Development and Validation of a Risk Prediction Model for Silent Cerebral Infarction in Maintenance Hemodialysis Patients: A Multicenter Study Postprint

Authors: Li Qiuling, Tang Wenwu, Yu Yiwen, Deng Huan, Yang Xiaohua, Chen Xiaoxia, Ji Yifei, Ji Yifei

Date: 2024-05-10T00:00:00+00:00

Abstract

Background Maintenance hemodialysis (MHD) patients have a high incidence of silent brain infarction (SBI), which represents the preclinical stage of symptomatic cerebral infarction and vascular dementia. Therefore, it is essential to investigate the risk of SBI in MHD patients to enable early identification and reduce adverse outcomes.

Objective To investigate the risk factors for SBI in MHD patients, construct a predictive model, and evaluate its performance.

Methods A total of 486 MHD patients from four centers (Nanchong Central Hospital, Guangyuan Central Hospital, Suining Central Hospital, and Peng' an County People' s Hospital) between January 2017 and October 2022 were enrolled. Using the development of SBI in MHD patients as the outcome event, they were divided into an SBI group (n=102) and a non-SBI group (n=384), and baseline characteristics were compared between the two groups. Patients were randomly divided into a training set (n=340) and a validation set (n=146) at a 7:3 ratio. Predictive variables were identified through LASSO regression and multivariate Logistic regression analysis, and a risk prediction model for SBI in MHD patients was constructed with a nomogram drawn. The predictive performance, accuracy, and clinical application value of the model were evaluated using the area under the receiver operating characteristic (ROC) curve, calibration curve, and decision curve analysis.

Results SBI occurred in 70 (20.6%) MHD patients in the training set and 32 (21.9%) patients in the validation set. LASSO regression combined with multivariate Logistic regression analysis revealed that age (OR=1.027, 95%CI=1.005~1.050), alcohol consumption history (OR=4.487,

95%CI=2.075~9.706), BMI (OR=1.082, 95%CI=1.011~1.156), insufficient or excessive sleep (OR=6.286, 95%CI=3.560~11.282), history of chronic diseases (chronic obstructive pulmonary disease, diabetes mellitus, chronic hepatitis B) (OR=1.873, 95%CI=1.067~3.347), serum lactate level (OR=1.452, 95%CI=1.152~1.897), urea reduction ratio (URR) (OR=0.922, 95%CI=0.875~0.970), and history of antiplatelet medication use (OR=0.149, 95%CI=0.030~0.490) were independent influencing factors for SBI in MHD patients (P<0.05). A prediction model incorporating these eight influencing factors was constructed and a nomogram was drawn. The area under the ROC curve of this prediction model was 0.816 (95%CI=0.759~0.854) in the training set and 0.808 (95%CI=0.723~0.893) in the validation set, with the calibration curve demonstrating good consistency. The DCA curve indicated that this model could maximize clinical benefit for patients.

Conclusion The risk prediction model for SBI in MHD patients established based on age, alcohol consumption history, BMI, insufficient or excessive sleep, history of chronic diseases (chronic obstructive pulmonary disease, diabetes mellitus, chronic hepatitis B), serum lactate level, URR, and history of antiplatelet medication use demonstrates good predictive performance and clinical utility, and is expected to enable accurate and personalized assessment of SBI risk in MHD patients and facilitate early intervention to reduce incidence.

Full Text

Establishment and Validation of a Risk Prediction Model for Silent Brain Infarction in Maintenance Hemodialysis Patients: A Multicenter Study

Li Qiuling[1], Tang Wenwu[2], Yu Yiwen[1], Deng Huan[1], Yang Xiaohua[3], Chen Xiaoxia[4], Ji Yifei[1]*

[1]Department of Neurology, Nanchong Central Hospital Affiliated to North Sichuan Medical College, Nanchong Central Hospital, Nanchong 637000, China
[2]Department of Nephrology, Nanchong Central Hospital Affiliated to North Sichuan Medical College, Nanchong Central Hospital, Nanchong 637000, China
[3]Department of Nephrology, Guangyuan Central Hospital, Guangyuan 628000, China
[4]Department of Nephrology, Suining Central Hospital, Suining 629000, China

Corresponding author: Ji Yifei, Chief physician; E-mail: jiyifei_{2003}@163.com

---

Abstract

Background: Maintenance hemodialysis (MHD) patients have a high incidence of silent brain infarction (SBI), which represents a preclinical stage of symptomatic stroke and vascular dementia. Therefore, exploring SBI risk in MHD

patients is essential for early identification and reduction of poor prognosis.

Objective: To investigate risk factors for SBI occurrence in MHD patients, construct a prediction model, and evaluate its performance.

Methods: We enrolled 486 MHD patients from four centers (Nanchong Central Hospital, Guangyuan Central Hospital, Suining Central Hospital, and Peng' an County People' s Hospital) between January 2017 and October 2022. Patients were divided into SBI group (n=102) and non-SBI group (n=384) based on SBI occurrence. Patients were randomly assigned to a modeling set (n=340) and validation set (n=146) at a 7:3 ratio. Predictor variables were identified through LASSO regression and multivariate logistic regression analysis. A risk prediction model for SBI in MHD patients was constructed and presented as a nomogram. Model predictive performance, accuracy, and clinical utility were evaluated using area under the ROC curve, calibration curve, and decision curve analysis.

Results: SBI occurred in 70 patients (20.6%) in the modeling set and 32 patients (21.9%) in the validation set. LASSO regression combined with multivariate logistic regression analysis identified eight independent influencing factors: age (OR=1.027, 95%CI=1.005-1.050), alcohol consumption history (OR=4.487, 95%CI=2.075-9.706), BMI (OR=1.082, 95%CI=1.011-1.156), insufficient or excessive sleep (OR=6.286, 95%CI=3.560-11.282), chronic disease history (chronic obstructive pulmonary disease, diabetes, chronic hepatitis B) (OR=1.873, 95%CI=1.067-3.347), serum lactate level (OR=1.452, 95%CI=1.152-1.897), urea reduction ratio (URR) (OR=0.922, 95%CI=0.875-0.970), and antiplatelet medication history (OR=0.149, 95%CI=0.030-0.490) (P<0.05). The prediction model incorporating these eight factors yielded areas under the ROC curve of 0.816 (95%CI=0.759-0.873) in the modeling set and 0.808 (95%CI=0.723-0.893) in the validation set. Calibration curves demonstrated good consistency, and DCA curves indicated the model could provide maximum clinical benefit.

Conclusion: The SBI risk prediction model for MHD patients based on age, alcohol consumption history, BMI, sleep duration, chronic disease history, serum lactate level, URR, and antiplatelet medication history demonstrated good predictive performance and clinical utility. This model may enable accurate, personalized risk assessment and facilitate early intervention to reduce SBI incidence in MHD patients.

Keywords: Silent brain infarction; Maintenance hemodialysis; Prediction model; Multicenter; Risk factors

1. Subjects and Methods

1.1 Study Subjects

We enrolled 521 MHD patients from four centers (Nanchong Central Hospital, Guangyuan Central Hospital, Suining Central Hospital, and Peng' an County People' s Hospital) between January 2017 and October 2022. The inclusion criteria were: (1) age >18 years; (2) CKD stage 5 dialysis patients meeting the Kidney Disease: Improving Global Outcomes (KDIGO) criteria, receiving regular dialysis for $ $3 months at $ $2 sessions/week; (3) completion of brain CT or MRI around baseline data collection. Exclusion criteria were: (1) history of transient ischemic attack (TIA) or stroke before first SBI diagnosis; (2) history of mental illness or dementia; (3) incomplete clinical data.

SBI diagnosis followed the *Chinese Consensus on Diagnosis and Treatment of Silent Brain Infarction*: (1) CT and/or MRI showing cerebral infarction or softening lesions; (2) absence of corresponding clinical manifestations; (3) exclusion of non-vascular diseases and cerebral hemorrhage-induced softening lesions; (4) new infarcts identified by high signal on DWI; (5) no history of cerebral infarction or TIA.

According to reports, the incidence of SBI in MHD patients is 49.6% [9]. Following TRIPOD guidelines and assuming an events-per-variable (EVP) ratio of 10, we calculated that 161 cases were needed for the modeling set [(8$×$10)/49.6%]. The final modeling set included 340 patients. This retrospective study was approved by the Ethics Committee of Nanchong Central Hospital (Approval No.: [2023] 伦审研第 (072) 号).

1.2 Data Collection and Definitions

1.2.1 Data Collection: We systematically searched PubMed, CNKI, Wanfang Data, and VIP databases to identify relevant literature and compiled a clinical data collection form based on guidelines and consensus [7-8,11]. Thirty variables were included: (1) Basic and clinical data from electronic medical record systems and physical examination systems, including gender, age, smoking history, alcohol consumption history, BMI, sleep duration, pulmonary infection, chronic disease history [chronic obstructive pulmonary disease (COPD), diabetes, chronic hepatitis B], coronary heart disease, atrial fibrillation history, NYHA heart failure classification, hypertension grade, and antiplatelet medication history; (2) Dialysis-related data from dialysis management systems, including dialysis age, dialysis cause, vascular access, dialysis duration, residual renal function (calculated using the Cockcroft-Gault formula), ultrafiltration rate, and urea reduction ratio (URR); (3) Laboratory measurements from fasting venous blood samples collected before MHD treatment in a dry weight state after 8-hour overnight fasting, including hematocrit, total cholesterol, triglycerides, high-density lipoprotein cholesterol, homocysteine, parathyroid hormone, lactate, serum calcium, and serum phosphorus; (4) Imaging examinations completed in dry weight state, including cardiac valve calcification. All imaging

data were collected and analyzed by radiology departments at each center. According to medical quality control requirements, MHD patients undergo annual brain CT or MRI, ensuring complete imaging data. All blood samples were analyzed at laboratory departments of each center.

1.2.2 Definitions and Quality Control: Smoking history was defined as total consumption >100 cigarettes [13]. Alcohol consumption history was defined as $ $12 standard drinking units (10 g pure alcohol per unit) according to WHO recommendations [14]. Insufficient sleep was defined as <5 h/day and excessive sleep as >9 h/day [15]. Data were collected from hospital electronic medical record systems by two uniformly trained researchers. Patients with incomplete data were excluded. Ten percent of data were randomly reviewed monthly to verify completeness, accuracy, and authenticity. Complete data were stored by designated personnel.

1.3 Statistical Analysis

Statistical analysis was performed using SPSS 26.0 and R version 4.2.2. Normally distributed continuous data were expressed as mean±SD and compared using independent samples t-test. Non-normally distributed continuous data were expressed as median (P25, P75) and compared using Mann-Whitney U test. Categorical data were expressed as percentages and compared using ^{2} test.

Pearson correlation coefficient (r) was used to assess potential collinearity among candidate predictors, with r>0.7 indicating potential collinearity. After strict data filtering and preprocessing, patients were randomly divided into modeling (n=340) and validation (n=146) sets at a 7:3 ratio. SBI occurrence during the 60-month observation period was the outcome variable. R software was used to perform Least Absolute Shrinkage and Selection Operator (LASSO) and multivariate logistic regression analyses to construct an SBI risk prediction model and generate a nomogram [16]. The R packages "rms6.2.0" and "timeROC0.4" were used to construct ROC curves for both sets, calculating area under the curve (AUC) and C-statistics to validate model accuracy [17]. Calibration curves were plotted using R packages "rms6.2.0"and "timeROC0.4"to assess predictive ability and consistency between predicted and actual risks [17]. P<0.05 was considered statistically significant.

---

2. Results

2.1 General Characteristics

According to inclusion and exclusion criteria, 486 patients were finally enrolled. The patient screening flowchart is shown in Figure 1 [Figure 1: see original paper]. Seventy percent of patients were allocated to the modeling set (n=340),

with 70 cases (20.6%) developing SBI, while 30% were allocated to the validation set (n=146), with 32 cases (21.9%) developing SBI.

Significant differences between SBI and non-SBI groups were observed in age, smoking history, alcohol consumption history, cardiac valve calcification, BMI, chronic disease history, sleep duration, dialysis cause, URR, antiplatelet medication history, high-density lipoprotein cholesterol, and lactate level ($P<0.05$) (Table 1).

2.2 Correlation Analysis and LASSO Regression

Correlation analysis revealed no collinearity among candidate variables. LASSO regression analysis reduced the variables to eight: age, alcohol consumption history, BMI, sleep duration, chronic disease history, serum lactate level, URR, and antiplatelet medication history (Figure 2 [Figure 2: see original paper]).

2.3 Multivariate Logistic Regression Analysis

Using SBI (yes=1, no=0) as the dependent variable and the eight variables selected by LASSO regression as independent variables, multivariate logistic regression analysis showed that advanced age, alcohol consumption history, high BMI, sleep disturbance, comorbid chronic diseases, high lactate level, low URR, and absence of antiplatelet medication were independent risk factors for SBI in MHD patients (Table 2). These variables were incorporated into a nomogram prediction model (Figure 3 [Figure 3: see original paper]), where higher total scores indicate greater SBI risk.

2.4 Predictive Value of the Model in Modeling and Validation Sets

ROC curves were plotted for both sets, yielding AUC values of 0.816 (95%CI=0.759-0.873) in the modeling set and 0.808 (95%CI=0.723-0.893) in the validation set. The AUC in the validation set decreased by only 0.008 compared with the modeling set, indicating good discriminative ability in both populations (Figure 4 [Figure 4: see original paper]).

2.5 Calibration Curve

Calibration plots demonstrated high calibration across the entire predicted risk range, with curves consistently located on or near the reference line, reflecting good agreement between predicted and actual risks (Figure 5 [Figure 5: see original paper]).

2.6 DCA Curve

The horizontal line in the DCA curve represents no intervention with zero net benefit, while the diagonal line represents intervention for all patients. The prediction model showed good net benefit across threshold probabilities of 10%-80%, indicating a wide applicable range of high-risk threshold probabilities for

both modeling and validation sets and demonstrating clinical utility (Figure 6 [Figure 6: see original paper]).

---

3. Discussion

This study developed a nomogram prediction model for SBI in MHD patients. Given the scarcity of relevant research, SBI risk remains difficult to predict. Unlike previous studies, we incorporated dialysis-related variables of current interest, including dialysis duration, residual renal function, URR, and ultrafiltration rate [18]. This study is innovative and can provide more intuitive, accurate, and personalized risk assessment for patients.

3.1 Key Findings

3.1.1 Dialysis-Related Variables: This study included URR, which is recommended by multiple guidelines to measure dialysis adequacy [19]. Higher URR was associated with lower SBI incidence. Previous studies have shown that adequate dialysis effectively removes residual urea and toxins, thereby reducing cardiovascular and cerebrovascular damage [20]. Additionally, antiplatelet medication was found to reduce SBI risk (OR=0.149, 95%CI=0.030–0.490). Antiplatelet drugs prevent thrombosis by inhibiting platelet aggregation and activation, thereby reducing stroke events [21]. While antiplatelet medication shows substantial benefits in the general population, bleeding tendency from routine anticoagulation therapy (low molecular weight heparin 60–80 U/kg, intravenous) in MHD patients limits its use. Most clinical trials evaluating antiplatelet efficacy and safety have excluded CKD patients, leaving a lack of evidence for use in MHD patients, with guidelines recommending it only as secondary prevention [22]. Our findings on the protective effect of antiplatelet medication may provide reference for clinical use in MHD patients.

3.1.2 Sleep Disturbance: Interestingly, this study found that MHD patients with sleep disturbances had a 6-fold increased risk of SBI. MHD patients often experience pruritus, depression, and anxiety, leading to disordered sleep duration [23]. Research has shown a J-shaped association between sleep duration and all-cause mortality, with both insufficient and excessive sleep increasing stroke risk [24]. Additionally, our model demonstrated that lactate has important predictive value for SBI (OR=1.452, 95%CI=1.152–1.897). Lactate, primarily metabolized in the liver and kidneys, is a marker of tissue hypoperfusion and disease severity. Loss of renal function may lead to lactate accumulation, causing stroke through kidney-brain connections (reduced oxidative capacity, atherosclerosis) [25]. Ensuring sleep quality and monitoring lactate levels can effectively reduce SBI risk and delay disease progression.

3.1.3 Traditional Risk Factors: Advanced age, heavy alcohol consumption, and obesity are well-established risk factors for diabetes and cardiovascular disease. Age has consistently been identified as a definitive risk factor for SBI

[26]. Our results showed that each 10-year increase in age among MHD patients increased SBI risk by 27%. Previous studies have reported alcohol' s damaging effects on the cardiovascular system and its positive correlation with stroke [27]. We found that MHD patients with long-term alcohol consumption history had a 3-fold increased SBI risk. Obesity, diabetes, and hepatitis B share similar pathogenic mechanisms [28]; long-term chronic inflammation and atherosclerosis induced by these diseases further increase SBI risk in MHD patients [29]. With increasing attention to lung-kidney-brain interactions, SÖDERHOLM et al. [30] found that COPD increased incidence of all stroke subtypes independent of other comorbidities. Therefore, healthcare providers should closely monitor condition changes and daily care in elderly patients with multiple chronic diseases, guiding them to control weight, follow low-sugar/low-fat diets, abstain from alcohol, and adopt healthy lifestyles.

3.2 Limitations

(1) This cross-sectional study cannot establish causal relationships. (2) Although multicenter, varying diagnostic and treatment levels across centers may affect model results and performance. (3) The sample size remains relatively small, requiring further expansion for broader generalizability.

---

4. Conclusion

This study confirms that age, alcohol consumption history, BMI, sleep duration, chronic disease history, lactate level, URR, and antiplatelet medication history are independent influencing factors for SBI in MHD patients. By incorporating both common SBI risk factors and dialysis-related variables, we developed a multicenter prediction model with good predictive performance and clinical utility, providing a valuable tool for early SBI risk assessment and intervention in MHD patients.

Acknowledgments

We thank https://www.xsmartanalysis.com/model/index/ for technical support and the Science and Technology Innovation Center and Institute of Tissue Engineering and Stem Cells of North Sichuan Medical College for providing the work platform.

Author Contributions: Li Qiuling proposed the main research objectives, designed and implemented the study, and drafted and revised the manuscript. Li Qiuling and Tang Wenwu collected and organized data, performed statistical analysis, and prepared figures and tables. Yu Yiwen and Deng Huan collected and organized data. Yang Xiaohua and Chen Xiaoxia performed data collection. Ji Yifei was responsible for quality control, review, and supervision.

Conflict of Interest: The authors declare no conflict of interest.

ORCID IDs: - Li Qiuling: https://orcid.org/0000-0003-4479-8037 - Ji Yifei: https://orcid.org/0000-0001-9518-0486

References

[1] BELLO A K, OKPECHI I G, LEVIN A, et al. An update on the global disparities in kidney disease burden and care across world countries and regions[J]. Lancet Glob Health, 2024, 12(3): e382-e395. DOI: 10.1016/S2214-109X(23)00570-3.

[2] OZELSANCAK R, MICOSKADIOGLU H, TORUN D, et al. Cerebrovascular events in hemodialysis patients; a retrospective observational study[J]. BMC Nephrol, 2019, 20(1): 466. DOI: 10.1186/s12882-019-1629-y.

[3] GUPTA A, GIAMBRONE A E, GIALDINI G, et al. Silent brain infarction and risk of future stroke: a systematic review and meta-analysis[J]. Stroke, 2016, 47(3): 719-725. DOI: 10.1161/STROKEAHA.115.011889.

[4] GHOSHAL S, FREEDMAN B I. Mechanisms of stroke in patients with chronic kidney disease[J]. Am J Nephrol, 2019, 50(4): 229-239. DOI: 10.1159/000502446.

[5] FU S Y, LEUNG L Y, WANG Y S, et al. Natural language processing for the identification of silent brain infarcts from neuroimaging reports[J]. JMIR Med Inform, 2019, 7(2): e12109. DOI: 10.2196/12109.

[6] FANNING J P, WESLEY A J, WONG A A, et al. Emerging spectra of silent brain infarction[J]. Stroke, 2014, 45(11): 3461-3471. DOI: 10.1161/STROKEAHA.114.005919.

[7] STEVENS P E, LEVIN A, Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group Members. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline[J]. Ann Intern Med, 2013, 158(11): 825-830. DOI: 10.7326/0003-4819-158-11-201306040-00007.

[8] Chinese Society of Neurology, Chinese Society of Neurology Cerebrovascular Disease Group. Chinese consensus on diagnosis and treatment of silent brain infarction[J]. Chinese Journal of Neurology, 2018, 51(9): 692-698. DOI: 10.3760/cma.j.issn.1006-7876.2018.09.006.

[9] JOHANSEN K L, GARIMELLA P S, HICKS C W, et al. Central and peripheral arterial diseases in chronic kidney disease: conclusions from a Kidney Disease: improving Global Outcomes (KDIGO) Controversies Conference[J]. Kidney Int, 2021, 100(1): 35-48. DOI: 10.1016/j.kint.2021.04.029.

[10] COLLINS G S, REITSMA J B, ALTMAN D G, et al. Transparent reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): the TRIPOD statement[J]. J Clin Epidemiol, 2015, 68(2): 134-143. DOI: 10.1016/j.jclinepi.2014.11.010.

[11] ZOCCALI C, MARK P B, SARAFIDIS P, et al. Diagnosis of cardiovascular disease in patients with chronic kidney disease[J]. Nat Rev Nephrol, 2023, 19(11): 733-746. DOI: 10.1038/s41581-023-00747-4.

[12] DELANAYE P, MARIAT C. The applicability of eGFR equations to different populations[J]. Nat Rev Nephrol, 2013, 9(9): 513-522. DOI: 10.1038/nrneph.2013.143.

[13] CHEN R L, HE T F, TAO L J, et al. Study on the effect of cardiovascular risk factors on carotid intima-media progression[J]. Chinese General Practice, 2023, 26(14): 1709-1715. DOI: 10.12114/j.issn.1007-9572.2022.0750.

[14] KUO C C, WEAVER V, FADROWSKI J J, et al. Arsenic exposure, hyperuricemia, and gout in US adults[J]. Environ Int, 2015, 76: 32-40. DOI: 10.1016/j.envint.2014.11.015.

[15] HE Q, SUN H, WU X M, et al. Sleep duration and risk of stroke: a dose-response meta-analysis of prospective cohort studies[J]. Sleep Med, 2017, 32: 66-74. DOI: 10.1016/j.sleep.2016.12.012.

[16] SONG X, LIU X Y, LIU F, et al. Comparison of machine learning and logistic regression models in predicting acute kidney injury: a systematic review and meta-analysis[J]. Int J Med Inform, 2021, 151: 104484. DOI: 10.1016/j.ijmedinf.2021.104484.

[17] EOM B W, RYU K W, NAM B H, et al. Survival nomogram for curatively resected Korean gastric cancer patients: multicenter retrospective analysis with external validation[J]. PLoS One, 2015, 10(2): e0119671. DOI: 10.1371/journal.pone.0119671.

[18] FANNING J P, WONG A A, FRASER J F. The epidemiology of silent brain infarction: a systematic review of population-based cohorts[J]. BMC Med, 2014, 12: 119. DOI: 10.1186/s12916-014-0119-9.

[19] CHEN Y K, CHU C S, NIU S W, et al. The prognostic value of URR equals that of Kt/V for all-cause mortality in Taiwan after 10-year follow-up[J]. Sci Rep, 2023, 13(1): 8923. DOI: 10.1038/s41598-023-35353-8.

[20] VANHOLDER R, SCHEPERS E, PLETINCK A, et al. The uremic toxicity of indoxyl sulfate and p-cresyl sulfate: a systematic review[J]. J Am Soc Nephrol, 2014, 25(9): 1897-1907. DOI: 10.1681/ASN.2013101062.

[21] KAMAROVA M, BAIG S, PATEL H, et al. Antiplatelet use in ischemic stroke[J]. Ann Pharmacother, 2022, 56(10): 1159-1173. DOI: 10.1177/10600280211073009.

[22] KELLY D M, ADEMI Z, DOEHNER W, et al. Chronic kidney disease and cerebrovascular disease: consensus and guidance from a KDIGO controversies conference[J]. Stroke, 2021, 52(7): e328-e346. DOI: 10.1161/STROKEAHA.120.029680.

[23] FLETCHER B R, DAMERY S, AIYEGBUSI O L, et al. Symptom burden and health-related quality of life in chronic kidney disease: a global systematic review and meta-analysis[J]. PLoS Med, 2022, 19(4): e1003954. DOI: 10.1371/journal.pmed.1003954.

[24] JOUNDI R A, PATTEN S B, WILLIAMS J V A, et al. Association between excess sleep duration and risk of stroke: a population-based study[J]. Can J Neurol Sci, 2023, 50(1): 17-22. DOI: 10.1017/cjn.2021.242.

[25] MATSUSHITA K, WILLIAMS E K, MONGRAW-CHAFFIN M L, et al. The association of plasma lactate with incident cardiovascular outcomes: the ARIC Study[J]. Am J Epidemiol, 2013, 178(3): 401-409. DOI: 10.1093/aje/kwt002.

[26] RYDÉN L, SACUIU S, WETTERBERG H, et al. Atrial fibrillation, stroke, and silent cerebrovascular disease: a population-based MRI study[J]. Neurology, 2021, 97(16): e1608-e1619. DOI: 10.1212/WNL.0000000000012675.

[27] WOOD A M, KAPTOGE S, BUTTERWORTH A S, et al. Risk thresholds for alcohol consumption: combined analysis of individual-participant data for 599,912 current drinkers in 83 prospective studies[J]. Lancet, 2018, 391(10129): 1513-1523. DOI: 10.1016/S0140-6736(18)30134-X.

[28] WANG X Y, HUANG Y N, CHEN Y R, et al. The relationship between body mass index and stroke: a systemic review and meta-analysis[J]. J Neurol, 2022, 269(12): 6279-6289. DOI: 10.1007/s00415-022-11318-1.

[29] BARRACLOUGH K A, PLAYFORD E G. Hepatitis B virus infection in hemodialysis populations: progress toward prevention[J]. Kidney Int, 2010, 77(3): 177-180. DOI: 10.1038/ki.2009.456.

[30] SÖDERHOLM M, INGHAMMAR M, HEDBLAD B, et al. Incidence of stroke and stroke subtypes in chronic obstructive pulmonary disease[J]. Eur J Epidemiol, 2016, 31(2): 159-168. DOI: 10.1007/s10654-015-0113-7.

Received: November 10, 2023; Revised: March 25, 2024
Edited by: Jia Mengmeng

Note: Figure translations are in progress. See original paper for figures.