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ORIGINAL RESEARCH

Creatine Kinase Is Associated With Recurrent Stroke and Functional Outcomes of Ischemic Stroke or Transient Ischemic Attack

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BACKGROUND: Many patients after stroke are found to have elevated serum creatine kinase (CK). This study aimed to investigate the associations between serum CK levels and clinical outcomes in patients with acute ischemic stroke or transient ischemic attack.

METHODS AND RESULTS: The study included 8910 patients with acute ischemic stroke or transient ischemic attack from the CNSR-III (Third China National Stroke Registry). Baseline serum CK levels after admission were measured. The associations between CK and clinical outcomes (stroke recurrence, death, and disability, defined as modified Rankin scale score 3–6 or 2–6) were analyzed. Patients with elevated CK levels had higher risks of recurrent stroke (hazard ratio [HR], 1.53; 95% CI, 1.21–1.93), death (HR, 1.68; 95% CI, 1.10–2.58), and disability (modified Rankin scale score, 3–6; odds ratio, 1.57; 95% CI, 1.29–1.90) at 3 months after adjusting confounding factors. Similar results were found at 1 year. The effects of CK on death and disability were more significant in male patients than female patients (*P* value for interaction <0.05). Elevated CK-MB levels were not associated with clinical outcomes in this study.

CONCLUSIONS: Elevated serum CK after ischemic stroke or transient ischemic attack is associated with higher risks of recurrent stroke, death, and disability at 3 months and 1 year. Serum CK may act as a useful predictor for recurrent stroke and poor functional outcomes in patients with acute ischemic stroke or transient ischemic attack. Sex modifies the relationship between elevated CK and disability or death.

Key Words: creatine kinase ■ disability ■ ischemic stroke ■ recurrence

As a key enzyme of cell energy metabolism, creatine kinase (CK) is expressed widely in tissues, especially in muscle and brain tissues. CK has tissue distribution specificity, and there are 3 isozymes (CK-MM, CK-MB, and CK-BB) in cytoplasm.[1] CK-MM mainly exists in skeletal muscle, CK-MB mainly exists in cardiac muscle, and CK-BB exists primarily in brain. CK and CK isozymes were found to be elevated in cerebrovascular events,[2] muscle disease,[3] and myocardial ischemia,[4] and were used as markers of tissue damage.

Many studies found that serum CK was increased in patients with stroke,[5] although tissue sources and potential mechanism were not entirely clear. However, studies were limited about the relationship between serum CK and clinical outcomes after stroke. In this study, we aimed to investigate the associations of elevated serum CK and clinical outcomes, including recurrent events and functional outcomes, in patients with acute ischemic stroke (AIS) or transient ischemic attack (TIA).

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CLINICAL PERSPECTIVE

What Is New?
- Many studies found serum creatine kinase (CK) was increased in patients with stroke, but studies were limited about the relationship between serum CK and clinical outcomes after stroke.
- This study showed that elevated serum CK after ischemic stroke or transient ischemic attack is associated with higher risks of recurrent stroke, death, and disability at 3 months and 1 year.
- Sex might modify the relationship between elevated CK and disability or death.

What Are the Clinical Implications?
- Measurement of CK level might be helpful for identifying patients at high risk of poor outcomes.
- Further research is needed to confirm the effect of elevated CK on clinical outcomes after ischemic stroke or transient ischemic attack.

Nonstandard Abbreviations and Acronyms

AIS	acute ischemic stroke
CNSR-III	Third China National Stroke Registry
CVE	combined vascular events
mRS	modified Rankin scale
NIHSS	National Institutes of Health Stroke Scale
TOAST	Trial of Org 10172 in Acute Stroke Treatment

METHODS

The data that support the findings of this study are available from the corresponding author.

Study Population

The CNSR-III (Third China National Stroke Registry) was a nationwide prospective registry that included patients with AIS or TIA from 201 hospitals between 2015 and March 2018 in China. Participants were consecutively enrolled if meeting the following criteria: (1) aged >18 years; (2) diagnosis of ischemic stroke or TIA within 7 days; and (3) informed consent from participant or legally authorized representative. The study was approved by ethics committees, and written informed consent was obtained. The detailed design and main results of the CNSR-III trial[6] were described previously.

Basic Data Collection

The baseline data were collected prospectively using an electronic data capture system by face-to-face interviews, including age, sex, current smoking, medical history (hypertension, diabetes, dyslipidemia, ischemic stroke, TIA, coronary heart diseases, atrial fibrillation/flutter, or epilepsy), previous medication, TOAST (Trial of Org 10 172 in Acute Stroke Treatment) criteria, National Institutes of Health Stroke Scale (NIHSS) score, systolic blood pressure, diastolic blood pressure, baseline blood tests, such as total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride, fasting blood glucose, estimated glomerular filtration rate, CRP (C-reactive protein), and discharge diagnosis (AIS, TIA, hypertension, diabetes, dyslipidemia, coronary heart diseases, atrial fibrillation, or epilepsy).

Measurement of CK and CK-MB

Serum CK and CK-MB were measured by activity assay in fasting blood samples within 24 hours of admission in participating hospitals, and the results were uploaded in the electronic data capture system.

Outcomes Assessment

Clinical outcomes included ischemic stroke, stroke (new ischemic stroke or hemorrhagic stroke), combined vascular events (CVE; including stroke, myocardial infarction, or vascular death), all-cause mortality, and modified Rankin scale (mRS) score. Recurrent events or death during follow-up period and the time of occurrence were recorded. Functional outcomes (mRS score) were evaluated at 3 months (face-to-face interview) and 1 year (telephone interview). Confirmation of cerebrovascular events was sought from the treating hospital, and suspected recurrent cerebrovascular events without hospitalization were judged by independent end point judgment committee. Each case fatality was either confirmed on a death certificate from the attended hospital or the local citizen registry.

Statistical Analysis

Patients were classified into 2 groups according to CK levels, and baseline characteristics were compared between 2 groups. Different normal upper limits were used in men and women (men, 171 U/L; women, 145 U/L).[7] Continuous variables were described by median with interquartile range, and categorical variables were described by frequencies with percentages. The Wilcoxon rank-sum test was used to compare group differences for continuous variables, and χ^2 test was used for categorical variables. The associations of CK and recurrent events or death at 3 months and 1 year were investigated with Cox proportional hazards regression analysis, and

all the models satisfied proportional hazards assumption ($P>0.05$ for all). The proportional hazard assumption was evaluated by visualization of Schoenfeld residuals, and no potential violation was observed. Hazard ratios (HRs) and their 95% CIs were calculated. The competing risk model (Fine and Gray) was applied to assess the associations between CK levels and the outcomes, with death being regarded as a competing risk event. Associations of CK and disability were tested with logistic regression model, and odds ratios (ORs) with 95% CIs were calculated. CK levels varied according to sex, age, and race in general population. We adjusted age and sex first in model 1 in the multivariable analyses. Model 2 added variables that were associated with CK or outcomes in univariate analysis with $P<0.05$, including age, sex, history of diabetes, atrial fibrillation/flutter, hypoglycemic agents, TOAST subtype, epilepsy (discharge diagnosis), NIHSS score on admission, high-density lipoprotein cholesterol, estimated glomerular filtration rate, CRP, and infarction patterns. The Kaplan-Meier product-limit method was used to estimate the incidence rates of recurrent stroke, ischemic stroke, combined vascular events, and death during the follow-up period. We also used the Cox proportional-hazards model or multivariable regression model to test the interaction between CK and sex or age. Similar analysis was used to investigate the associations of CK-MB and clinical outcomes, with a normal upper limit of 25 U/L in all patients.

Overall, a 2-sided $P<0.05$ was considered statistically significant. All analyses were performed with SAS software version 9.4 (SAS Institute Inc, Cary, NC).

RESULTS

Baseline Characteristics

Among 15 166 patients with final diagnosis of AIS or TIA, 5953 without CK values and 303 without available mRS score at 3 months or 1 year were excluded. Thus, a total of 8910 patients were included in this study. Baseline characteristics of patients included and excluded were balanced, except that the patients included had slightly higher proportions of coronary heart diseases and atrial fibrillation and lower proportion of history of ischemic stroke or TIA ($P<0.05$ for all). In addition, included patients had slightly higher levels of total cholesterol, low-density lipoprotein cholesterol, and fasting blood glucose ($P<0.05$; Table S1).

Among all included patients, the median age was 63 years, and 6120 (68.7%) patients were men. There were 12.5% patients with elevated CK levels in men and 8.4% in women ($P<0.05$). Men had higher levels of serum CK than women (median, 86.0 versus 66.0 U/L; $P<0.05$). Compared with patients with normal CK, those with elevated CK had higher proportions of atrial fibrillation, subtype of large-artery atherosclerosis, epilepsy, and multiple infarctions, and higher NIHSS score and CRP level (Table 1).

CK and Clinical Outcomes

Patients with elevated CK levels had higher incidence of stroke, ischemic stroke, and CVE at 3 months compared with patients in normal CK group (Table 2 and Figure 1). The adjusted HRs (95% CIs) for the elevated versus normal CK were 1.53 (1.21–1.93), 1.52 (1.20–1.94), and 1.56 (1.25–1.96) for recurrent stroke, ischemic stroke, and CVE at 3 months after adjusting for potential confounding factors, including age, sex, history of diabetes, atrial fibrillation/flutter, hypoglycemic agents, TOAST subtype, epilepsy (discharge diagnosis), NIHSS score on admission, high-density lipoprotein cholesterol, estimated glomerular filtration rate, CRP, and infarction patterns. Similar results were found at 1 year (Table 2 and Figure S1).

Elevated CK levels were also associated with higher incidence of death (adjusted HR, 1.68; 95% CI, 1.10–2.58) and disability (mRS score 3–6; adjusted OR, 1.57; 95% CI, 1.29–1.90) at 3 months after adjusting for potential confounding factors. There were significant shifts in the distributions of the mRS scores according to CK groups (Figure 2), and the common OR is 1.58 (95% CI, 1.40–1.78) for mRS scores at 3 months. Similar results were found at 1 year (Table 3).

Effects of Sex on CK and Outcomes

In this study, we analyzed whether the effects of CK on clinical outcomes were different in men and women. Stratified analysis by sex showed men with elevated CK levels (versus normal CK) had higher incidence of stroke (HR, 1.59; 95% CI, 1.21–2.08), ischemic stroke (HR, 1.59; 95% CI, 1.20–2.10), CVE (HR, 1.66; 95% CI, 1.28–2.15), death (HR, 2.33; 95% CI, 1.40–3.90), mRS score 2 to 6 (OR, 1.57; 95% CI, 1.29–1.90), and mRS score 3 to 6 (OR, 1.70; 95% CI, 1.35–2.13) at 3 months after adjusting for potential confounding factors. Similar results were found at 1 year. However, similar associations were not found in women. The adjusted HRs/ORs (95% CIs) of elevated CK group versus normal CK were 1.50 (0.91–2.46) for stroke, 1.41 (0.84–2.37) for ischemic stroke, 1.41 (0.87–2.31) for CVE, 0.99 (0.37–2.67) for death, 1.00 (0.70–1.42) for mRS score 2 to 6, and 1.26 (0.84–1.87) for mRS score 3 to 6. P value for interaction was significant ($P<0.05$) between CK and sex for death and disability. However, there was no significant interaction ($P>0.05$) between CK and sex for recurrent events (Table S2).

CK-MB and Clinical Outcomes

Excluding 1296 patients without CK-MB, total 7614 patients were included in the analysis of CK-MB and clinical outcomes. Baseline characteristics according

Table 1. Baseline Characteristics According to CK Level

Variables	Overall (n=8910)	CK level		P value
		Normal (n=7910)	High (n=1000)	
CK level, median (IQR), U/L				
Total	79.0 (56.8–114.1)	73.2 (54.0–100.0)	228.4 (190.0–327.0)	<0.0001
Men	86.0 (62.0–123.0)	79.0 (59.0–106.0)	235.0 (196.0–342.0)	<0.0001
Women	66.0 (49.0–94.1)	63.0 (47.0–85.0)	200.0 (162.0–282.0)	<0.0001
Age, median (IQR), y	63 (54–70)	63 (54–70)	62 (54–71)	0.9989
Men, n (%)	6120 (68.7)	5353 (67.7)	767 (76.7)	<0.0001
BMI, median (IQR), kg/m^2	24.5 (22.6–26.6)	24.5 (22.6–26.6)	24.5 (22.6–26.6)	0.6093
SBP, median (IQR), mm Hg	149 (135–164)	148 (135–164)	149 (135–165)	0.4038
DBP, median (IQR), mm Hg	86 (79–96)	86 (79–95)	87 (80–97)	0.2714
NIHSS score, median (IQR)	3 (1–6)	3 (1–6)	4 (2–7)	<0.0001
Current smoker, n (%)	2793 (31.4)	2478 (31.3)	315 (31.5)	0.9117
Medical history, n (%)				
Hypertension	5528 (62.0)	4896 (61.9)	632 (63.2)	0.4235
Diabetes	2065 (23.2)	1888 (23.9)	177 (17.7)	<0.0001
Dyslipidemia	719 (8.1)	643 (8.1)	76 (7.6)	0.5628
Ischemic stroke or TIA	1879 (21.1)	1671 (21.1)	208 (20.8)	0.8123
Coronary heart diseases	1016 (11.4)	912 (11.5)	104 (10.4)	0.2896
Atrial fibrillation/flutter	646 (7.3)	558 (7.1)	88 (8.8)	0.0449
Epilepsy	25 (0.3)	23 (0.3)	2 (0.2)	0.6091
Previous medication, n (%)				
Cholesterol-lowering agents	953 (10.7)	859 (10.9)	94 (9.4)	0.1594
Statins	910 (10.2)	819 (10.4)	91 (9.1)	0.2173
Antihypertensive agents	3947 (44.3)	3502 (44.3)	445 (44.5)	0.8917
Hypoglycemic agents	1638 (18.4)	1497 (18.9)	141 (14.1)	0.0002
Antiplatelet agents	1472 (16.5)	1310 (16.6)	162 (16.2)	0.7719
Anticoagulant agents	94 (1.1)	80 (1.0)	14 (1.4)	0.2571
Stroke type, n (%)				
Ischemic stroke	8323 (93.4)	7377 (93.3)	946 (94.6)	0.1080
TIA	587 (6.6)	533 (6.7)	54 (5.4)	
TOAST subtype, n (%)				
Large-artery atherosclerosis	2236 (25.1)	1956 (24.7)	280 (28.0)	0.0130
Cardioembolism	557 (6.3)	488 (6.2)	69 (6.9)	
Small-vessel occlusion	1780 (20.0)	1617 (20.4)	163 (16.3)	
Other determined cause	119 (1.3)	108 (1.4)	11 (1.1)	
Undetermined cause	4218 (47.3)	3741 (47.3)	477 (47.7)	
Epilepsy (discharge diagnosis), n (%)	38 (0.4)	28 (0.4)	10 (1.0)	0.0031
Lipid levels, median (IQR), mmol/L				
TC	4.01 (3.33–4.77)	4.00 (3.31–4.77)	4.05 (3.44–4.77)	0.1072
LDL	2.34 (1.73–3.01)	2.33 (1.73–3.01)	2.40 (1.84–3.02)	0.1313
HDL	0.93 (0.78–1.13)	0.93 (0.77–1.13)	0.96 (0.80–1.15)	0.0330
Triglyceride	1.37 (1.03–1.88)	1.37 (1.03–1.88)	1.35 (0.99–1.87)	0.3173
FBG, median (IQR), mmol/L	5.59 (4.92–6.97)	5.58 (4.91–7.01)	5.63 (5.00–6.65)	0.7737
eGFR, median (IQR), mL/min per 1.73 m^2	93.10 (81.24–102.03)	93.49 (81.64–102.35)	90.98 (76.57–100.68)	<0.0001

(Continued)

Table 1. Continued

Variables	Overall (n=8910)	CK level		P value
		Normal (n=7910)	High (n=1000)	
CRP, median (IQR), mg/L	2.99 (1.10–6.60)	2.82 (1.10–6.30)	4.13 (1.44–9.42)	0.0015
Infarction pattern, n (%)				0.0007
No infarction	905 (12.02)	814 (12.17)	91 (10.82)	
Single infarction	3169 (42.07)	2848 (42.56)	321 (38.17)	
Multiple infarction	3458 (45.91)	3029 (45.27)	429 (51.01)	

BMI indicates body mass index; CK, creatine kinase; CRP, C-reactive protein; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure; TC, total cholesterol; TIA, transient ischemic attack; and TOAST, Trial of Org 10172 in Acute Stroke Treatment.

to CK-MB levels are shown in Table S3. There was no significant difference between patients with normal and elevated CK-MB levels in clinical outcomes of recurrent events, death, and disability at 3 months and 1 year (Table S4).

DISCUSSION

This study showed that elevated CK was associated with stroke recurrence, death, and disability at 3 months and 1 year in patients with AIS or TIA. Serum CK-MB had little effect on clinical outcomes in this study.

The function of CK is catalyzing the reaction between creatine and ATP to form creatine phosphate and ADP, which is important for cell energy production and metabolism. Many studies showed serum CK levels were increased in patients with acute stroke, but the tissue sources of elevated CK remained controversial. Most serum CK in healthy people is CK-MM, which is also proved to be the main isozyme in patients with stroke.[2] Many researchers considered that increased serum CK activity following AIS probably originated from skeletal muscle rather than cardiac muscle or brain tissue.[5] As a specific marker of myocardial ischemia, serum CK-MB was elevated in some patients after acute stroke,[8] which is usually accompanied by nonspecific changes on ECG.[9] However, this manifestation was usually not accompanied by significant troponin elevation and final diagnosis of acute myocardial infarction.[8] Studies found that plasma catecholamine levels in patients with

Table 2. Association of CK With Stroke Recurrence: HRs (95% CIs)

Outcomes	3 mo		1 y	
	Normal (n=7910)	High (n=1000)	Normal (n=7910)	High (n=1000)
Stroke	470 (5.94)	92 (9.20)	763 (9.65)	135 (13.50)
Unadjusted	Reference	1.59 (1.27–2.00)	Reference	1.44 (1.20–1.74)
Model 1	Reference	1.60 (1.28–2.02)	Reference	1.45 (1.21–1.75)
Model 2	Reference	1.53 (1.21–1.93)	Reference	1.40 (1.16–1.69)
Model 2*	Reference	1.54 (1.22–1.94)	Reference	1.40 (1.16–1.69)
Ischemic stroke	446 (5.64)	85 (8.50)	718 (9.08)	123 (12.30)
Unadjusted	Reference	1.55 (1.22–1.96)	Reference	1.39 (1.14–1.69)
Model 1	Reference	1.56 (1.23–1.98)	Reference	1.41 (1.16–1.71)
Model 2	Reference	1.52 (1.20–1.94)	Reference	1.38 (1.13–1.68)
Model 2*	Reference	1.53 (1.20–1.94)	Reference	1.37 (1.13–1.67)
CVE	488 (6.17)	98 (9.80)	805 (10.18)	147 (14.70)
Unadjusted	Reference	1.63 (1.31–2.04)	Reference	1.49 (1.25–1.79)
Model 1	Reference	1.64 (1.31–2.05)	Reference	1.51 (1.26–1.80)
Model 2	Reference	1.56 (1.25–1.96)	Reference	1.45 (1.21–1.74)
Model 2*	Reference	1.57 (1.25–1.96)	Reference	1.45 (1.21–1.73)

Model 1 was adjusted for age and sex. Model 2 was adjusted for age, sex, history of diabetes, atrial fibrillation/flutter, hypoglycemic agents, TOAST (Trial of Org 10172 in Acute Stroke Treatment) subtype, epilepsy (discharge diagnosis), National Institutes of Health Stroke Scale score on admission, high-density lipoprotein, estimated glomerular filtration rate, CRP (C-reactive protein), and infarction pattern. CK indicates creatine kinase; CVE, combined vascular events; and HR, hazard ratio.

*Competing risk model.
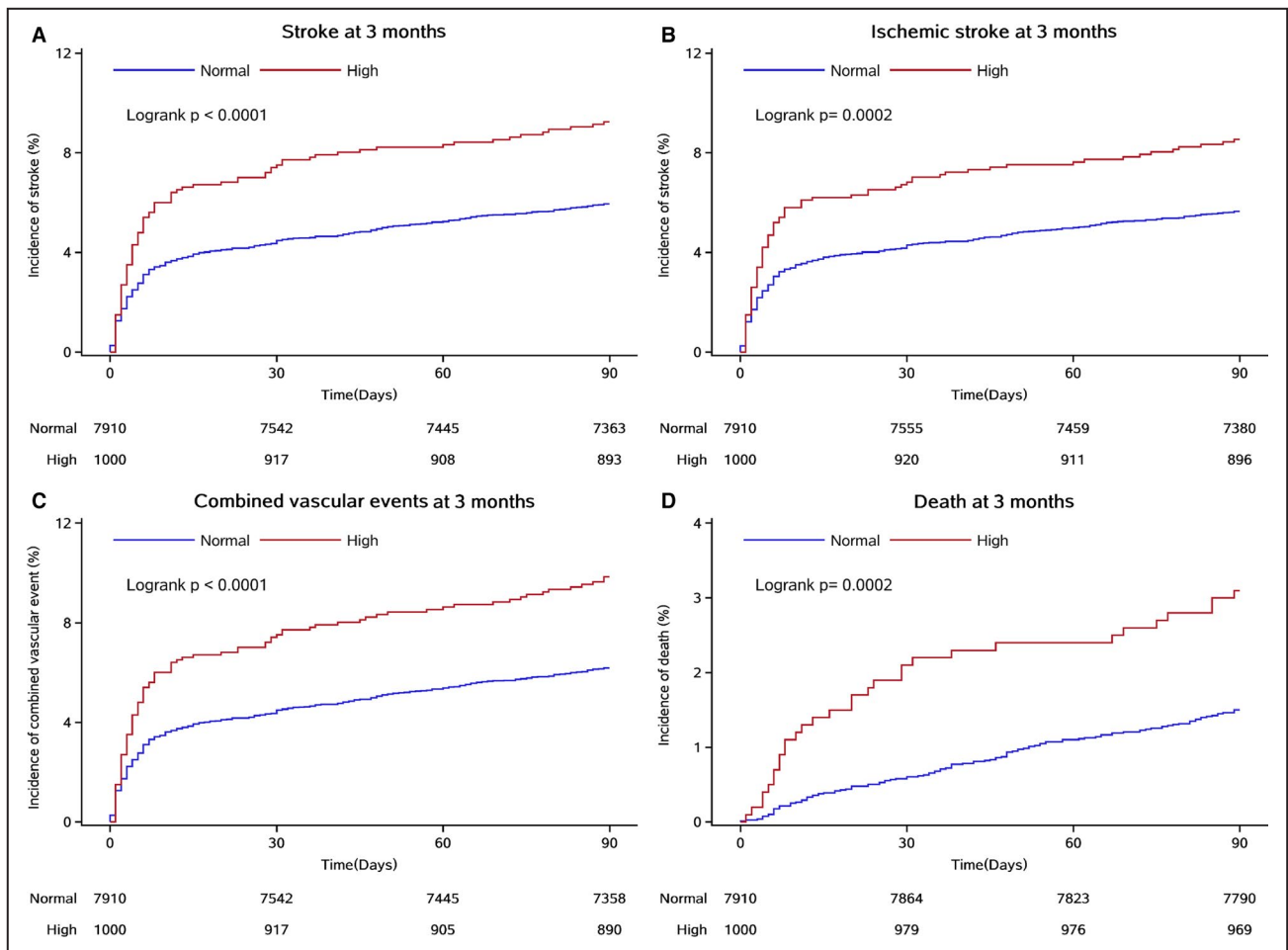
Figure 1. Kaplan-Meier curves of creatine kinase (CK) for stroke recurrence and death at 3 months.
A, Kaplan-Meier curve for stroke recurrence. **B**, Kaplan-Meier curve for ischemic stroke recurrence. **C**, Kaplan-Meier curve for composite vascular events. **D**, Kaplan-Meier curve for all-cause mortality. High indicates elevated serum CK level; and Normal, normal serum CK level.

stroke were significantly increased[10]; thus, elevated CK-MB and electrocardiographic changes following acute stroke might be neurogenic instead of cardiac in origin.[11] In this study, we found that elevated CK-MB was not associated with stroke recurrence and functional outcomes after AIS or TIA. CK-BB mainly exists in the brain tissue, and it is rarely or even not detected in blood in healthy people. Many studies found increased CK-BB in cerebrospinal fluid of patients with stroke.[12] However, it is still controversial whether serum CK-BB is elevated in patients with stroke.[13] Some studies detected CK-BB in serum in acute cerebral disorders,[14] suggesting that clinical brain damage might cause release of brain tissue enzymes into peripheral blood,[15] whereas others found the opposite.[5] This inconsistency might be related to the timing of poststroke detection, location of infarction, and extent of brain tissue or blood-brain barrier damage. Elevated CK after stroke might consist of either part or all 3 isozymes, which might depend

on infarct size,[12] infarct location,[16] and concomitant diseases. Therefore, serum CK may reflect the total damage of systemic tissues after stroke.

Possible mechanisms of how elevated CK influenced outcomes were also unclear. It is possible that CK is an intermediate indicator in the pathway, instead of a direct risk factor affecting the outcomes. Patients with elevated CK levels had higher proportions of subtype of large-artery atherosclerosis, multiple infarctions, and higher CRP levels, which showed that these patients might have higher inflammatory or oxidative stress loads, leading to a higher risk of stroke recurrence. In our study, CK was still associated with stroke recurrence after adjusting for confounding factors in the multivariable analyses. Further research is needed to investigate the role of CK in stroke recurrence. In addition, patients with elevated CK levels had higher NIHSS scores, and elevated CK was also associated with disability independent of NIHSS score. Further studies are needed to investigate the relationship
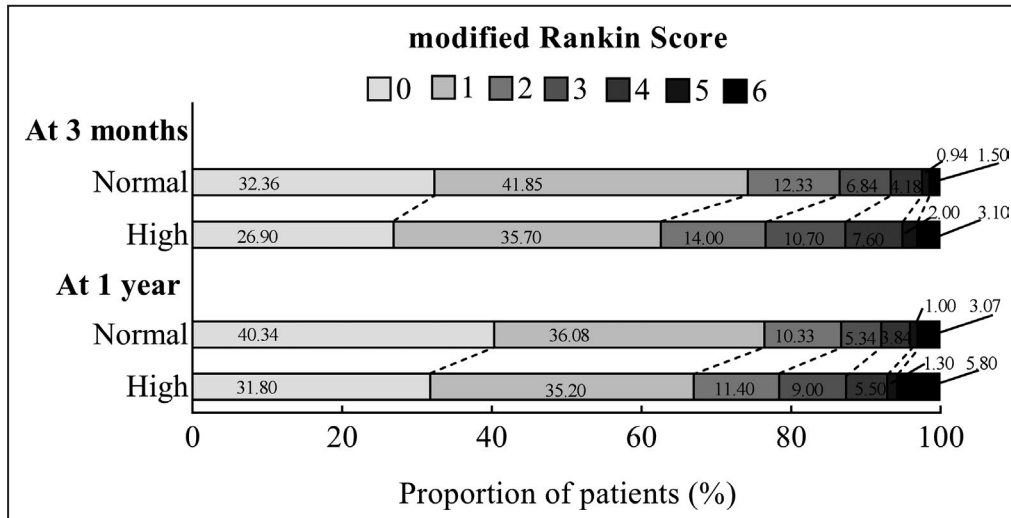
Figure 2. Distribution of modified Rankin scale score between creatine kinase (CK) groups at 3 months and 1 year.
High indicates elevated serum CK level; and Normal, normal serum CK level.

between CK and neuroimaging indicators, such as infarct size or specific infarct location.[16]

CK levels varied according to many factors, such as race, sex, age, physical activity, and so on. It is known that baseline CK levels are higher in Black than in White individuals, and men have higher CK levels than women.[17] Studies found an age-dependent decrease in CK levels, especially in men, which was thought to be related to decreases in muscle mass with age.[17] In this study, we used the upper limit of normal for serum CK recommended by International Federation of Clinical Chemistry and Laboratory Medicine,[7] which is close to the manufacturer's recommended level (men, 174 U/L; women,

140 U/L). Although evidence suggested that the variation of CK activity in the general population was wider than reference intervals in current use,[18] there were not recognized reference limits in guidelines based on general population, especially in Asia. We analyzed the impact of CK on stroke outcomes in men and women separately. Results showed elevated CK was only associated with death and disability in men. Although stratified analysis showed that male patients with elevated CK seemed to have a higher risk of stroke recurrence, the interaction was not statistically significant. We also analyzed the impact of CK on stroke outcomes in patients classified by age (<60 and ≥60 years), and no significant difference

Table 3. Association of CK With Death and Disability

Outcomes	3 mo		1 y	
	Normal (n=7910)	High (n=1000)	Normal (n=7910)	High (n=1000)
Death	119 (1.50)	31 (3.10)	243 (3.07)	58 (5.80)
Unadjusted HR	Reference	2.12 (1.41–3.18)	Reference	1.88 (1.40–2.52)
Model 1 HR	Reference	2.12 (1.41–3.21)	Reference	1.85 (1.38–2.49)
Model 2 HR	Reference	1.68 (1.10–2.58)	Reference	1.38 (1.01–1.87)
mRS score 3–6	1065 (13.46)	234 (23.40)	1048 (13.25)	216 (21.60)
Unadjusted OR	Reference	1.88 (1.59–2.23)	Reference	1.72 (1.44–2.04)
Model 1 OR	Reference	1.98 (1.67–2.35)	Reference	1.77 (1.49–2.12)
Model 2 OR	Reference	1.57 (1.29–1.90)	Reference	1.38 (1.13–1.67)
mRS score 2–6	2040 (25.79)	374 (37.40)	1865 (23.58)	330 (33.00)
Unadjusted OR	Reference	1.65 (1.42–1.98)	Reference	1.53 (1.31–1.77)
Model 1 OR	Reference	1.71 (1.47–1.98)	Reference	1.57 (1.35–1.83)
Model 2 OR	Reference	1.38 (1.17–1.63)	Reference	1.28 (1.08–1.51)

Data are given as HR/OR (95% CI). Model 1 was adjusted for age and sex. Model 2 was adjusted for age, sex, history of diabetes, atrial fibrillation/flutter, hypoglycemic agents, TOAST (Trial of Org 10172 in Acute Stroke Treatment) subtype, epilepsy (discharge diagnosis), National Institutes of Health Stroke Scale score on admission, high-density lipoprotein, estimated glomerular filtration rate, CRP (C-reactive protein), and infarction pattern. CK indicates creatine kinase; HR, hazard ratio; mRS, modified Rankin scale; and OR, odds ratio.

was found (*P* for interaction >0.05 for all; Table S5). Use of statins and seizures may also influence baseline serum CK levels. In this study, there was no difference between 2 groups in previous use of statins and epilepsy history. Although a higher proportion of patients in high CK group was diagnosed with epilepsy at discharge, we adjusted it in multivariable analyses.

The strength of this study was that it is based on a large population of AIS or TIA from a multicenter registry. To date, there is a lack of similar articles on the relationship between CK and clinical outcomes after AIS. This study also had limitations: (1) we did not do isoenzyme analysis to distinguish CK-MM and CH-BB; thus, tissue sources of elevated CK and potential mechanisms could not be further explained; and (2) this study only monitored baseline CK levels and did not examine changes of CK over time. Therefore, further research is needed to verify the relationship between CK and clinical outcomes of ischemic stroke and confirm underlying mechanisms. Possible sex differences between CK and stroke outcomes need more research to investigate.

CONCLUSIONS

Elevated serum CK after ischemic stroke or TIA is associated with higher risks of recurrent stroke, death, and disability at 3 months and 1 year.

Supplemental Material

Tables S1–S5
Figure S1

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Supplemental Material

Table S1. Baseline characteristics of included and excluded patients.

Variables	Overall	Included	Excluded	P
n	15166	8910	6256	
Age, median (IQR), y	63 (54-70)	63 (54-70)	62 (54-70)	0.1167
Male (n,%)	10364 (68.3)	6120 (68.7)	4244 (67.8)	0.2691
BMI, kg/m^2	24.5 (22.6-26.6)	24.5 (22.6-26.6)	24.5 (22.7-26.5)	0.4391
SBP, median (IQR), mmHg	148 (135-164)	149 (135-164)	148 (135-163)	0.3294
DBP,median (IQR), mmHg	86 (79-95)	86 (79-96)	86 (79-95)	0.4122
NIHSS score on admission	3 (1-6)	3 (1-6)	3 (1-6)	0.5797
Current smoker (n,%)	4752 (31.3)	2793 (31.4)	1959 (31.3)	0.9657
Medical history (n,%)				
Hypertension	9494 (62.6)	5528 (62.0)	3966 (63.4)	0.0902
Diabetes mellitus	3510 (23.1)	2065 (23.2)	1445 (23.1)	0.9103
Dyslipidemia	1191 (7.9)	719 (8.1)	472 (7.5)	0.2369
Ischemic stroke or TIA	3355 (22.1)	1879 (21.1)	1476 (23.6)	0.0003
Coronary heart diseases	1608 (10.6)	1016 (11.4)	592 (9.5)	0.0001
Atrial fibrillation/flutter	1019 (6.7)	646 (7.3)	373 (6.0)	0.0018
Epilepsy	48(0.32)	23(0.37)	25(0.28)	0.3474
Previous medication (n,%)				
Cholesterol-lowering agents	1671 (11.0)	953 (10.7)	718 (11.5)	0.1304
Antihypertensive agents	6795 (44.8)	3947 (44.3)	2848 (45.5)	0.1351
Hypoglycemic agents	2773 (18.3)	1638 (18.4)	1135 (18.1)	0.7051
Antiplatelet agents	2605 (17.2)	1472 (16.5)	1133 (18.1)	0.0106
Anticoagulant agents	147 (1.0)	94 (1.1)	53 (0.8)	0.1985
Stroke type (n,%)				
Ischemic stroke	14146 (93.3)	8323 (93.4)	5823 (93.1)	0.4199
TIA	1020 (6.7)	587 (6.6)	433 (6.9)	
TOAST subtype (n,%)				

Variables	Overall	Included	Excluded	P
Large-artery atherosclerosis	3856 (25.4)	2236 (25.1)	1620 (25.9)	0.0015
Cardioembolism	917 (6.0)	557 (6.3)	360 (5.8)	
Small-vessel occlusion	3165 (20.9)	1780 (20.0)	1385 (22.1)	
Other determined etiology	182 (1.2)	119 (1.3)	63 (1.0)	
Undetermined etiology	7046 (46.5)	4218 (47.3)	2828 (45.2)	
Epilepsy (discharge diagnosis)	72(0.47)	34(0.54)	38(0.43)	0.3022
Lipid levels, median (IQR), mmol/L				
TC	3.97 (3.31-4.72)	4.01 (3.33-4.77)	3.92 (3.29-4.66)	0.0010
LDL	2.31 (1.73-2.97)	2.34 (1.73-3.01)	2.27 (1.71-2.93)	0.0037
HDL	0.93 (0.78-1.12)	0.93 (0.78-1.13)	0.93 (0.77-1.10)	0.2105
TG	1.37 (1.03-1.87)	1.37 (1.03-1.88)	1.37 (1.03-1.86)	0.7163
FBG, median (IQR), mmol/L	5.52 (4.90-6.89)	5.59 (4.92-6.97)	5.45 (4.84-6.76)	<0.0001
eGFR, median (IQR), mL/min/1.73 m^2	93.20 (81.57-102.03)	93.10 (81.24-102.03)	93.39 (82.14-102.02)	0.3615
CRP, median (IQR), mg/L	2.87 (1.10-6.40)	2.99 (1.10-6.60)	2.69 (1.11-6.00)	0.1655
Infarction pattern (n, %)				0.2842
No Infarction	1593(12.24)	688(12.55)	905(12.02)	
Single Infarction	5519(42.41)	2350(42.88)	3169(42.07)	
Multiple Infarction	5900(45.34)	2442(44.56)	3458(45.91)	

BMI indicates body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TIA, transient ischemic attack; NIHSS, National Institutes of Health Stroke Scale; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglyceride; FBG, fasting blood glucose; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; IQR, interquartile range.

Table S2. The association of CK with outcomes stratified by sex.

Outcomes	Male		Female		P for interaction
	Normal	High	Normal	High	(adjusted)
3 months					
Stroke	304 (5.68)	71 (9.26)	166 (6.49)	21 (9.01)	
Adjusted HR*	Ref.	1.59(1.21-2.08)	Ref.	1.50(0.91-2.46)	0.6010
Ischemic Stroke	285 (5.32)	66 (8.60)	161 (6.30)	19 (8.15)	
Adjusted HR	Ref.	1.59(1.20-2.10)	Ref.	1.41(0.84-2.37)	0.5171
CVE	315 (5.88)	77 (10.04)	173 (6.77)	21 (9.01)	
Adjusted HR	Ref.	1.66(1.28-2.15)	Ref.	1.41(0.87-2.31)	0.3954
Death	63 (1.18)	26 (3.39)	56 (2.19)	5 (2.15)	
Adjusted HR	Ref.	2.33(1.40-3.90)	Ref.	0.99(0.37-2.67)	0.0425
mRS 3-6	615 (11.49)	173 (22.56)	450 (17.60)	61 (26.18)	
Adjusted OR	Ref.	1.70(1.35-2.13)	Ref.	1.26(0.84-1.87)	0.1917
mRS 2-6	1265 (23.63)	286 (37.29)	775 (30.31)	88 (37.77)	
Adjusted OR	Ref.	1.57(1.29-1.90)	Ref.	1.00(0.70-1.42)	0.0275
1 year					
Stroke	498 (9.30)	102 (13.30)	265 (10.36)	33 (14.16)	
Adjusted HR*	Ref.	1.44(1.15-1.79)	Ref.	1.43(0.96-2.12)	0.8013
Ischemic Stroke	466 (8.71)	92 (11.99)	252 (9.86)	31 (13.30)	
Adjusted HR	Ref.	1.40(1.11-1.76)	Ref.	1.43(0.95-2.15)	0.9794
CVE	526 (9.83)	113 (14.73)	279 (10.91)	34 (14.59)	
Adjusted HR	Ref.	1.52(1.23-1.88)	Ref.	1.38(0.94-2.03)	0.5610
Death	136 (2.54)	50 (6.52)	107 (4.18)	8 (3.43)	
Adjusted HR	Ref.	1.98(1.39-2.81)	Ref.	0.70(0.32-1.51)	0.0056
mRS 3-6	626 (11.69)	163 (21.25)	422 (16.50)	53 (22.75)	
Adjusted OR	Ref.	1.61(1.28-2.02)	Ref.	1.07(0.71-1.61)	0.0500
mRS 2-6	1167 (21.80)	255 (33.25)	698 (27.30)	75 (32.19)	
Adjusted OR	Ref.	1.50(1.24-1.82)	Ref.	0.93(0.65-1.33)	0.0203

CVE, Combined vascular events; mRS, modified Rankin scale; HR, hazards ratios; OR, odds ratios.

*Adjusted for age, sex, history of diabetes mellitus, atrial fibrillation/flutter, hypoglycemic agents, TOAST subtype, epilepsy (discharge diagnosis), NIHSS score on admission, HDL, eGFR, CRP and infarction pattern.

Table S3. Baseline characteristics according to CK-MB.

Variables	Overall	CK-MB, U/L		P
		Normal	High	
n	7614	7291	323	
CK-MB, median (IQR), U/L				
Total	13.0 (10.0-16.2)	12.7 (10.0-16.0)	32.0 (28.0-40.0)	<0.0001
Male	13.0 (10.0-16.7)	13.0 (10.0-16.0)	31.0 (28.0-38.0)	<0.0001
Female	12.9 (10.0-16.0)	12.0 (9.7-15.6)	32.8 (28.0-47.0)	<0.0001
Age, median (IQR), y	63 (54-70)	63 (54-70)	63 (54-70)	0.5903
Male (n,%)	5218 (68.5)	4996 (68.5)	222 (68.7)	0.9373
BMI, median (IQR), kg/m^2	24.5 (22.6-26.6)	24.49 (22.6-26.6)	24.6 (22.5-26.3)	0.7110
SBP, median (IQR), mmHg	149 (135-164)	149 (135-164)	147 (133-163)	0.6027
DBP, median (IQR), mmHg	87 (80-96)	86 (80-96)	89 (79-96)	0.4141
NIHSS, median (IQR)	3 (1-6)	3 (1-6)	4 (2-6)	0.0250
Current smoker (n,%)	2362 (31.0)	2260 (31.0)	102 (31.6)	0.8249
Medical history (n,%)				
Hypertension	4702 (61.8)	4516 (61.9)	186 (57.6)	0.1151
Diabetes mellitus	1768 (23.2)	1696 (23.3)	72 (22.3)	0.6860
Dyslipidemia	614(8.1)	595 (8.2)	19 (5.9)	0.1411
Ischemic stroke or TIA	1603 (21.1)	1529 (21.0)	74 (22.9)	0.4029
Coronary heart diseases	867 (11.4)	833 (11.4)	34 (10.5)	0.6188
Atrial fibrillation/flutter	536 (7.0)	512 (7.0)	24 (7.4)	0.7791
Epilepsy	22(0.29)	22(0.30)	0(0.00)	0.3228
Previous medication (n,%)				
Cholesterol-lowering agents	801 (10.5)	764 (10.5)	37 (11.5)	0.5757
Statins	763 (10.0)	726 (10.0)	37 (11.5)	0.3804
Antihypertensive agents	3372 (44.3)	3236 (44.4)	136 (42.1)	0.4199
Hypoglycemic agents	1396 (18.3)	1338 (18.4)	58 (18.0)	0.8576

Variables	Overall	CK-MB, U/L		
		Normal	High	P
Antiplatelet agents	1232 (16.2)	1168 (16.0)	64 (19.8)	0.0700
Anticoagulant agents	77 (1.0)	73 (1.0)	4 (1.2)	0.6768
Stroke type (n,%)				
Ischemic stroke	7111 (93.4)	6808 (93.4)	303 (93.8)	0.7594
TIA	503 (6.6)	483 (6.6)	20 (6.2)	
TOAST subtype (n,%)				
Large-artery atherosclerosis	1926 (25.3)	1836 (25.2)	90 (27.9)	0.1552
Cardioembolism	458 (6.0)	438 (6.0)	20 (6.2)	
Small-vessel occlusion	1522 (20.0)	1475 (20.2)	47 (14.6)	
Other determined etiology	110 (1.4)	104 (1.4)	6 (1.9)	
Undetermined etiology	3598 (47.3)	3438 (47.2)	160 (49.5)	
Epilepsy (discharge diagnosis)	33(0.43)	29(0.40)	4(1.24)	0.0244
Lipid levels, median (IQR), mmol/L				
TC	4.02 (3.34-4.77)	4.02 (3.34-4.78)	3.97 (3.23-4.66)	0.1429
LDL	2.36 (1.75-3.01)	2.36 (1.75-3.02)	2.31 (1.69-2.85)	0.0845
HDL	0.93 (0.77-1.13)	0.93 (0.77-1.13)	0.94 (0.79-1.13)	0.7259
TG	1.37 (1.03-1.88)	1.37 (1.03-1.89)	1.36 (0.94-1.77)	0.0958
FBG, median (IQR), mmol/L	5.60 (4.92-7.00)	5.60 (4.92-7.00)	5.50 (4.85-6.64)	0.1521
eGFR, median (IQR), mL/min/1.73 m^2	93.30 (81.40-102.11)	93.30 (81.48-102.12)	93.44 (79.76-102.10)	0.8927
CRP, median (IQR), mg/L	2.80 (1.01-6.40)	2.79 (1.00-6.27)	4.50 (1.48-9.12)	0.0188
Infarction pattern (n, %)				0.2480
No Infarction	765(11.81)	738(11.89)	27(9.96)	
Single Infarction	2724(42.04)	2618(42.17)	106(39.11)	
Multiple Infarction	2990(46.15)	2852(45.94)	138(50.92)	

BMI indicates body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TIA, transient ischemic attack;

NIHSS, National Institutes of Health Stroke Scale; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density

lipoprotein; TG, triglyceride; FBG, fasting blood glucose; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein;

IQR, interquartile range.

Table S4. The association of CK-MB with clinical outcomes.

Outcomes	3 months		1 year	
	Normal	High	Normal	High
Stroke	461 (6.32)	22 (6.81)	758 (10.40)	31 (9.60)
Unadjusted HR	Ref.	1.08 (0.70-1.67)	Ref.	0.97 (0.67-1.40)
Adjusted*	Ref.	1.02(0.66-1.58)	Ref.	0.92(0.64-1.33)
Adjusted#	Ref.	1.04(0.67-1.60)	Ref.	0.91(0.64-1.31)
Ischemic Stroke	438 (6.01)	20 (6.19)	711 (9.75)	29 (8.98)
Unadjusted HR	Ref.	1.04 (0.66-1.64)	Ref.	0.97 (0.67-1.42)
Adjusted*	Ref.	0.99(0.63-1.57)	Ref.	0.93(0.64-1.37)
Adjusted#	Ref.	1.01(0.64-1.58)	Ref.	0.93(0.64-1.34)
CVE	482 (6.61)	23 (7.12)	805 (11.04)	34 (10.53)
Unadjusted HR	Ref.	1.07 (0.70-1.65)	Ref.	0.99 (0.70-1.41)
Adjusted*	Ref.	1.01(0.66-1.55)	Ref.	0.94(0.66-1.34)
Adjusted#	Ref.	1.03(0.67-1.58)	Ref.	0.94(0.67-1.32)
Death	121 (1.66)	6 (1.86)	245 (3.36)	16 (4.95)
Unadjusted HR	Ref.	1.12 (0.48-2.59)	Ref.	1.44 (0.85-2.42)
Adjusted	Ref.	0.64(0.27-1.54)	Ref.	1.04(0.61-1.78)
mRS 3-6	1066 (14.62)	54 (16.72)	1035 (14.20)	56 (17.34)
Unadjusted OR	Ref.	1.12 (0.81-1.53)	Ref.	1.17 (0.86-1.60)
Adjusted	Ref.	0.92(0.64-1.32)	Ref.	1.01(0.72-1.43)
mRS 2-6	1995 (27.36)	94 (29.10)	1820 (24.96)	92 (28.48)
Unadjusted OR	Ref.	1.04 (0.80-1.36)	Ref.	1.12 (0.86-1.45)
Adjusted	Ref.	0.90(0.67-1.21)	Ref.	1.00(0.75-1.33)

*Adjusted for NIHSS score on admission, CRP, and epilepsy (discharge diagnosis).

#competing risk model

Table S5. The association of CK with outcomes stratified by age.

Outcomes	<60y		≥60y		P for interaction (adjusted)
	Normal	High	Normal	High	
3 months					
Stroke	160 (5.26)	29 (7.36)	310 (6.37)	63 (10.40)	
Adjusted HR*	Ref.	1.29(0.80-2.09)	Ref.	1.61(1.17-2.23)	0.5594
Ischemic Stroke	150 (4.93)	28 (7.11)	296 (6.08)	57 (9.41)	
Adjusted HR	Ref.	1.37(0.84-2.23)	Ref.	1.52(1.08-2.14)	0.8645
CVE	165 (5.42)	29 (7.36)	323 (6.64)	69 (11.39)	
Adjusted HR	Ref.	1.28(0.79-2.05)	Ref.	1.72(1.27-2.35)	0.3359
Death	17 (0.56)	5 (1.27)	102 (2.10)	26 (4.29)	
Adjusted HR	Ref.	5.53(1.02-30.05)	Ref.	2.27(1.30-3.99)	0.9148
mRS 3-6	278 (9.13)	60 (15.23)	787 (16.17)	174 (28.71)	
Adjusted OR	Ref.	1.17(0.77-1.78)	Ref.	1.97(1.52-2.55)	0.1454
mRS 2-6	605 (19.88)	115 (29.19)	1435 (29.49)	259 (42.74)	
Adjusted OR	Ref.	1.28(0.93-1.77)	Ref.	1.51(1.20-1.90)	0.5389
1 year					
Stroke	253 (8.31)	45 (11.42)	510 (10.48)	90 (14.85)	
Adjusted HR*	Ref.	1.32(0.91-1.92)	Ref.	1.34(1.02-1.76)	0.9366
Ischemic Stroke	235 (7.72)	43 (10.91)	483 (9.93)	80 (13.20)	
Adjusted HR	Ref.	1.39(0.94-2.04)	Ref.	1.26(0.94-1.67)	0.6867
CVE	264 (8.67)	46 (11.68)	541 (11.12)	101 (16.67)	
Adjusted HR	Ref.	1.32(0.91-1.91)	Ref.	1.44(1.12-1.86)	0.6350
Death	30 (0.99)	11 (2.79)	213 (4.38)	47 (7.76)	
Adjusted HR	Ref.	3.23(1.20-8.69)	Ref.	1.59(1.08-2.34)	0.2664
mRS 3-6	219 (7.19)	58 (14.72)	829 (17.04)	158 (26.07)	
Adjusted OR	Ref.	1.57(1.02-2.41)	Ref.	1.42(1.10-1.85)	0.3879
mRS 2-6	495 (16.26)	103 (26.14)	1370 (28.15)	227 (37.46)	

Outcomes	<60y		≥60y		P for interaction (adjusted)
	Normal	High	Normal	High	
Adjusted OR	Ref.	1.45(1.04-2.02)	Ref.	1.30(1.03-1.63)	0.3517

CVE, Combined vascular events; mRS, modified Rankin scale; HR, hazards ratios; OR, odds ratios.

*Adjusted for age, sex, history of diabetes mellitus, atrial fibrillation/flutter, hypoglycemic agents, TOAST subtype, epilepsy (discharge diagnosis), NIHSS score on admission, HDL, eGFR, CRP and infarction pattern.

Figure S1. Kaplan-Meier curves of CK for stroke recurrence and death at 1 year.
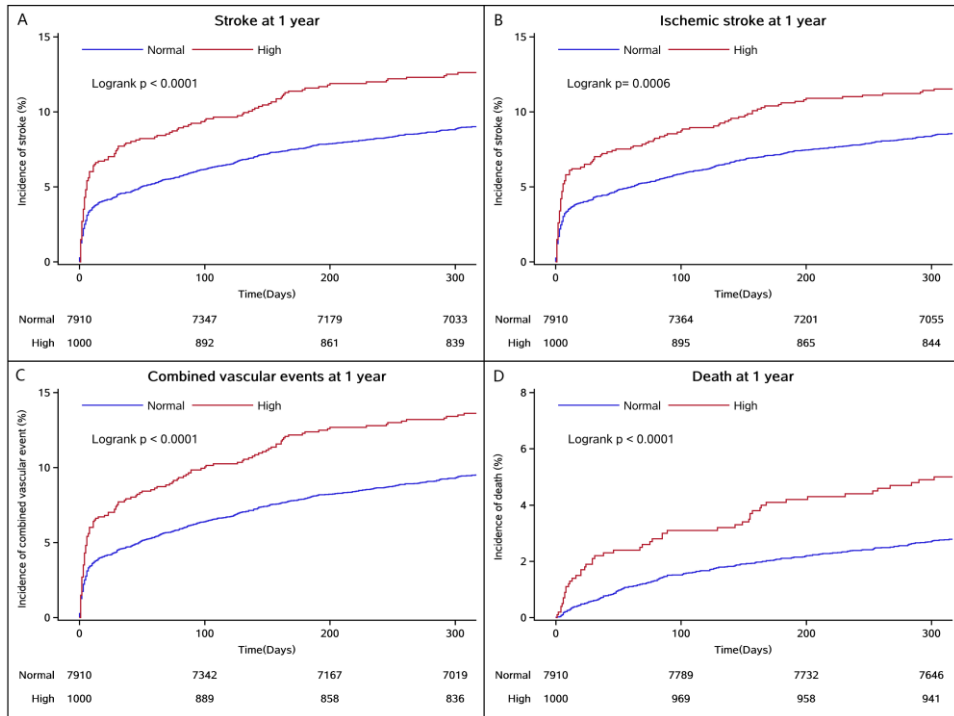
A, Kaplan-Meier curve for stroke recurrence.

B, Kaplan-Meier curve for ischemic stroke recurrence.

C, Kaplan-Meier curve for composite vascular events.

D, Kaplan-Meier curve for all-cause mortality.

Normal, normal serum CK level.

High, elevated serum CK level.