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ESTABLISHMENT OF A RISK PREDICTION MODEL FOR MILD COGNITIVE IMPAIRMENT AMONG ELDERLY CHINESE

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Abstract: *Background:* Mild cognitive impairment (MCI) is a transitional stage of cognitive function between normal aging and dementia. Substantial variations in the prevalence of MCI in different countries have been studied including China. In this study, we established a prediction system to assess the risk of MCI among the elderly in China. *Methods:* The Rothman-Keller model was conducted on the basis of the risk factors of MCI obtained by the combined results of a meta-analysis. The accuracy of the model was verified using actual population data. *Results:* A total of 1826 subjects as a verification set were enrolled in this study in February 2019. There were statistically significant differences in the combined results of 10 risk factors including hypertension, diabetes, educational level, hyperlipidemia, smoking, physical exercise, living alone, stroke, drinking and heart disease ($P<0.05$). The area under the curve (AUC) of the actual data and the predictive results of this model was 0.859 (95%CI: 0.812-0.906, $P<0.05$), the sensitivity was 86.6% and the specificity was 76.5%. *Conclusions:* This model performs an effective prediction that may be applied to the primary prevention for patients with MCI, helping to reduce the risk of MCI.

Key words: Mild cognitive impairment, elderly Chinese, Rothman-Keller model, prediction system.

Introduction

With rapid changes in the demographic structure, the proportion of the elderly is gradually increased especially in developing countries that will lead to more the older adults being at risk of dementia. Mild cognitive impairment (MCI), a transitional stage of cognitive function between normal aging and dementia (1), is characterized by cognitive decline exceeded the expectation of age and education level without obvious functional limitations (2). As a heterogeneous disease, MCI is diverse in etiology, clinical manifestation and prognosis. Compared with the healthy individuals, patients with MCI may have several troubles in completing complex daily works in spite of functional independence. Studies have demonstrated that MCI was often discovered among the older adults in clinic. Previous reporters showed that the occurrence of MCI would increase risk of dementia (3).

At present, evidences indicate that the incidence of MCI has wide differences (4, 5), which may be correlative with diverse diagnostic criteria applied (6-8). Recent researches have mentioned that the prevalence of MCI is ranged from 6.5%-39.1% among the older adults in America, Australia, Bulgaria, Mexica and Japan (9-15). It is estimated that the number of the elderly in China will reach a peak of 487 million, accounting for 34.9% of the total population in 2050 (16). Therefore, it is crucial to identify the prevalence of MCI that assesses the potential disease burden in China, and presents the interventions to prevent or alleviate the development of dementia. Early protocols suggested that the cognitive impairment was screened using the Mini-Mental State Examination (MMSE) (17-19) or the Montreal Cognitive Assessment (MOCA) (20-22) which were lack of standard definitions of test failure. It is necessary to understand the etiologies of MCI, and to the best of our knowledge, the risk of MCI is closely associated with the age, education and chronic diseases. The Rothman-Keller model applied for evaluating the risk of chronic diseases was proposed by Rothman and Keller (23) in 1972, and this model is a common multiple-factor disease prediction model utilized for individuals in recent years, which considers the independent and interactive effects of influence factors. However, the prediction of MCI risk among elderly Chinese based on Rothman-Keller model has never been reported.

Accordingly, we established a prediction system to assess the risk of MCI among the elderly in China, which would conduct early interventions to improve the independence, cognitive function and quality of life in individuals with MCI.

Methods

Patients

Cluster random sampling method was used to select four community health service centers from Baoshan District of Shanghai. This research was approved by the Institutional Review Board (IRB) of Shanghai First People's Hospital Baoshan Branch (approval number: 2016Y02). People over 60 years old were included in this study. The exclusion criteria were as follows: (1) patients with malignant tumors; (2) patients with dysaudia or visual impairment; (3) patients with a history of psychosis, hepatic encephalopathy and post-traumatic stress disorder. Finally, a total of 1826 people as a verification set were enrolled in this research on February 2019.

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Diagnostic criteria

The diagnostic criteria of MCI were based on Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-V) published by American Psychiatric Association (2013) (24): (1) MCI with subjective and objective examinations; (2) cognitive decline in one or more domains including complex attention, executive function, learning and memory, language, perception-activity and social cognition; (3) unaffected daily living ability; (4) failing to meet the diagnostic criteria for dementia; (5) excluding other systemic diseases that may cause brain function decline; (6) MOCA scores at 22-26.

Data extraction

The risk factors of MCI were confirmed on the basis of a meta-analysis. All the patients' information including basic characteristics (age and educational level), lifestyle (smoking, drinking, physical exercise and living alone) and disease history (hypertension, diabetes, hyperlipidemia, stroke and heart disease) were noted in the present study.

Rothman-Keller model

The predictive system of MCI was based on Rothman-Keller model (23). The previous research suggested that the incidence of MCI in the elderly was 2.17% (25). The odds ratio (OR) could estimate the relative ratio (RR) with low incidence of MCI.

The calculation methods of Rothman-Keller model are as follows:

(1) The baseline incidence ratio (ρ)

$$\rho = \frac{1}{RR_1 \times P_1 + \cdots + RR_i \times P_n} = \frac{1}{\sum_{i=1}^{n} RR_i \times P_i}$$

Or

$$\rho = 1 - PAR\%$$

$$PAR\% = \frac{P_i(RR_i - 1)}{P_i(RR_i - 1) + 1} \times 100\%$$

Pi: the exposure rate of a risk factor in the whole population; RRi: the relative risk of a risk factor; PAR%: the percentage of population attributable risk.

(2) Risk score (S)

$$S = \rho \times RR_i$$

(3) Total score (T)

$$T = (M_1 - 1) + (M_2 - 1) + \cdots + (M_i - 1) + N_1 \times N_2 \times \cdots \times N_i$$

Mi: the risk score of S≥1; *Ni*: the risk score of S<1.

(4) Individual risk of MCI (R)

$$R = M_{MCI} \times T$$

M_{MCI}: the incidence of MCI.

Statistical analysis

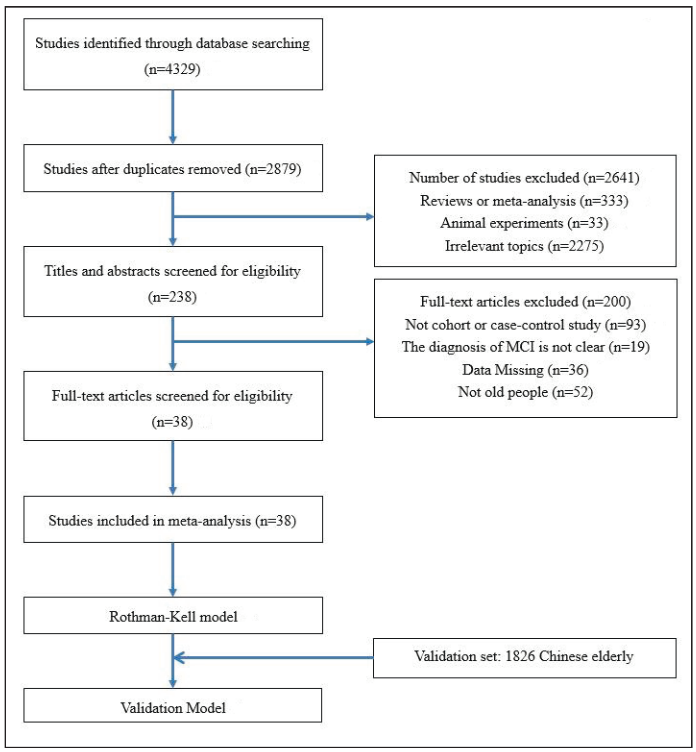
The statistical analysis was performed by STATA 14.0 software (Stata Corporation, College Station, TX, USA) and R software (version 3.5.0). Association between MCI and risk factors was reported as odds ratios (ORs) and 95% confidence intervals (CIs) by the fixed effect model and the random-effects model. Publication bias was performed with Begg's test and Egger's test (n≥10). The receiver operating characteristic (ROC) curves were conducted to assess the performance of the risk prediction Rothman-Keller model and the multivariate Logistic regression model. $P<0.05$ was considered as significant.

Results

The risk factors of MCI

A total of 4329 citations were screened in this study. 38 articles were fully evaluated for eligibility after removing duplications, laboratory studies, reviews and meta-analyses, including 4 cohort researches and 34 case-control studies from 2006 to 2018 (26-63). The subjects were all from China, containing 21741 cases and 41924 controls. The flowchart of the study selection process was exhibited in Fig. 1.

Figure 1
The flowchart of the study selection process



As shown in Table 1, there were statistically significant differences in the combined results of 10 risk factors including

Table 1
The combined results of various risk factors

Risk factors	No. of study	Case Exposure/ Total	Control Exposure/ Total	Sample size	Fixed effect model			Random-effects model			References
					OR	95%CI	*P*	OR	95%CI	*P*	
Hypertension	25	2659/5027	3423/9000	14027							27, 30, 34-38,43, 44, 46-49, 52-56, 59-63
Yes					1.670	1.547-1.802	0.001	1.880	1.509-2.344	0.001	
No					1			1			
Diabetes	18	1190/3360	1596/7121	10481							30, 35, 38, 40, 46, 48-50, 52-55, 57, 59-63
Yes					1.549	1.3963-1.719	0.001	1.627	1.24-2.315	0.001	
No					1			1			
Educational level	15	1717/2378	4346/5200	7578							26, 29, 31-33, 38,41-43, 46, 49, 51, 55, 58, 61, 62
≤middle school					1.864	1.572-2.212	0.001	2.068	1.135-3.769	0.018	28, 36-38, 44, 49, 55, 60, 61
>middle school					1			1			
Hyperlipidemia	9	941/2107	1027/3730	5837							
Yes					1.779	1.562-2.025	0.001	1.764	1.309-2.377	0.001	
No					1			1			
Smoking	10	547/1414	400/1557	2971							27, 29, 45, 49, 52, 56, 58, 61-63
Yes					2.132	1.791-2.537	0.001	1.950	1.261-3.015	0.003	
No					1			1			
Physical exercise	7	910/1526	1281/2051	3577							29-31, 45, 46, 51, 61
Yes					1			1			
No					0.914	0.794-1.051	0.205	2.282	1.05-4.957	0.037	
Living alone	7	1045/1478	3070/3660	5138							25,32, 33, 38, 39, 48, 49, 52
Yes					2.171	1.868-2.523	0.001	2.052	1.433-2.938	0.001	
No					1				1		
Stroke	5	219/1039	389/3238	4277							25, 43, 48, 51, 59
Yes					1.879	1.555-2.272	0.001	3.165	1.417-7.071	0.005	
No					1				1		
Drinking	8	321/1105	282/1527	2632							30, 38, 43, 52, 56, 57, 61, 63
Yes					2.026	1.663-2.469	0.001	1.897	1.222-2.943	0.004	
No					1			1			
Heart disease	5	431/955	338/1235	2190							26, 38, 43, 53, 54
Yes					2.144	1.782-2.579	0.001	2.407	1.569-3.691	0.001	
No					1			1			
Age	5	552/1352	2143/3605	4957							30, 38, 48, 49, 55
≤70					2.389	2.088-2.726	0.001	1.633	0.737-3.618	0.227	
>70					1			1			

hypertension, diabetes, educational level, hyperlipidemia, smoking, physical exercise, living alone, stroke, drinking and heart disease, and the values of combined OR were 1.880, 1.627, 2.068, 1.764, 1.950, 2.282, 2.052, 3.165, 1.897 and 2.407, respectively ($P<0.05$). Through the sensitivity analysis which the fixed effect model transfused to the random-effects model, the combined effect of age was unstable, and the combined results of the fixed effect model were statistically significant (OR=2.389, 95%CI: 2.088-2.726, $P<0.001$). While the merged results of the random-effects model were no statistical differences (OR=1.633, 95%CI: 0.737-3.618, $P=0.227$). Thus, the age was excluded in the model. Four factors containing hypertension, diabetes, educational level and smoking which the included studies were no less than 10, performed the publication bias using Begg's test and Egger's test. Our results showed that no publication bias was discovered in these four factors.

Table 2
The risk scores for predicting MCI among elderly Chinese

Risk factors	OR	P_i	PAR%	ρ	Risk score
Hypertension					
Yes	1.88	0.3803	0.2508	0.7492	1.4086
No	-				0.7492
Diabetes					
Yes	1.627	0.2241	0.1232	0.8768	1.4267
No	-				0.8768
Educational level					
≤middle school	2.068	0.8358	0.4716	0.5284	1.093
>middle school	-				0.5284
Hyperlipidemia					
Yes	1.764	0.2753	0.1738	0.8262	1.4574
No	-				0.8262
Smoking					
Yes	1.95	0.2569	0.1962	0.8038	1.5674
No	-				0.8038
Physical exercise					
Yes	-				0.6751
No	2.282	0.3754	0.3249	0.6751	1.5405
Living alone					
Yes	2.052	0.1612	0.145	0.855	1.754
No	-				0.855
Stroke					
Yes	3.165	0.1201	0.2064	0.7936	2.5117
No	-				0.7936
Drinking					
Yes	1.897	0.1847	0.1421	0.8579	1.627
No	-				0.8579
Heart disease					
Yes	2.407	0.2737	0.278	0.722	1.7378
No	-				0.722

The parameters of Rothman-Keller model

The exposure levels of these pathogenic factors were respectively obtained to calculate the average exposure rate (P_i) through various studies. The combined OR values (presented as RR_i) of each risk factor were assessed via merging the risk value of risk factors. The parameters of Rothman-Keller model for elderly Chinese with MCI were shown in Table 2.

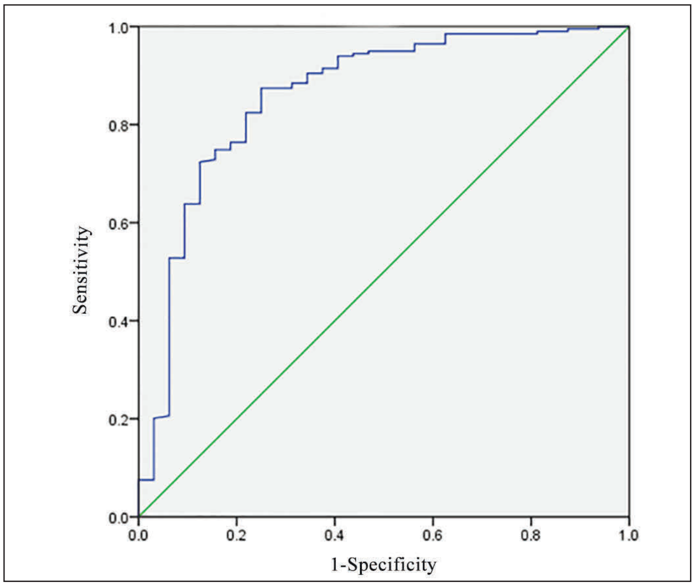
The risk calculation of individuals

On the basis of the risk scores in Table 2, the combined risk scores were obtained according to the individuals' situation (referring to Formula 3). For example, a 65-year-old people (subject A) without hyperlipidemia, living alone and heart disease, had several characteristics including hypertension, educational level >middle school, smoking, regularly physical exercise and drinking. The risk scores of these mentioned risk factors in Table 3 were 0.8262, 0.855, 0.722, 1.4086, 0.5284, 1.5674, 1.627 and 0.6751, respectively. Therefore, the combined risk score of subject A= (1.4086-1) + (1.5674-1) + (1.627-1) + 0.8262, 0.855, 0.722, 0.5284, 0.6751= 1.784. The previous study revealed that the incidence of MCI in the elderly was 2.17% (24). Thereby, the MCI risk of subject A= 2.17% x 1.784= 0.0387.

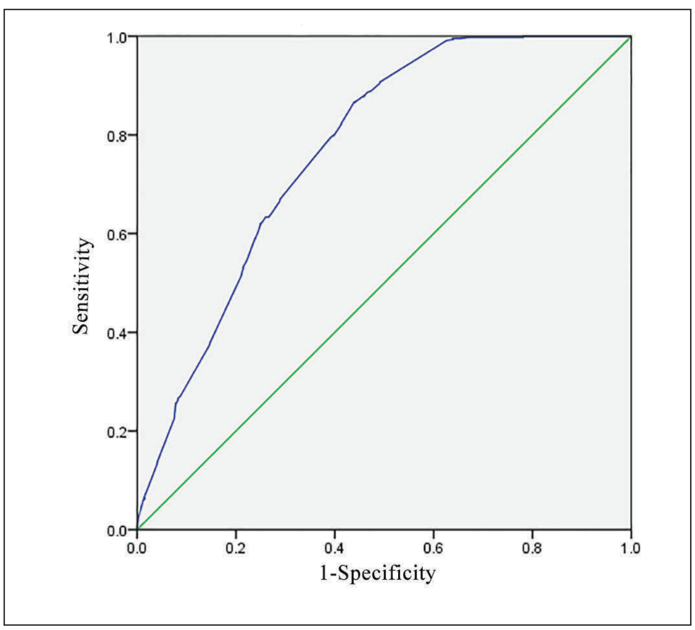
Figure 2

The predictive analysis of different models for MCI among the elderly. (A) Rothman-Keller model and (B) multivariate Logistic regression model

A



B



Model verification

In the present study, 1826 elderly Chinese as a verification set were screened by a random sample survey. Of these subjects, 442 cases were diagnosed as MCI containing 195 males and 247 females, and the average age was 78.22±6.64 years. 1384 normal persons (606 males and 778 females) were included, with the mean age of 71.39±4.90 years. The risk grades of the elderly with MCI were verified using the predictive results of Rothman-Keller model. The factor of onset risk over the median was defined as a high-risk factor with assignment 1, and the factor below the median was defined as a low-risk factor with assignment 0. The predictive analysis of Rothman-Keller model for MCI among the elderly was depicted in Fig. 2A. The area under the curve (AUC) of the actual data and the predictive results of this model was 0.859 (95%CI: 0.812-0.906), the sensitivity was 86.6% and the specificity was 76.5%. As shown in Fig. 2B, the AUC of multivariate Logistic regression model was 0.770 (95%CI: 0.745-0.791), the sensitivity and specificity were 86.7% and 56.1%, respectively. There were significant differences between the two models ($Z=2.005$, $P<0.05$). Our findings demonstrated that the predictive performance of Rothman-Keller model outperformed the multivariate Logistic regression model for MCI among the elderly Chinese.

Discussion

In the present study, we established a risk assessment model (Rothman-Keller model) of MCI for elderly Chinese based on a meta-analysis, and the actual data were conducted to validate the effects of this model. To the best of our knowledge, however, the prediction model has been never applied for predicting MCI among elderly Chinese, and we supposed it may be effective for the elderly to prevent the occurrence of MCI as early as possible.

MCI is a common symptom among old adults in clinic, and the prevalence of MCI in the elderly over 65 years old is 10%-20% (64). More than half of MCI patients will progress to dementia within 5 years, and only the minority of patients can maintain stable or even normal cognitive function (2). The previous study reported that approximately 10% of MCI patients were converted to Alzheimer's disease (AD) every year, and MCI was 10 times more likely to develop dementia than healthy people (65). Early researches suggested that the occurrence of MCI was closely associated with the age, education and chronic diseases (9, 11, 66). In the presented research, the main factors included characteristics, lifestyles and current diseases. The data from our study demonstrated that multiple indicators including hypertension, diabetes, educational level, hyperlipidemia, smoking, physical exercise, living alone, stroke, drinking and heart disease, can serve as the risk factors to predict MCI among Chinese elderly population. It is an approach of the causal prophylaxis for MCI patients to intervene unhealthy lifestyles and dietary habits. In this study, our findings found that the predictive performance of Rothman-Keller model was superior to the multivariate Logistic regression model for MCI among the elderly Chinese. The risk calculation of individuals was conducted based on the risk scores of Table 2. According to the Rothman-Keller model, the risk of MCI was obtained among the elderly. It is of clinical significance to improve the development of MCI among elderly Chinese. We suggested that high-risk groups should strengthen physical exercises, reduce the intake of high-fat, high-cholesterol and high-carbohydrate food, take regularly antihypertensive and antidiabetic drugs, and quit smoking and drinking. Furthermore, this prediction model may be used to assess the risk of the MCI elderly after intervention.

In addition, we evaluated the quality of 38 literatures according to the modified Newcastle-Ottawa Scale (NOS) score in this study, of which included 19 high quality researches and 19 low-and-moderate quality articles. It is indicated that large-scale and well-designed cohort studies should be investigated in the future, meanwhile be focused on several factors which may be greatly contributed to the prediction model, to explore the MCI risk. Then new high quality studies included in the model will be analyzed to further improve and increase the applicability of the model. Rothman-Keller model, however, is merely appropriate for the Chinese elderly, whether it can be extrapolated to other people needs further verification.

MMSE is the most widely used cognitive function assessment scale which is not sensitive to MCI. Nasreddine et al (67) finalized the MOCA scale through partially modifying the MMSE scale, which was more sensitive and specific for rapid screening of MCI patients than the MMSE scale. However, there are several differences in cultural backgrounds and living habits between the East and the West. The scale is indigestible to the Chinese people due to unfamiliar words, strange illustrations and not easily acceptable for the subjects, and the specific operations are controversial and difficult so as to affect the testing results. Furthermore, the scale is also influenced by various factors, including educational levels, skills and experience of examiners, checked environment, as well as emotional and mental state of the subjects. The Rothman-Keller model as a multiple-factor disease prediction model, is also applied for individuals in recent years, which considers the independent and interactive effects of influence factors. Our investigation extracted 10 pathogenic factors, of which 4 factors containing hypertension, diabetes, educational level and smoking were predominantly considered in diverse protocols, and our research validated the prediction model with actual data to judge the predictive power and accuracy of the model.

The advantages of this study were included as follows: Firstly, we established a risk assessment model for the Chinese elderly with MCI based on a meta-analysis. Secondly, Rothman-Keller model was first applied for predicting MCI among the elderly. Additionally, the limitation of this study was that the local population were collected to verify the efficiency of the risk assessment model. Thus, it needs multi-center, large-scale and well-designed studies to further evaluate the prediction model.

Conclusion

In summary, we established a risk assessment model to predict the risk of MCI that may be applied to the primary prevention for the elderly in China, helping to reduce the occurrence of MCI.

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Conflict of interest: All authors declare that they have no conflict of interest.

Ethical standard: This research was approved by the Institutional Review Board of Shanghai First People's Hospital Baoshan Branch (approval number: 2016Y02).

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