training group and verify the stability of the model with the validation group. C-index (Harrell's concordance index) and Calibration curves were used to estimate the accuracy and consistency of the nomogram model.

The nomogram model was built based on the four characteristics of the training group: age, HDL, DBP, and Red_bp_med (Figure 2). It was clear that age had the greatest impact on white matter lesions, and that it was more likely for older patients to develop white matter lesions.

Evaluation of the Application Value of Clinical Predictive Models

The receiver operating curve (ROC) (Figures 3A and 3B) and calibration curve were plotted (Figures 3C and 3D) to verify the accuracy and discrimination of this model. The area under the curve (AUC) in the training group is 0.625, while 0.729 in the validation group, which suggests that our model has good accuracy. The calibration curve of training group and validation group shows that there was excellent consistency between the predicted survival probability and the actual survival probability. The decision curve

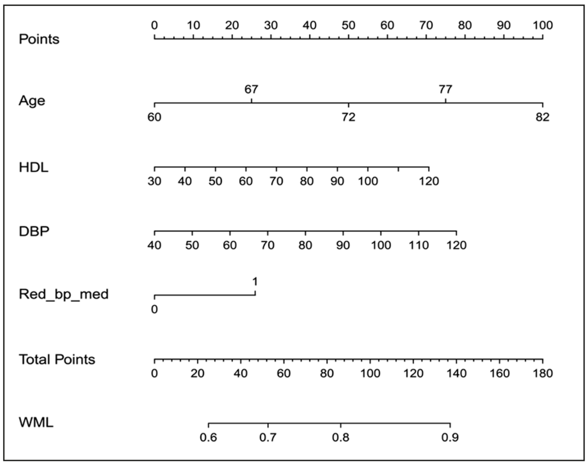

Figure 2. Nomogram for cerebral white matter lesions based on training group.

(Figures 4A and 4B) and clinical impact curve (Figures 4C and 4D) were drawn to verify the clinical practical value, which implies that the clinical prediction model has good clinical application value.

Discussion

With the development of society and the improvement of medical conditions, the aging of the population also brings more and more age-related disease, such as white matter lesion[12]. Therefore, early detection, early prediction, and early treatment were of great significance to age-related diseases[13]. For this study, we divide patients older than 60 years into a white matter lesion group and a non-white matter lesion group. Through the logistics regression model, we screened out the risk factors related to white matter lesions. Finally, we concluded that age, HDL, diastolic blood pressure (DBP), and the use of antihypertensive drugs were risk factors for white matter lesions.

Based on these risk factors, we constructed a nomogram for predicting the incidence of white matter lesions, and then we established a clinical prediction model to evaluate its accuracy. The results show that the prediction model has good clinical application value.

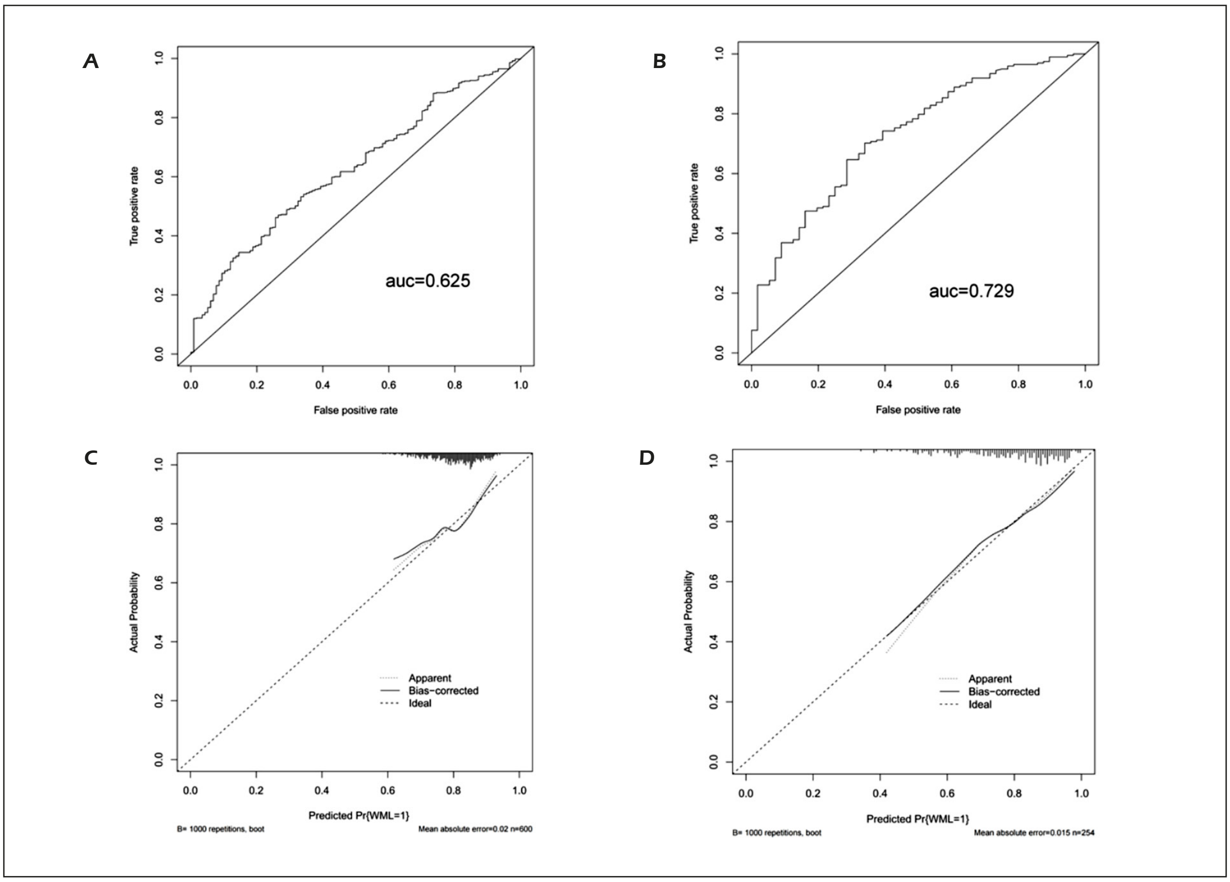

Figure 3. Receiver operating curve (ROC) and area under the curve (AUC) in training group (**A**) and validation group (**B**). Calibration curve of training group (**C**) and validation group (**D**).

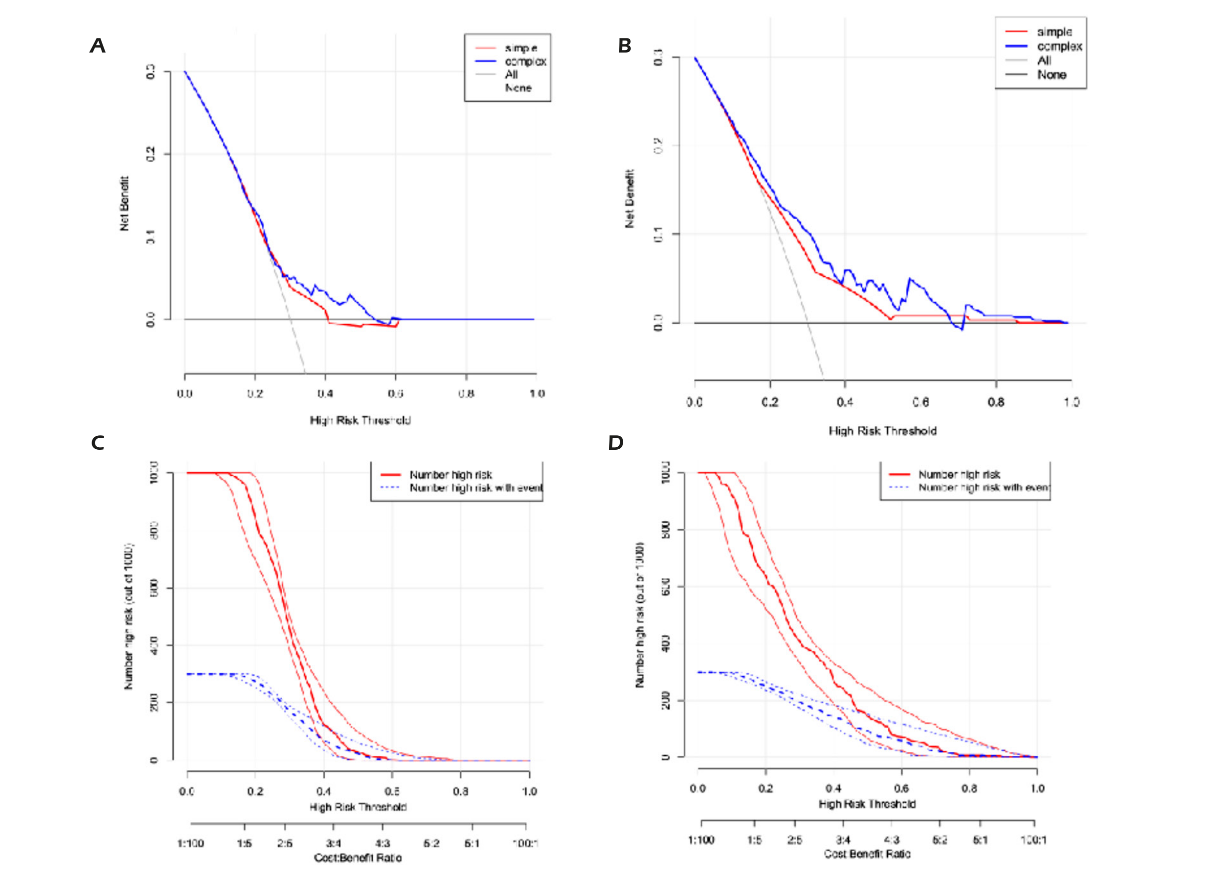

Figure 4. Decision curve of training group (**A**) and validation group (**B**). Clinical impact curve of training group (**C**) and validation group (**D**).

Our study found that it was more likely for older patients to develop white matter lesions. In addition, diastolic blood pressure, high-density lipoprotein, and whether taking medication to reduce blood pressure are independent risk factors for cerebral white matter lesions.

As the aging population increases, so does the incidence of white matter lesions, and more and more studies focus on this area[4,9,12,14,15]. Shinkawa et al[16] built a model based on clinical examination data, for the prediction of the incidence of cerebral white matter lesions, finding that age, gender, plaque score (PS), LDL, and systolic blood pressure (SBP) have great effect on white matter lesions, which is similar to our conclusions. Nevertheless, our research object is only for the elderly over 60 years old. Bots et al[17] found that white matter lesions were associated with atherosclerosis. With the increase of carotid intima-media thickness, the incidence of white matter lesions increased significantly. In the same way, Leeuw et al[18] predicted that aortic atherosclerosis in midlife was significantly associated with the presence of periventricular white matter lesions after 20 years. Pantoni et al[4] carried out a study and found that diabetes mellitus and hypertension were related to white matter lesions.

Limitations

Our study also has many limitations. First, the data available in Dryad Digital Repository databases are observational. This is an observational study with the general limitations of observational studies, and the allocation of objects is arbitrary and lacks randomization. Second, for the items in the questionnaire, such as taking hypoglycemic and antihypertensive drugs, we can only know the drugs taken by the patients, but not the names and dosages of these drugs, which has a great impact on our research. In addition, other important factors are not easily available in the Dryad Digital Repository database, which includes the patient's hobbies, occupation, the habit of staying up late, etc. Usually, these factors have a greater impact on white matter lesions. Therefore, it is necessary to conduct high-quality prospective studies for a better understanding of the influencing factors of white matter lesions.

Conclusions

Our research is a large-scale population-based study of patients in Shin Takeo Hospital. It was confirmed that age, HDL, diastolic blood pressure (DBP) and the use of antihypertensive drugs had greatest influences on the incidence of white matter lesions. However, our findings should be confirmed by further large-scale prospective cohort studies.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Informed Consent

The data of patients was searched in Dryad Digital. It is a public database, which means that the patient information in it can be directly used for scientific research and published in the form of papers.

Availability of Data and Materials

The data of patients was searched in Dryad Digital are freely available.

Authors' Contribution

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

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