Am J Transl Res 2025;17(6):4651-4662
www.ajtr.org /ISSN:1943-8141/AJTR0164509

Original Article

Prognostic value of lipid variability for recurrence and mortality in elderly patients with acute ischemic cerebrovascular disease

Changchun Zhu, Xiaole Pan, Ran Xie, Bin Liu

Department of Neurology, The Third People's Hospital of Hefei (The Third Clinical College of Anhui Medical University), Hefei 230022, Anhui, China

Received March 13, 2025; Accepted June 5, 2025; Epub June 15, 2025; Published June 30, 2025

Abstract: Objective: To investigate the relationship between lipid variability and the risk of recurrence and mortality during the acute phase of ischemic cerebrovascular disease (ICD) in elderly patients. Methods: Clinical data, lipid profiles, and follow-up information were retrospectively collected from 149 elderly ICD patients who underwent at least three lipid measurements (non-baseline) at The Third People's Hospital of Hefei (The Third Clinical College of Anhui Medical University) from May 2021 to May 2024. Lipid indices included low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), and triglycerides (TG). Variability was assessed using standard deviation (SD), coefficient of variation (CV), and variability independent of the mean (VIM). Follow-up concluded in May 2024. Patients were classified into no-recurrence, recurrence, and death groups. Logistic multivariate regression analysis was used to identify risk factors for recurrence and death. Receiver operating characteristic (ROC) curve analyses were applied to assess the predictive value of lipid variability. Results: Variabilities in LDL-C, HDL-C, TC, and TG were significantly higher in the recurrence and death groups compared to the no-recurrence group. Logistic regression analysis identified lipid variability indices as independent risk factors for recurrence and death. ROC analysis furtherdemonstrated their predictive value. Conclusion: Variabilities in LDL-C, HDL-C, TC, and TG are independent risk factors for recurrence and death in elderly ICD patients. Combined analysis of lipid variability enhances diagnostic accuracy and may improve the prognostic assessment in this population.

Keywords: Lipid variability, ischemic cerebrovascular disease, predictive value, endpoint events

Introduction

Cerebrovascular disease (CVD) is a major health threat to middle-aged and elderly individuals, characterized by high rates of mortality, recurrence, and disability. It encompasses transient ischemic attack and acute ischemic stroke [1]. In China, CVD, together with cancer and cardiovascular diseases, are the top three causes of death, with an incidence that continues to rise annually. Ischemic cerebrovascular disease (ICD), also known as ischemic stroke, belongs to a group of cerebrovascular diseases and, is the most common subtype. It accounts for about 80% of all strokes and results in over 2 million deaths each year in China [2, 3]. Globally, stroke is responsible for more than 10% of all deaths, and approximately 75% of survivors experience loss of working ability, with about 40% suffering from severe disability, imposing a substantial economic burden on families and society. Current treatment strategies include rapid thrombolysis, vascular intervention for reperfusion, and neuroprotection; however, the therapeutic window is relatively narrow, and ensuring favorable long-term outcomes remains challenging [4, 5].

There are multiple risk factors for ICD, including non-modifiable factors such as sex, age, and genetics and modifiable factors such as hypertension, diabetes, smoking, dyslipidemia, and unhealthy lifestyle habits [6, 7]. Modification of these risk factors such as maintaining stable blood pressure and glucose levels, lowering low-density lipoprotein cholesterol (LDL-C), raising high-density lipoprotein cholesterol (HDL-C), and adopting healthier dietary patterns, has been shown to reduce the incidence of ICDs [8,

https://doi.org/10.62347/RFBV1794

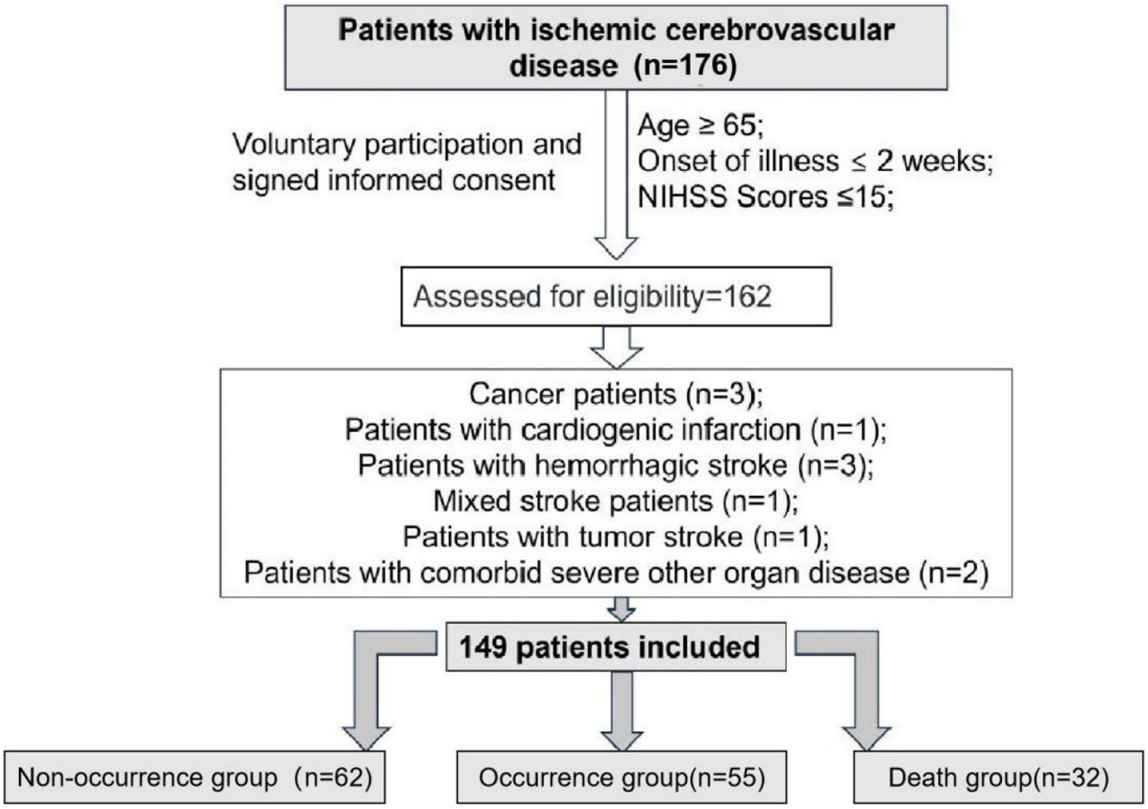

Figure 1. Patient seclection flow diagram.

9]. Therefore, early detection and active management of these risk factors are crucial.

Among the modifiable risk factors, lipid profiles are key indicators for predicting recurrence and mortality. However, the correlation between lipid variability and the risk of recurrence and mortality in elderly patients with acute ICD has not been fully elucidated. This study aimed to investigate the association between lipid variability and the recurrence of cerebrovascular events and mortality in elderly patients with acute ICD, in order to provide an effective tool for clinical prognosis.

Materials and methods

Study subjects

A total of 149 elderly patients with acute ICD admitted to The Third People's Hospital of Hefei (The Third Clinical College of Anhui Medical University) between May 2021 and May 2024 were retrospectively enrolled (**Figure 1**). This study was approved by the Ethics Committee of The Third People's Hospital of Hefei (The Third Clinical College of Anhui Medical University).

Inclusion criteria: (1) diagnosis of ischemic stroke (IS) or transient ischemic attack (TIA) according to the diagnostic criteria outlined in the *Guidelines for the Diagnosis and Treatment of Medium-Term Ischemic Stroke*, confirmed by cranial CT or MRI; (2) age ≥ 60 years; (3) within two weeks of symptom onset, representing the acute phase of ICD; (4) National Institutes of Health Stroke Scale (NIHSS) score of ≤ 15 at admission; and (5) availability of complete electronic medical records and valid long-term follow-up data.

Exclusion criteria: (1) history of malignancy or ongoing cancer treatment; (2) diagnosis of cardioembolic stroke, posterior circulation infarction, or stroke of undetermined etiology; (3) presence of hemorrhagic stroke, mixed stroke, or stroke secondary to brain tumor or metastases; (4) severe comorbid illnesses such as end-stage renal disease, severe hepatic dysfunction, or chronic respiratory failure; or (5) mental illness, dementia, or other cognitive impairments that compromised the ability to complete follow-up and treatment.

A standardized case report form was used to extract baseline demographic and clinical data from existing medical records. Data collected included socio-demographic data (gender, age, marital status), physical examination data (height, body mass index (BMI)), and disease-related data (history of alcohol consumption, smoking, family history of stroke, hypertension, hyperglycemia). Smoking history was defined as smoking more than one cigarette per day for more than 6 consecutive or cumulative months. Alcohol consumption was defined as an intake of more than 50 g per day for more than 6 consecutive or cumulative months. The study adhered to the ethical requirements outlined in the Declaration of Helsinki. All data were obtained through systematic review of archived medical records without additional patient intervention.

Assessment of lipid variability

For each patient, at least three lipid profile measurements were collected, with intervals of more than two weeks between consecutive tests. Lipid values included HDL-C, LDL-C, total cholesterol (TC), and triglycerides (TG). Lipid variability was assessed using standard deviation (SD), coefficient of variation (CV), and variability independent of the mean (VIM), calculated from these values.

Follow-up and grouping

Patients were followed through scheduled outpatient visits and structured telephone interviews conducted by trained research staff. Follow-up data, including clinical status, recurrence of IS, and survival outcomes, were collected at predefined intervals up to 12 months post-discharge. For patients lost to follow-up, supplemental data were obtained from the hospital's electronic medical records and the regional death registry. Predefined clinical endpoints, including stroke recurrence or all-cause mortality, were confirmed by the treating neurologists based on imaging findings, medical records, and standard diagnostic criteria.

Patients were divided into three groups: no recurrence, recurrence, and death, according to clinical outcomes within one year. Risk factors for recurrence and death were analyzed.

Statistical methods

Statistical analyses were performed using SPSS version 19.0. Continuous variables conforming to a normal distribution were expressed as mean ± standard deviation ($\overline{x}\pm s$) and compared using independent samples t-tests. Categorical variables were presented as frequencies and percentages [n (%)] and compared using the chi-square (χ^2) test. Multivariate logistic regression analysis was conducted to identify independent risk factors for recurrence and death among IS patients. Receiver operating characteristic (ROC) curve analysis was used to evaluate the predictive performance of lipid variability indices for recurrence and death. A P value of < 0.05 was considered significant.

Results

Comparison of clinical characteristics between non-occurrence group and recurrence or death groups

There were no significant differences in sex, BMI, history of diabetes, hypertension, smoking, or alcohol consumption between the no-recurrence group and either the recurrence or death group ($P > 0.05$). However, patients in the death group were significantly older than those in the non-occurrence group (84.00± 9.20 vs. 76.85±8.73 years, $P < 0.05$). No significant age difference was observed between the non-occurrence and the recurrence groups ($P > 0.05$) (**Table 1**).

Comparison of lipid variability between non-occurrence group and recurrenceor death groups

The variability measures of LDL-C, HDL-C, TC, and TG, including SD, CV, and VIM, were all significantly higher in both the recurrence group and death group compared with the non-occurrence group ($P < 0.05$) (**Table 2**).

Multivariate logistic regression analysis for recurrence

Multivariate logistic regression analysis identified LDL-C, HDL-C, TC, and TG as independent risk factors for disease recurrence in elderly patients with ICD ($P < 0.05$) (**Table 3**).

Table 1. Comparison of general information among three groups

Group		Non-occurrence Group (n=62)	Recurrence Group (n=55)	Death Group (n=32)	X_a^2/t_a	P_a	X_b^2/t_b	P_b
Age		76.85±8.73	79.14±9.02	84.00±9.20	1.395	0.166	3.690	< 0.001
Gender	male	32	22	14	1.582	0.209	0.728	0.394
	female	30	33	19				
BMI		22.02±1.06	21.88±0.99	21.5±1.58	0.735	0.464	1.900	0.061
Diabetes	Yes	22	16	9	0.543	0.461	0.517	0.472
	No	40	39	23				
Hypertension	Yes	42	45	26	3.028	0.082	1.925	0.340
	No	20	10	6				
Smoking history	Yes	7	7	1	0.057	0.811	0.911	0.340
	No	55	48	31				
Alcohol consumption history	Yes	6	6	1	0.104	0.747	0.536	0.464
	No	56	46	31				

BMI: body mass index; a: Non-occurrence group vs. recurrence group; b: Non-occurrence group vs. death group.

Table 2. Comparison of lipid variability among three groups

Group	Non-occurrence Group (n=62)	Recurrence Group (n=55)	Death Group (n=32)	t_a	P_a	t_b	P_b
LDL-C variability							
SD	12.21±3.22	16.31±2.64	14.81±3.25	7.473	< 0.001	3.678	< 0.001
CV	0.32±0.22	0.55±0.33	0.51±0.31	4.480	< 0.001	3.438	< 0.001
VIM	2.18±0.94	3.38±1.05	3.38±1.05	5.249	< 0.001	5.634	< 0.001
HDL-C variability							
SD	4.55±0.78	5.51±1.21	5.35±1.09	5.156	< 0.001	3.678	< 0.001
CV	0.385±0.30	0.66±0.31	0.59±0.33	4.960	< 0.001	3.438	0.001
VIM	1.55±0.67	2.21±0.92	2.12±0.81	4.469	< 0.001	5.634	< 0.001
TC variability							
SD	16.66±3.45	21.37±5.21	20.25±4.33	5.824	< 0.001	4.375	< 0.001
CV	0.33±0.25	0.61±0.40	0.58±0.36	4.594	< 0.001	3.937	< 0.001
VIM	1.73±0.77	2.35±1.03	2.41±0.97	2.994	< 0.001	3.707	< 0.001
TG variability							
SD	22.45±7.79	30.82±9.51	28.15±7.65	5.230	< 0.001	3.382	< 0.001
CV	0.35±0.26	0.63±0.33	0.61±0.32	5.125	< 0.001	4.241	< 0.001
VIM	1.53±0.75	2.39±1.03	2.18±0.95	5.202	< 0.001	3.629	< 0.001

a: Non-occurrence group vs. recurrence group; b: Non-occurrence group vs. death group. LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TC: total cholesterol; TG: triglycerides; SD: standard deviation; CV: coefficient of variation; VIM: variability independent of the mean.

Recurrence risk prediction based on lipid variability

ROC curve analysis indicated that all lipid variability models, including LDL-C, HDL-C, TC, and TG, showed consistently good predictive performance for assessing recurrence risk. The area under the curve (AUC) for LDL-C variability was 0.90 (95% CI: 0.85-0.96) (**Figure 2**), and for HDL-C variability it was 0.90 (95% CI: 0.87-0.93) (**Figure 3**). The TC variability model yielded an AUC of 0.86 (95% CI: 0.80-0.93) (**Figure 4**), and the TG variability model had an AUC of 0.86 (95% CI: 0.79-0.93) (**Figure 5**).

Multifactorial logistic regression analysis for death

Multivariate logistic regression analysis identified LDL-C, HDL-C, TC, and TG as independent

Table 3. Logistic regression analysis of factors associated with recurrence

	B	SE	Wald x^2	*P*	OR	95% CI
LDL-C variability						
SD	0.471	0.108	18.951	< 0.001	1.601	1.295-1.979
CV	2.046	1.019	4.034	0.045	7.735	1.051-56.945
VIM	0.922	0.286	10.425	0.001	2.514	1.437-4.400
HDL-C variability						
SD	1.440	.447	10.361	0.001	4.221	1.756-10.144
CV	3.670	1.217	9.098	0.003	39.246	3.615-426.033
VIM	2.399	.551	18.968	< 0.001	11.016	3.742-32.430
TC variability						
SD	0.251	.062	16.486	< 0.001	1.286	1.139-1.452
CV	2.895	.827	12.266	< 0.001	18.089	3.579-91.435
VIM	0.732	.287	6.510	0.011	2.078	1.185-3.646
TG variability						
SD	0.104	.030	11.882	0.001	1.109	1.046-1.176
CV	1.855	.836	4.929	0.026	6.392	1.243-32.872
VIM	0.882	.312	7.968	0.005	2.415	1.309-4.454

LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TC: total cholesterol; TG: triglycerides; SD: standard deviation; CV: coefficient of variation; VIM: variability independent of the mean.

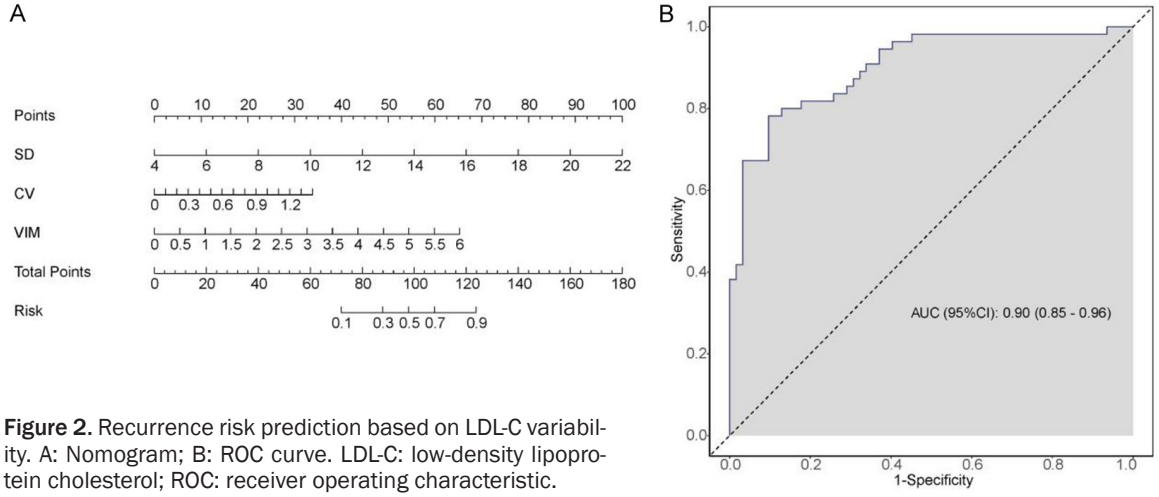

Figure 2. Recurrence risk prediction based on LDL-C variability. A: Nomogram; B: ROC curve. LDL-C: low-density lipoprotein cholesterol; ROC: receiver operating characteristic.

risk factors for death in elderly patients with ICD (P < 0.05) (**Table 4**).

Death risk prediction based on lipid variability

ROC curve analysis showed that all lipid variability models demonstrated good predictive ability for assessing death risk. The AUC for LDL-C variability was 0.88 (95% CI: 0.80 to 0.96) (**Figure 6**), for HDL-C variability it was 0.81 (95% CI: 0.71 to 0.91) (**Figure 7**), for TC variability it was 0.86 (95% CI: 0.78 to 0.93) (**Figure 8**), and for TG variability it was 0.83 (95% CI: 0.74 to 0.93) (**Figure 9**).

Discussion

Ischemic cerebrovascular disease (ICD) is attributed to a variety of factors, including increased vascular permeability or damage to the vessel wall [10], heart disease leading to hemodynamic changes [11], elevated blood cell counts and altered blood viscosity [12], as well as other etiologies such as embolism [13], congenital vascular malformations [14], and cerebral vasospasm [15]. However, the most common etiology is vessel wall damage and vascular occlusion by emboli, with atherosclerotic injury and embolization from plaque or

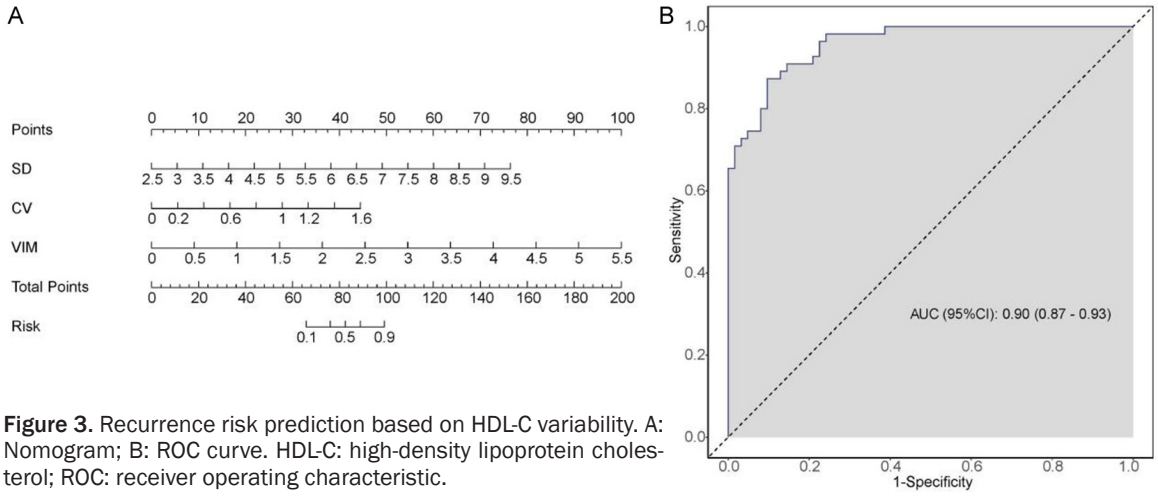

Figure 3. Recurrence risk prediction based on HDL-C variability. A: Nomogram; B: ROC curve. HDL-C: high-density lipoprotein cholesterol; ROC: receiver operating characteristic.

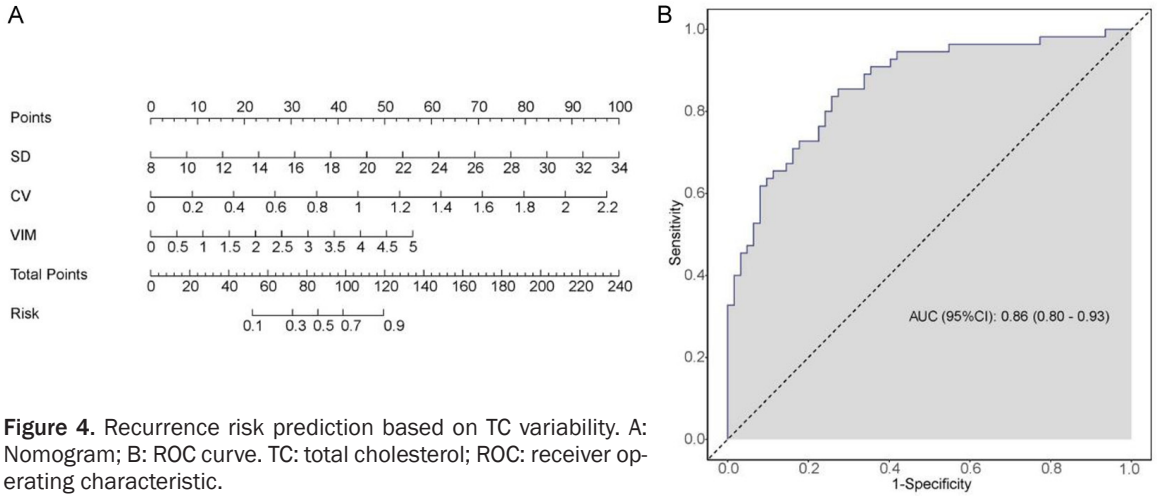

Figure 4. Recurrence risk prediction based on TC variability. A: Nomogram; B: ROC curve. TC: total cholesterol; ROC: receiver operating characteristic.

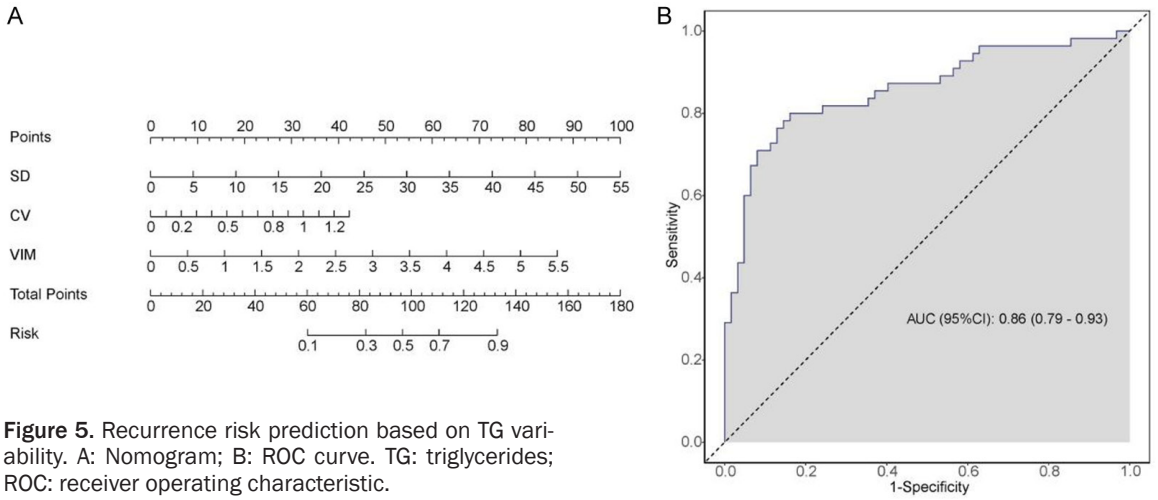

Figure 5. Recurrence risk prediction based on TG variability. A: Nomogram; B: ROC curve. TG: triglycerides; ROC: receiver operating characteristic.

thrombus formation being the predominant causes [15]. Growing attention has been paid to the prognostic significance of variability in several physiological functions, such as heart

Table 4. Logistic regression analysis of factors associated with mortality

	B	SE	Wald x^2	*P*	OR	95% CI
LDL-C variability						
SD	0.287	0.101	8.028	0.005	1.332	1.092-1.624
CV	2.102	1.107	3.605	0.058	8.181	0.935-71.627
VIM	1.337	0.352	14.398	0.000	3.808	1.909-7.597
HDL-C variability						
SD	0.791	0.298	7.066	0.008	2.206	1.231-3.955
CV	2.190	0.874	6.287	0.012	8.938	1.613-49.525
VIM	1.019	0.366	7.771	0.005	2.771	1.353-5.673
TC variability						
SD	0.278	.079	12.335	< 0.001	1.320	1.131-1.542
CV	2.567	1.098	5.469	0.019	13.029	1.515-112.021
VIM	0.887	.343	6.694	0.010	2.429	1.240
TG variability						
SD	0.091	0.034	7.032	0.008	1.095	1.024-1.172
CV	2.875	0.991	8.410	0.004	17.729	2.540-123.766
VIM	0.856	0.321	7.124	0.008	2.355	1.255-4.416

LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TC: total cholesterol; TG: triglycerides; SD: standard deviation; CV: coefficient of variation; VIM: variability independent of the mean.

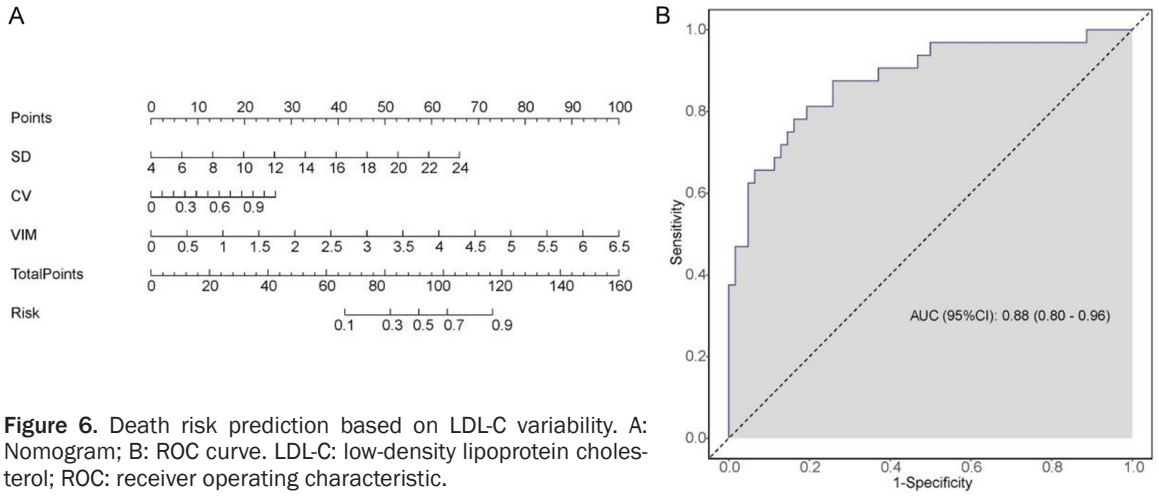

Figure 6. Death risk prediction based on LDL-C variability. A: Nomogram; B: ROC curve. LDL-C: low-density lipoprotein cholesterol; ROC: receiver operating characteristic.

rate variability and blood pressure variability, in cerebrovascular disease. Abnormal lipid levels is an established risk factor for the onset and progression of various cerebrovascular conditions [16-18]. Recent studies have further suggested that increased lipid variability, reflecting lipid fluctuations over time, may also increase the risk of major cerebrovascular events. The objective of this study was to investigate the association between lipid variability and the risks of recurrence and mortality in elderly patients with ICD.

Previous studies have indicated that poor ICD prognosis is predominantly associated with advanced age and a history of hypertension [19, 20]. However, in the present study, significant differences among the no-recurrence, recurrence, and death groups were observed only for age, with patients in the death group being significantly older than those in the non-occurrence group. No significant age difference was found between the recurrence and non-occurrence groups. These findings differ from those reported in previous studies. This dis-

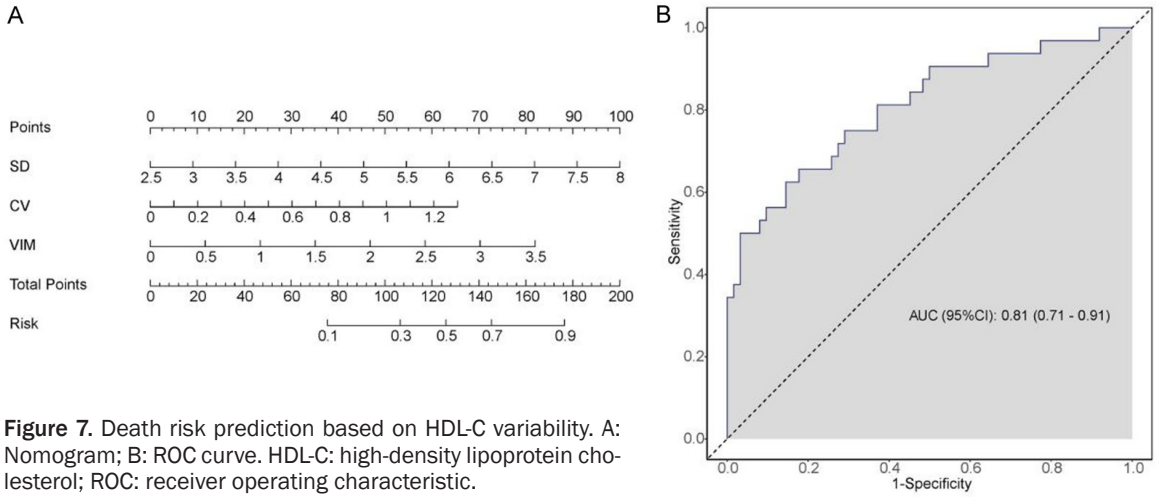

Figure 7. Death risk prediction based on HDL-C variability. A: Nomogram; B: ROC curve. HDL-C: high-density lipoprotein cholesterol; ROC: receiver operating characteristic.

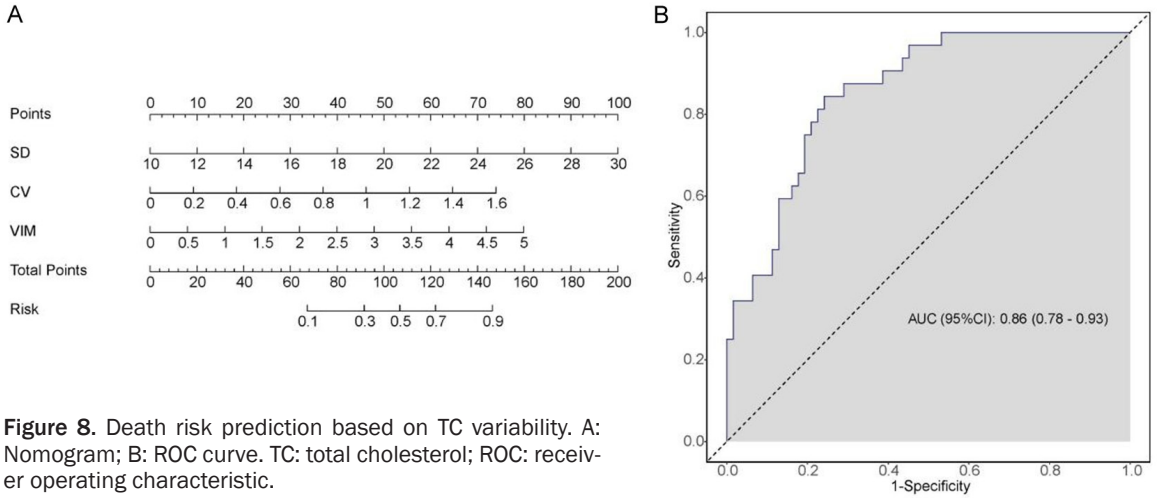

Figure 8. Death risk prediction based on TC variability. A: Nomogram; B: ROC curve. TC: total cholesterol; ROC: receiver operating characteristic.

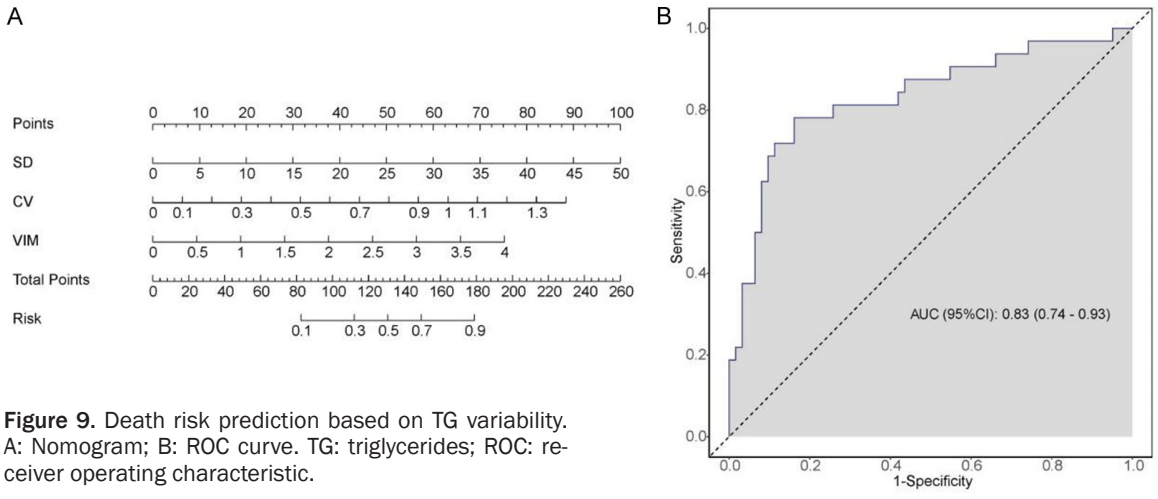

Figure 9. Death risk prediction based on TG variability. A: Nomogram; B: ROC curve. TG: triglycerides; ROC: receiver operating characteristic.

crepancy may be explained by several factors. First, the sample size in the death group of this study is relatively small. Second, more than 50% of patients in all three groups had a histo-

ry of hypertension, a known risk factor for cardiovascular disease. The uniformly high prevalence of hypertension may have obscured potential differences in other risk factors, such as diabetes mellitus, smoking, and alcohol consumption.

Lipids constitute the largest proportion of the brain's dry weight among all biochemical components [21]. Dyslipidemia is common in patients with ICD and can promote vascular coagulation abnormalities, leading to vascular occlusion and perpetuating the cycle of atherosclerosis, which serves as a major pathologic basis for cerebrovascular disease [22]. Chronic endothelial injury induced by inflammation results in localized vascular lipid deposition, fibrous tissue proliferation, and calcium deposition, ultimately leading to plaque formation and vascular stiffening [23, 24]. Currently, more than 300 lipid species have been identified in atherosclerotic plaques. Of these, TC represents the sum of cholesterol in all circulating lipoproteins, including free cholesterol and cholesteryl esters [25]. LDL-C, characterized by small particle size and high cholesterol content, primarily transports cholesterol to extrahepatic tissues and plays a key role in the pathogenesis of atherosclerosis [26]. HDL-C is the smallest and densest lipoprotein, composed primarily of phospholipids, free cholesterol, cholesteryl esters, and apolipoprotein A-I (Apo A-I) [27]. While triglyceride (TG) were previously thought to have little effect on the development of atherosclerosis, recent studies have demonstrated that elevated plasma TG levels stimulate cholesterol-lipid transporter proteins, disrupt lipid metabolism, and promote cholesterol accumulation in LDL-C and intermediate-density lipoproteins. These particles, resistant to clearance by LDL receptor pathways, persist in plasma and contribute to atherogenesis [28]. Due to the differences in structure and physiologic function, the roles of different lipid components vary in ICD. Most studies have indicated that elevated TC, TG, and LDL-C levels are risk factors, whereas HDL-C is considered protective against cerebrovascular disease [29].

However, lipid levels often fluctuate over time, making single-point measurements insufficient for risk assessment. Variability measures such as standard deviation (SD), coefficient of variation (CV), and variability independent of the mean (VIM) offer more comprehensive evaluations by quantifying the extent of lipid fluctuations, independent of data distribution. It is postulated that greater lipid variability contributes to poor outcomes by accelerating atherosclerotic plaque progression. High lipid variability may trigger inflammatory stress responses and endothelial dysfunction, leading to intracellular lipid accumulation and potential statin resistance, which collectively enhance the risk of thrombosis and subsequent recurrence or death [30]. Consistent with this hypothesis, this study demonstrated that lipid variability indices were significantly higher in the recurrence and death groups than in the non-recurrence group, suggesting that lipid variability may adversely affect patient prognosis. No significant difference in lipid variability was observed between the recurrence and death groups. This may be explained by the fact that recurrent stroke often signifies an unfavorable prognosis, particularly in elderly ICD patients whose physiologic reserve is diminished. Consequently, the interval between recurrence and death may be shortened. Our follow-up data indicated that some patients who relapsed eventually succumbed to their illness, often due to delays in seeking or receiving timely medical intervention. This reflects the clinical reality that, in elderly ICD patients, the distinction between recurrence and death becomes less clear.

The results of the logistic regression analysis indicated that the variability in LDL, HDL, TC, and TG was associated with both relapse and death in elderly patients with acute ICD. Further ROC curve analysis demonstrated that these variabilities possessed moderate to high predictive value for relapse and death, suggesting their use in risk stratification. The observed correlation between lipid variability and increased risk of recurrence and mortality may be explained by several mechanisms. First, oxidized LDL particles penetrate the arterial endothelium, exacerbating local inflammatory response and leading to endothelial damage [31]. Increased lipid variability may destabilize the vascular wall, promoting abnormal lipid efflux and elevating the risk of plaque vulnerability and rupture [32]. Conversely, high HDL variability may impede cholesterol efflux from peripheral tissues and macrophages, contributing to plaque instability.

Furthermore, increased lipid variability has been linked to genetic factors affecting cholesterol metabolism, such as polymorphisms in the gene encoding HMG-CoA reductase [33]. Another potential explanation may related to the systemic nature of atherosclerosis, which typically progresses from the aorta to the coronary, cerebral, and peripheral arteries. High lipid variability could contribute to systemic vascular instability, increasing the risk of recurrence or death not only from cerebrovascular events but also from comorbid cardiovascular or peripheral vascular diseases [34].

Monitoring lipid variability in clinical practice is beneficial for risk management in elderly patients with acute ICD. Timely adjustments to postoperative treatment based on fluctuations in lipid variability may improve overall clinical outcomes. It is important to note that this study is not without limitations. First, the relatively small sample size may have introduced bias and limited the generalizability of the findings. Second, although elderly ICD patients are at an increased risk of mortality following disease recurrence, the relatively short follow-up period may have affected the accuracy of the observed outcomes. Third, the underlying mechanisms linking lipid variability to adverse outcomes were not fully explored. Future studies should involve larger, multicenter cohorts and employ prospective design to further elucidate the mechanistic pathways and enhance the reliability and clinical applicability of the findings.

Conclusion

Lipid variability is associated with adverse cerebrovascular events in elderly patients with acute ICD and serves as an independent risk factor for recurrence and mortality.

Disclosure of conflict of interest

None.

Address correspondence to: Bin Liu, Department of Neurology, The Third People's Hospital of Hefei (The Third Clinical College of Anhui Medical University), No. 204 Wangjiang East Road, Baohe District, Hefei 230022, Anhui, China. Tel: +86-0551-63687032; E-mail: doc_liub@163.com

References

[1] Lv B, Jiang XM, Wang DW, Chen J, Han DF and Liu XL. Protective effects and mechanisms of action of ulinastatin against cerebral ischemia-reperfusion injury. Curr Pharm Des 2020; 26: 3332-3340.

[2] Zhong C, Yin C, Niu G, Ning L and Pan J. MicroRNA miR-497 is closely associated with poor prognosis in patients with cerebral ischemic stroke. Bioengineered 2021; 12: 2851-2862.

[3] Gao L, Qin JX, Shi JQ, Jiang T, Wang F, Xie C, Gao Q, Zhi N, Dong Q and Guan YT. Fine particulate matter exposure aggravates ischemic injury via NLRP3 inflammasome activation and pyroptosis. CNS Neurosci Ther 2022; 28: 1045-1058.

[4] Davis CM, Zhang WH, Allen EM, Bah TM, Shangraw RE and Alkayed NJ. Soluble epoxide hydrolase blockade after stroke onset protects normal but not diabetic mice. Int J Mol Sci 2021; 22: 5419.

[5] Almekhlafi MA, Goyal M, Dippel DWJ, Majoie CBLM, Campbell BCV, Muir KW, Demchuk AM, Bracard S, Guillemin F, Jovin TG, Mitchell P, White P, Hill MD, Brown S and Saver JL; HERMES Trialists Collaboration. Healthy life-year costs of treatment speed from arrival to endovascular thrombectomy in patients with ischemic stroke: a meta-analysis of individual patient data from 7 randomized clinical trials. JAMA Neurol 2021; 78: 709-717.

[6] Lemmerman LR, Balch MHH, Moore JT, Alzate-Correa D, Rincon-Benavides MA, Salazar-Puerta A, Gnyawali S, Harris HN, Lawrence W, Ortega-Pineda L, Wilch L, Risser IB, Maxwell AJ, Duarte-Sanmiguel S, Dodd D, Guio-Vega GP, McTigue DM, Arnold WD, Nimjee SM, Sen CK, Khanna S, Rink C, Higuita-Castro N and Gallego-Perez D. Nanotransfection-based vasculogenic cell reprogramming drives functional recovery in a mouse model of ischemic stroke. Sci Adv 2021; 7: eabd4735.

[7] Campanella A, Iacovazzi PA, Misciagna G, Bonfiglio C, Mirizzi A, Franco I, Bianco A, Sorino P, Caruso MG, Cisternino AM, Buongiorno C, Liuzzi R and Osella AR. The effect of three mediterranean diets on remnant cholesterol and non-alcoholic fatty liver disease: a secondary analysis. Nutrients 2020; 12: 1674.

[8] Lee M, Cheng CY, Wu YL, Lee JD, Hsu CY and Ovbiagele B. Association between intensity of low-density lipoprotein cholesterol reduction with statin-based therapies and secondary stroke prevention: a meta-analysis of randomized clinical trials. JAMA Neurol 2022; 79: 349-358.

[9] Dong Q, Yan S, Li D, Zhou C, Tian S, Wang Y, Miao P, Zhu W, Zhu S and Pan C. Feeding foliar nano-selenium biofortified panax notoginseng could reduce the occurrence of glycolipid metabolism disorder in mice caused by high-fat diets. Front Nutr 2022; 9: 973027.

[10] Lie IA, Wesnes K, Kvistad SS, Brouwer I, Wergeland S, Holmøy T, Midgard R, Bru A, Edland A, Eikeland R, Gosal S, Harbo HF, Kleveland G, Sørenes YS, Øksendal N, Barkhof F, Vrenken H, Myhr KM, Bø L and Torkildsen Ø. The effect of smoking on long-term gray matter atrophy and clinical disability in patients with relapsing-remitting multiple sclerosis. Neurol Neuroimmunol Neuroinflamm 2022; 9: e200008.

[11] Nguyen VT, Lu YH, Wu CW, Sung PS, Lin CC, Lin PY, Wang SM, Chen FY and Chen JJ. Evaluating interhemispheric synchronization and cortical activity in acute stroke patients using optical hemodynamic oscillations. J Neural Eng 2022; 19.

[12] Samiun WS, Ashari SE, Salim N and Ahmad S. Optimization of processing parameters of nanoemulsion containing aripiprazole using response surface methodology. Int J Nanomedicine 2020; 15: 1585-1594.

[13] Gu T, Just J, Stenz KT, Yan Y, Sieljacks P, Wang J, Groennebaek TS, Jakobsgaard JE, Rindom E, Herskind J, Gravholt A, Lassen TR, Jørgensen M, Bæk R, Gutiérrez-Jiménez E, Iversen NK, Rasmussen PM, Nyengaard JR, Jørgensen MM, de Paoli F, Bøtker HE, Kjems J, Vissing K and Drasbek KR. The role of plasma extracellular vesicles in remote ischemic conditioning and exercise-induced ischemic tolerance. Int J Mol Sci 2022; 23: 3334.

[14] Kobialka P, Sabata H, Vilalta O, Gouveia L, Angulo-Urarte A, Muixí L, Zanoncello J, Muñoz-Aznar O, Olaciregui NG, Fanlo L, Esteve-Codina A, Lavarino C, Javierre BM, Celis V, Rovira C, López-Fernández S, Baselga E, Mora J, Castillo SD and Graupera M. The onset of PI3K-related vascular malformations occurs during angiogenesis and is prevented by the AKT inhibitor miransertib. EMBO Mol Med 2022; 14: e15619.

[15] Hernandez I, Chissey A, Guibourdenche J, Atasoy R, Coumoul X, Fournier T, Beaudeux JL and Zerrad-Saadi A. Human placental NADPH oxidase mediates sFlt-1 and PlGF secretion in early pregnancy: exploration of the TGF-β1/p38 MAPK pATHWays. Antioxidants (Basel) 2021; 10: 281.

[16] Brechtel L, Poupore N, Monroe M, Knisely K, Sanders C, Edrissi C, Rathfoot C and Nathaniel TI. Role of dyslipidemia in ischemic stroke patients treated in the telestroke network. Adv Med Sci 2021; 66: 254-261.

[17] Bakeberg MC, Gorecki AM, Kenna JE, Jefferson A, Byrnes M, Ghosh S, Horne MK, McGregor S, Stell R, Walters S, Mastaglia FL and Anderton RS. Elevated HDL levels linked to poorer cognitive ability in females with Parkinson's disease. Front Aging Neurosci 2021; 13: 656623.

[18] Xu Q, Zhang Y, Zhang X, Liu L, Zhou B, Mo R, Li Y, Li H, Li F, Tao Y, Liu Y and Xue C. Medium-chain triglycerides improved cognition and lipid metabolomics in mild to moderate Alzheimer's disease patients with APOE4-/-: a double-blind, randomized, placebo-controlled crossover trial. Clin Nutr 2020; 39: 2092-2105.

[19] Che F, Wang A, Ju Y, Ding Y, Duan H, Geng X, Zhao X and Wang Y. Early neurological deterioration in acute ischemic stroke patients after intravenous thrombolysis with alteplase predicts poor 3-month functional prognosis - data from the thrombolysis implementation and monitor of acute ischemic stroke in China (TIMS-China). BMC Neurol 2022; 22: 212.

[20] Cho SM, Premraj L, Fanning J, Huth S, Barnett A, Whitman G, Arora RC, Battaglini D, Porto DB, Choi H, Suen J, Bassi GL, Fraser JF, Robba C and Griffee M. Ischemic and hemorrhagic stroke among critically ill patients with coronavirus disease 2019: an international multicenter coronavirus disease 2019 critical care consortium study. Crit Care Med 2021; 49: e1223-e1233.

[21] Kreiser RP, Wright AK, Sasser LR, Rinauro DJ, Gabriel JM, Hsu CM, Hurtado JA, McKenzie TL, Errico S, Albright JA, Richardson L, Jaffett VA, Riegner DE, Nguyen LT, LeForte K, Zasloff M, Hollows JE, Chiti F, Vendruscolo M and Limbocker R. A brain-permeable aminosterol regulates cell membranes to mitigate the toxicity of diverse pore-forming agents. ACS Chem Neurosci 2022; 13: 1219-1231.

[22] Shi H, Guo J, Yu Q, Hou X, Liu L, Gao M, Wei L, Zhang L, Huang W, Wang Y, Liu G, Tontonoz P and Xian X. CRISPR/Cas9 based blockade of IL-10 signaling impairs lipid and tissue homeostasis to accelerate atherosclerosis. Front Immunol 2022; 13: 999470.

[23] Tikellis C, Robinson GN, Rosado CJ, Batu D, Zuniga-Gutierrez MA, Pickering RJ and Thomas MC. Circulating soluble ACE2 plays an independent role to protect against vascular damage in diabetic mice. Antioxidants (Basel) 2022; 11: 987.

[24] Sutton NR, Bouïs D, Mann KM, Rashid IM, McCubbrey AL, Hyman MC, Goldstein DR, Mei A and Pinsky DJ. CD73 promotes age-dependent accretion of atherosclerosis. Arterioscler Thromb Vasc Biol 2020; 40: 61-71.

[25] Pan Z, Wang K, Wang X, Jia Z, Yang Y, Duan Y, Huang L, Wu ZX, Zhang JY and Ding X. Choles-

terol promotes EGFR-TKIs resistance in NSCLC by inducing EGFR/Src/Erk/SP1 signaling-mediated ERRα re-expression. Mol Cancer 2022; 21: 77.

[26] Moldovan R, Mitrea DR, Florea A, Chiş IC, Suciu Ş, David L, Moldovan BE, Mureşan LE, Lenghel M, Ungur RA, Opriş RV, Decea N and Clichici SV. Effects of gold nanoparticles functionalized with bioactive compounds from cornus mas fruit on aorta ultrastructural and biochemical changes in rats on a hyperlipid diet-a preliminary study. Antioxidants (Basel) 2022; 11: 1343.

[27] Yan J, Nie Y, Liu Y, Li J, Wu L, Chen Z and He B. Yiqi-bushen-tiaozhi recipe attenuated high-fat and high-fructose diet induced nonalcoholic steatohepatitis in mice via gut microbiota. Front Cell Infect Microbiol 2022; 12: 824597.

[28] Vallée A. Association between lipids and arterial stiffness for primary cardiovascular prevention in a general middle-aged european population. Front Cardiovasc Med 2022; 9: 899841.

[29] Nanashima N, Horie K, Yamanouchi K, Tomisawa T, Kitajima M, Oey I and Maeda H. Blackcurrant (Ribes nigrum) extract prevents dyslipidemia and hepatic steatosis in ovariectomized rats. Nutrients 2020; 12: 1541.

[30] Kalani R, Bartz TM, Suchy-Dicey A, Elkind MSV, Psaty BM, Leung LY, Rice K, Tirschwell D and Longstreth WT. Cholesterol variability and cranial magnetic resonance imaging findings in older adults: the cardiovascular health study. Stroke 2020; 51: 69-74.

[31] Hajouj H, Khattib A, Atrahimovich D, Musa S and Khatib S. S-nitrosylation of paraxonase 1 (PON1) elevates its hydrolytic and antioxidant activities. Biomolecules 2022; 12: 414.

[32] Wang MC, Li CI, Liu CS, Lin CH, Yang SY, Li TC and Lin CC. Effect of blood lipid variability on mortality in patients with type 2 diabetes: a large single-center cohort study. Cardiovasc Diabetol 2021; 20: 228.

[33] Allott EH, Csizmadi I, Howard LE, Muller RL, Moreira DM, Andriole GL, Roehrborn CG and Freedland SJ. Statin use and longitudinal changes in prostate volume; results from the reduction by dutasteride of prostate cancer events (REDUCE) trial. BJU Int 2020; 125: 226-233.

[34] Cui L, Xing Y, Wang L, Liu K, Chen H, Li C and Chen Y. Carotid intraplaque neovascularization and future vascular events in patients with asymptomatic carotid stenosis. Front Pharmacol 2022; 13: 804810.