Original Article

Lipid Accumulation Product and Hypertension Related to Stroke: a 9.2-Year Prospective Study Among Mongolians in China

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***Aims*: We aimed to assess the relationship between lipid accumulation product (LAP) and stroke incidence and whether increased LAP would further enlarge the risk of stroke in participants with hypertension in an Inner Mongolian population of China.**

***Methods*: Based on the baseline survey conducted in 2002−2003, a prospective cohort study was conducted among 2547 Mongolian people from Inner Mongolia, China. LAP was calculated by waist circumference (WC) and triglyceride (TG) concentration for men and women, respectively. Cox proportional hazards models and receiver operating characteristic (ROC) curves were used to evaluate the associations between LAP, hypertension, and stroke incidence.**

***Results*: During the follow-up period, a total of 121 stroke events were observed. Participants with higher LAP were associated with higher risk of stroke [adjusted hazard ratio (HR), 1.67; 95% confidence interval (CI), 1.08−2.58] than the participants in the lower LAP group. However, no significant dose−response relationship was detected between LAP levels and risk of stroke (P-trend=0.103). The Kaplan−Meier curves showed that hypertensives with high LAP had highest cumulative stroke incidence rate (log-rank $P<0.001$). The multivariate-adjusted HRs (95% CIs) of stroke for normotensives with high LAP, hypertensives with low LAP, and hypertensives with high LAP were 1.80 (0.84−3.89), 2.94 (1.51−5.74), and 4.23 (2.15−8.34), respectively, compared with normotensives with low LAP.**

***Conclusions*: The present study showed that high LAP was associated with an increased risk of future stroke, and hypertensives with high LAP had the highest risk of stroke among Inner Mongolians. These findings indicate that LAP and hypertension may be valuable to predict and prevent stroke incidence.**

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Key words: Lipid accumulation product, Hypertension, Stroke, Prospective study, Mongolian population

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Introduction

Stroke is a major cause of premature death and disability[1)]. The burden of stroke is high and is increasing in economically developing countries[2)]. In China, stroke accounts for 21.6% and 20.8% of total mortality in males and females[3)], respectively. Obesity is a

major public health concern worldwide and is associated with increased risk of atherosclerotic vascular disease, including myocardial infarction and stroke[4].

As opposed to general obesity, abdominal obesity is more closely related with metabolic dysfunctions associated with cardiovascular disease (CVD)[5]. Epidemiological studies have shown that visceral adipose tissue secretes higher amounts of inflammatory cytokines and is more closely associated with insulin resistance as well as carries a greater prediction of mortality relative to subcutaneous fat[6-9]. Waist circumference (WC) is a fairly good marker of the total abdominal fat accumulation; however, an elevated WC alone is not sufficient to diagnose visceral obesity[10, 11]. Previous studies suggested that the simultaneous presence of an elevated fasting triglyceride (TG) concentration and an increased WC could distinguish visceral adiposity from subcutaneous abdominal fat[12, 13]. Lipid accumulation product (LAP), which is a concept of a combination of WC and TG, is considerably superior than body mass index (BMI) and WC for identifying adults with CVD[14-16]. A prospective study demonstrated that the LAP was independently associated with an increased risk of incident CVD among women after 8.6 years of follow-up[17]. Furthermore, high LAP values had been found to be a predictor of mortality, which is independent of other cardiovascular risk factors in postmenopausal women[18], and results from the PreCIS database including high cardiovascular disease risk subjects showed an association of LAP with all-cause mortality[19]. However, few studies have examined the association between LAP and stroke incidence. Moreover, a previous study indicated that increased LAP was positively and significantly associated with the risk of prevalent hypertension among Inner Mongolians[15], while the cumulative effect of LAP and hypertension on the development of stroke has not been sufficiently studied.

Aim

We aim to evaluate the relationship between LAP and stroke incidence and whether increased LAP would further increase the risk of stroke among the population with hypertension on the basis of a 9.2-year follow-up study in Inner Mongolia, China.

Methods

Study Participants

Baseline survey was conducted between 2002 and 2003 in Inner Mongolia, an autonomous region in north China. Based on the cross-sectional study, a prospective cohort study was conducted from June 2003 to July 2012. The detailed methods for study participant recruitments have been described elsewhere[20]. Briefly, study participants aged 20 years or older were recruited from 32 villages in two adjacent townships located in the counties of Kezuohou Banner and Naiman Banner in Inner Mongolia. The majority of local residents are Mongolians who have lived there for many generations; they have maintained traditional manners and customs of Mongolian ethnicity, and their diets are high in fat and salt content. A total of 3475 Mongolian people aged 20 years or older live in these villages. Among them, 889 people were excluded because they refused to participate or had CVDs or endocrine diseases, including hyper/hypothyroidism. Finally, a total of 2589 individuals were included in this study. This study was approved by the Soochow University Ethics Committee. Written informed consent was obtained from all study participants.

Data Collection

Data collection with regard to demographic characteristics, medical history, and lifestyle risk factors followed a standard questionnaire applied by the trained staff. Three blood pressure measurements were taken for each participant while participants were seated using a mercury sphygmomanometer according to a standard protocol[21]. The first and fifth Korotkoff sounds were recorded as systolic blood pressure (SBP) and diastolic blood pressure (DBP), respectively. The mean of these three blood pressure measurements was used for data analysis. Normotension was defined as SBP of <140 mmHg and DBP of <90 mmHg and non-use of antihypertensive medication, and hypertension was defined as SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg and/or use of antihypertensive medication in last 2 weeks. Body weight and height were measured with subjects wearing light clothing and no shoes. The WC was measured at the level of 1 cm above the umbilicus. Hip circumference was measured around the widest portion of the buttocks, with the tape parallel to the floor. The BMI was calculated as the weight in kilograms divided by the squared height in meters. The waist-to-hip ratio (WHR) was calculated as the ratio of WC to hip circumference.

Fasting blood samples were collected in the morning after at least 8 h of fasting for all participants. Plasma and serum samples were frozen at -80℃ for laboratory testing. A modified hexokinase enzymatic method was applied to test plasma glucose levels, and the participants were classified as follows according to fasting plasma glucose (FPG) value: normoglycemia

Table 1. Baseline characteristics of study participants according to lipid accumulation product quartiles

Characteristics	Lipid accumulation product (LAP)				*P*-trend
	Q1 (<9.24)	Q2 (9.24-16.83)	Q3 (16.83-32.13)	Q4 (≥32.13)	
N	635	636	640	636	
Age, mean ± SD, y	43.7 ± 13.1	44.8 ± 12.0	47.7 ± 12.4	49.5 ± 11.0	<0.001
Male, No (%)	301 (47.4)	258 (40.6)	226 (35.3)	257 (40.4)	0.003
Cigarette smoking, No (%)	284 (44.7)	293 (46.1)	273 (42.7)	276 (43.4)	0.400
Alcohol drinking, No (%)	202 (31.8)	198 (31.1)	194 (30.3)	254 (39.9)	0.005
BMI, mean ± SD, kg/m^2	19.7 ± 2.0	21.4 ± 2.5	22.7 ± 2.9	25.2 ± 3.6	<0.001
WC, mean ± SD, cm	72.2 ± 5.2	77.7 ± 5.4	82.7 ± 6.9	90.6 ± 8.9	<0.001
SBP, mean ± SD, mm Hg	121.7 ± 21.2	128.0 ± 24.2	131.3 ± 24.2	137.8 ± 26.2	<0.001
DBP, mean ± SD, mm Hg	79.9 ± 11.4	83.6 ± 12.8	85.0 ± 12.5	89.6 ± 12.9	<0.001
Hypertension, No (%)	130 (20.5)	212 (33.3)	256 (40.0)	352 (55.4)	<0.001
Family history of CVD, No (%)	65 (10.2)	82 (12.9)	86 (13.4)	101 (15.9)	0.004
TG, mmol/L	0.6 (0.4-0.7)	0.8 (0.6-1.0)	1.1 (0.9-1.4)	1.9 (1.4-2.8)	<0.001
TC, mmol/L	3.1 (2.7-3.7)	3.5 (2.9-4.0)	3.7 (3.1-4.5)	4.20 (3.5-5.1)	<0.001
LDL, cholesterol mmol/L	1.73 (1.4-2.3)	2.1 (1.6-2.6)	2.3 (1.8-3.0)	2.7 (2.0-3.4)	<0.001
HDL, cholesterol mmol/L	1.2 (1.0-1.4)	1.2 (1.0-1.4)	1.1 (1.0-1.3)	1.0 (0.9-1.3)	<0.001
FPG, mmol/L	4.6 (4.1-5.2)	4.8 (4.2-5.4)	4.9 (4.3-5.4)	5.2 (4.6-5.8)	<0.001

Results are expressed with median (interquartile range) unless otherwise noted.
BMI, body mass index; WC, waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; CVD, cardiovascular disease; TG: triglyceride; TC: total cholesterol; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; FPG, fasting plasma glucose.

(FPG <6.1 mmol/l), impaired fasting glucose (FPG, 6.1−6.9 mmol/l), and diabetes mellitus (FPG ≥7.0 mmol/l)[22]. Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and TGs were enzymatically tested using a Beckman Synchron CX5 Delta Clinical System (Beckman Coulter, Inc., Fullerton, CA) with commercial reagents. Low-density lipoprotein cholesterol (LDL-C) levels were calculated using the Friedewald equation for participants who had TG level of <400 mg/dL[23].

LAP was calculated by WC and TG concentration as follows: LAP for men = [WC (cm) − 65] × [TG concentration (mmol/L)] and LAP for women = [WC (cm) − 58] × [TG concentration (mmol/L)][14]. To avoid having non-positive values for LAP, any WC values that were 65 cm or less were revised upward to 66.0 cm for men (n=5) and those that were 58 cm or less were revised upward to 59.0 cm for women (n=2), as suggested by Kahn[14]. High LAP was defined as LAP ≥ median.

Follow-up and Outcome Assessment

The follow-up and outcome assessment have been previously reported[24]. Briefly, all participants were followed up from June 2003 to July 2012. Stroke incidence during the follow-up period is the primary study outcome. Stroke was defined as evidence of an acute disturbance of focal 24 h and was considered to be because of intracranial hemorrhage or ischemia[25]. Study participants who did not have a stroke, who died from other causes, or who were lost to follow-up were defined as censored. If the participant was contacted and was found to have previously had a stroke, the stroke incidence date was defined as the endpoint date. Data were censored at the time of the contact if the participant was reached and was found not to have had a stroke and were censored at the day we contacted the participant last time if the patient was lost to follow-up. To those who died from other causes, data were censored at the time of death date in the medical records. Since 2004, household surveys of all participants were conducted every 2 years to determine new stroke cases. If a participant reported that a stroke occurred during the period since the last survey, the staff reviewed hospital records, including outpatient or admission records and discharge summary. All cases have been confirmed by CT or MRI scans.

Statistical Analysis

Participants were categorized into four subgroups according to the quartiles of LAP. Continuous variables are expressed as mean ± standard deviation or as median (interquartile range), whereas categorical variables are expressed as frequency (percent). Tests for

Table 2. Hazard ratios (HRs) for risk of stroke according to quartiles of LAP

	Cases	Person-years	Age and gender adjusted			Multivariable adjusted*		
			HR	95%CI	*P*-value	HR	95%CI	*P*-value
High LAP (LAP ≥ median)	72	11720	1.42	0.98-2.05	0.066	1.67	1.08-2.58	0.020
Quartiles								
Q1: < 9.24	28	5866	1.00	–	–	1.00	–	–
Q2: 9.24-16.83	21	5935	0.90	0.51-1.59	0.722	0.85	0.48-1.52	0.579
Q3: 16.83-32.13	37	5888	1.43	0.87-2.35	0.164	1.32	0.78-2.24	0.303
Q4: ≥ 32.13	35	5832	1.27	0.77-2.11	0.355	1.53	0.81-2.90	0.193
P value for trend					0.171			0.103

*Multivariable model adjusted for age, gender, body mass index, smoking and drinking status, family history of CVD, systolic blood pressure, levels of fasting glucose (normoglycemia, impaired fasting glucose or diabetes mellitus), total cholesterol, and high density lipoprotein cholesterol.

linear trend were performed using covariance analysis for continuous variables and chi-square trend analysis for categorical variables. According to hypertensive status and LAP, we divided participants into the following four groups: normotensives with low LAP, normotensives with high LAP, hypertensives with low LAP, hypertensives with high LAP. The cumulative risk of events among the four subgroups was estimated using Kaplan−Meier curves and compared using log-rank test. Cox proportional hazard models were used to evaluate the associations between LAP, hypertension, and stroke incidence. Hazard ratios (HRs) and 95% confidence intervals (CIs) for future stroke were calculated. The potential covariates including age, gender, BMI, smoking and drinking statuses, family history of CVD, SBP, DBP, levels of fasting glucose (normoglycemia, impaired fasting glucose or diabetes mellitus), total cholesterol, and HDL-C were included in the multivariate model. In addition, we assessed the discriminatory value of hypertension/LAP levels by computing the area under receiver operating characteristic curves (AUC) and comparing a model including hypertension and high LAP and other conventional risk factors with a model including only other conventional risk factors. All *P* values were two-tailed, and a significance level of 0.05 was used. Statistical analysis was conducted using SAS statistical software (version 9.2, Cary, North Carolina, USA).

Results

As of July 31, 2012, we have followed participants for an average of 9.2 years. Among 2589 participants, six were lost to follow-up; the follow-up rate was 99.8%.

Forty-two participants were excluded for missing key variables, and a total of 2547 people were included in the final analysis. During the follow-up period, stroke occurred in a total of 121 patients (75 ischemic strokes and 44 hemorrhagic strokes); the cumulative incidence rate was 4.75%, and the incidence density was 514/100 000 person-years.

There were 1042 males and 1505 females in our study. The mean age of the participants was 46.42 ± 12.35 years. **Table 1** summarizes the baseline characteristics of participants according to LAP quartiles. Participants with higher LAP levels tended to be older, men, drinkers, and hypertensives, and they had a higher rate of family history of CVD, higher levels of BMI, WC, SBP, DBP, TGs, total cholesterol, LDL-C, and FPG but lower levels of HDL-C.

Adjusted HRs for stroke incidence according to LAP levels are presented in **Table 2**. In a multivariate-adjusted model, participants with higher LAP were associated with higher risk of stroke (HR, 1.67; 95% CI, 1.08−2.58) than those with lower LAP. When participants were categorized into four groups according to the quartiles of LAP levels, HRs of stroke for upper quartiles were calculated with the lowest quartile as a reference. There was no significant dose–response relationship between LAP levels and risk of future stroke (*P*-trend = 0.103).

Fig. 1 shows the Kaplan−Meier curves for cumulative incidence rate of stroke among four subgroups according to hypertensive status and LAP. During 9.2 years of follow-up, the cumulative incidence rates among normotensives with low LAP, normotensives with high LAP, hypertensives with low LAP, and hypertensives with high LAP were 1.40%, 2.41%, 9.24%, and 10.50%, respectively; hypertensives with high LAP had highest cumulative stroke incidence rate (log-rank $P < 0.001$). **Table 3** presents adjusted HRs and 95% CIs of stroke according to hypertensive status and LAP. Among hypertensive participants, after

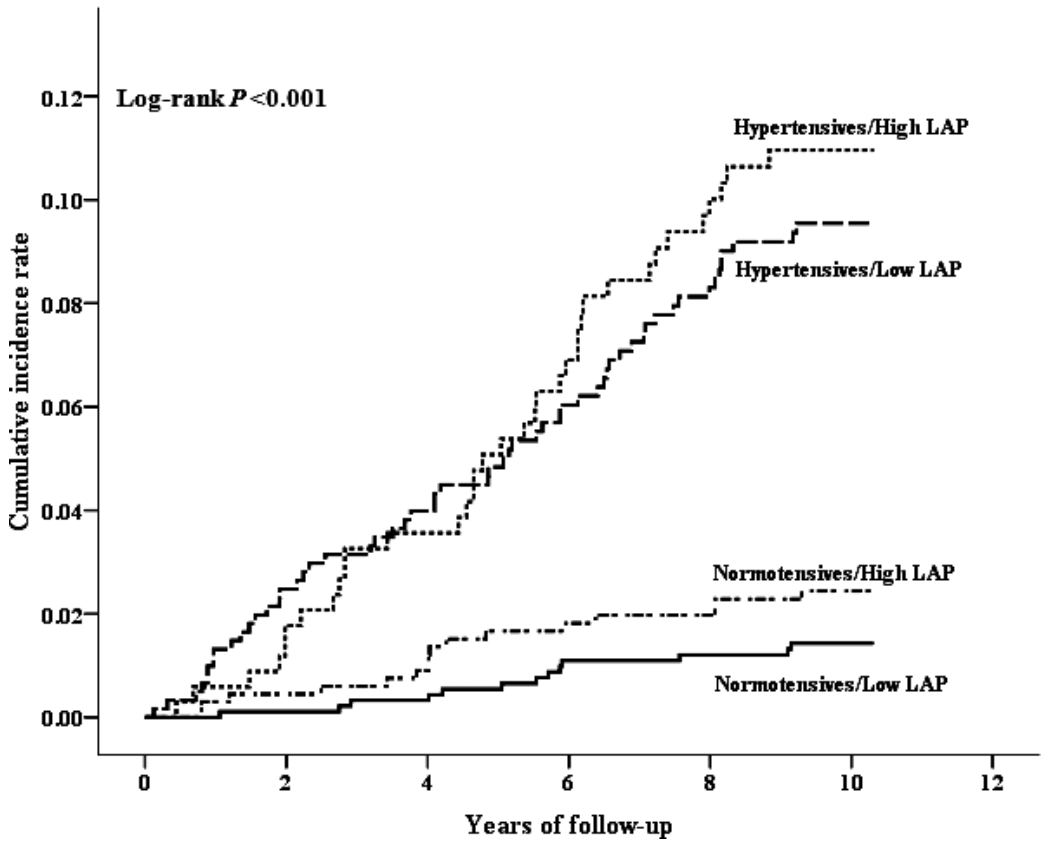

Fig. 1. Cumulative incidence curve of stroke according to hypertensive status and LAP.

adjusting for other cardiovascular risk factors, those with higher LAP were associated with increased risk of stroke (HR, 1.72; 95% CI, 1.04−2.85) compared with those in the lower LAP group. Among total participants, compared with normotensives with low LAP, adjusted HRs (95% CIs) for normotensives with high LAP, hypertensives with low LAP, and hypertensives with high LAP were 1.80 (0.84−3.89), 2.94 (1.51−5.74) and 4.23 (2.15−8.34), respectively. We therefore set a multiplicative interaction term of hypertension and LAP in a multivariable model, however, no significant interaction was detected between hypertension and LAP on the development of stroke (P=0.603). The AUC for the model including hypertension and high LAP as well as other conventional risk factors was larger than that for the model including only other conventional risk factors (0.854 vs. 0.837; P=0.036; **Fig. 2**).

Discussion

In this population-based prospective cohort study among the Inner Mongolian population, although no significant dose−response relationship was detected between LAP levels and risk of stroke, participants in high LAP group still had an increased risk of stroke than those in the low LAP group. Additionally, hypertensives with low LAP and hypertensives with high LAP were at a significantly higher risk of stroke than normotensives with low LAP. Hypertensives with high LAP were at a highest risk in this population. To the best of our knowledge, this is the first study conducted to assess the effect of LAP levels on stroke and the cumulative effect of higher LAP and hypertension on stroke incidence with regard to the Inner Mongolians, an ethnic minority in China.

In China, which has a rapidly developing economy, obesity has increased by 13% in urban and by 85% in rural areas[26]. Abdominal obesity is at a greater risk of future cardiovascular events and diabetes; thus, the measurements of abdominal obesity have been proposed to be more informative[27]. Previous studies have indicated that the simultaneous presence of fasting hypertriglyceridemia and an increased WC could represent a simple clinical phenotype to identify the individuals with an excess of visceral adipose tissue

Table 3. Adjusted HRs and 95% CIs for stroke incidence according to hypertensive status and LAP

	Cases	Person-years	Age and gender adjusted			Multivariable adjusted		
			HR	95%CI	*P*-value	HR	95%CI	*P*-value
Hypertensives (n=950)[†]								
Low LAP (LAP < median)	36	3029	1.00	−		1.00	−	
High LAP (LAP ≥ median)	56	5438	1.13	0.73-1.73	0.590	1.72	1.04-2.85	0.035
Total (n=2547)[‡]								
Normotensives/Low LAP	13	8772	1.00	−		1.00	−	
Normotensives/High LAP	16	6283	1.50	0.72-3.13	0.281	1.80	0.84-3.89	0.134
Hypertensives/Low LAP	36	3029	3.09	1.62-5.91	0.001	2.94	1.51-5.74	0.002
Hypertensives/High LAP	56	5438	3.61	1.96-6.63	<0.001	4.23	2.15-8.34	<0.001

[†]Multivariable model adjusted for age, gender, body mass index, smoking and drinking status, family history of CVD, systolic blood pressure, levels of fasting glucose (normoglycemia, impaired fasting glucose or diabetes mellitus), total cholesterol, and high density lipoprotein cholesterol.
[‡]Multivariable model adjusted for age, gender, body mass index, smoking and drinking status, family history of CVD, levels of fasting glucose (normoglycemia, impaired fasting glucose or diabetes mellitus), total cholesterol, and high density lipoprotein cholesterol.

with ectopic fat. Hypertriglyceridemic waist (HTGW), a combination of increased WC and TG level, was coined to emphasize the potential predictive value of CVD[13, 28]. However, HTGW is regarded as a dichotomous indicator in previous studies, and the quantitative relationships could be obscured by the use of a dichotomous variable[29]. The continuous LAP, an index of central lipid accumulation, is better to express a continuous risk function[30]. There is accumulating evidence indicating that LAP is an attractive new candidate maker for identifying the adults with metabolic syndrome or those having a cardiovascular risk[14, 31-34]. Kahn compared the LAP index to BMI in terms of an ability to identify cardiovascular risk in adults, suggesting that LAP might be a better predictor of the incidence of CVD[14]. A prospective study by Elisabeth *et al*. suggested that high LAP values are predictive of mortality independent of other cardiovascular risk factors in normal weight postmenopausal women and all diabetic postmenopausal women[32]. To date, few studies have examined the association between LAP and stroke incidence. In our study, although there was no significant dose−response relationship between LAP levels and risk of stroke, participants with high LAP still had a risk of stroke increased by 67% than those with low LAP. Further large-sample prospective cohort studies are still required to examine the relationship between LAP levels and risk of future stroke.

Hypertension is the most common and strongest modifiable risk factor for stroke. Clinical trials have documented that lowering blood pressure reduces the risk of stroke in hypertensives[35, 36]. Previous cross-sectional study indicated that increased LAP was positively and significantly associated with the risk of prevalent hypertension in both genders among Inner Mongolians[15]. It has been documented that several risk factors may interact or act synergistically with each other on stroke incidence[24, 37-39]. Therefore, we further evaluate the cumulative effect of LAP and hypertension on the development of stroke and found that hypertensives with high LAP had the highest risk of stroke incidence among four groups, with a 4.23-fold increased risk compared with normotensives with low LAP. Increased LAP seems to amplify the effect of hypertension on stroke. The coexistence of increased LAP and hypertension is a notable issue. Thus, reducing LAP may have an additional preventive effect on stroke based on the administration of antihypertensive treatment in hypertensives.

Early and accurate identification of the population at the high risk of stroke is important to predict and prevent stroke development. Moreover, LAP offers an inexpensive screening tool and has a high reproducibility to evaluate total-body lipid accumulation and facilitates the identification of individuals with an excess of visceral adipose tissue. To our knowledge, this is the first study to examine the association between hypertension, LAP, and stroke incidence in a minority population in China. The study participants were homogeneous regarding their genetic background and lifestyles as well as social economy status because they lived in relatively isolated ethnic minority areas. The study data were rigidly collected during baseline investigation and follow-up, and important co-variables were controlled in the analysis. The follow-up time was relatively long and the rate of lost to follow-up was low in our study, which enabled us to obtain a less biased association between exposure measurements and outcome events.

This study has some limitations. Firstly, blood

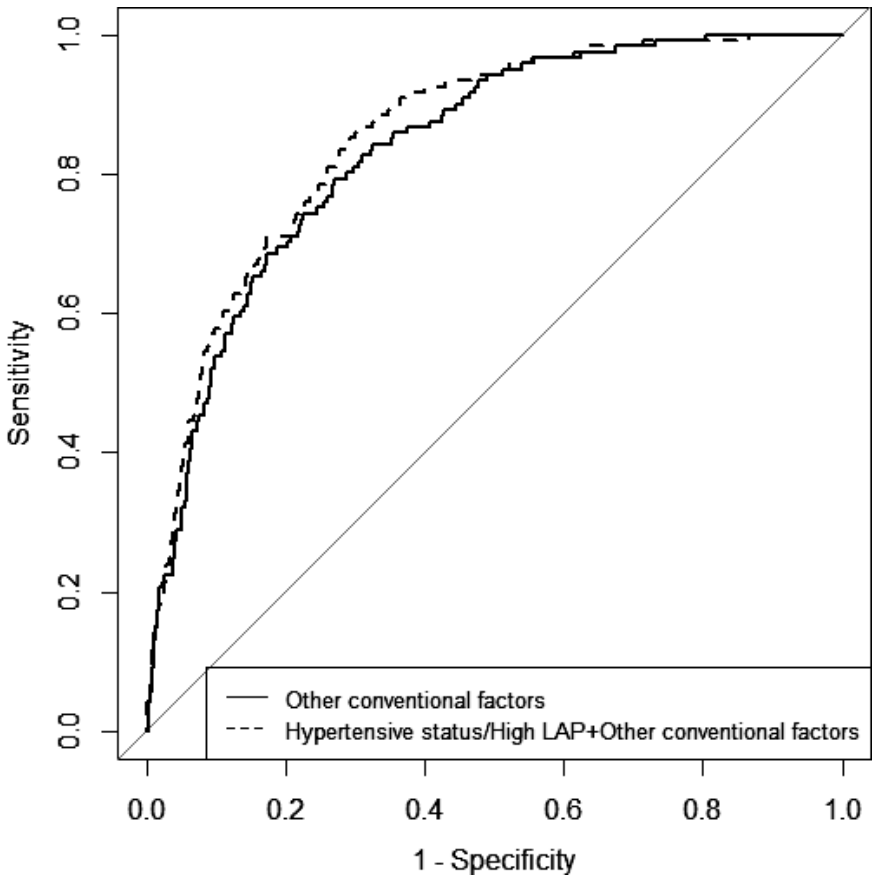

Fig. 2. Area under the curve for the prediction of stroke according to hypertension/high LAP and other conventional factors. Other conventional factors include age, sex, BMI, smoking and drinking statuses, family history of CVD, levels of fasting glucose (normoglycemia, impaired fasting glucose, or diabetes mellitus), total cholesterol, and HDL-C.

pressure measurements, WC, and TG concentration were recorded only once at baseline, and we have no data on possible changes in blood pressure and LAP during the follow-up. Secondly, there is evidence that lipid overaccumulation, such as increased WC and elevated TG level, has different importance in women and men in terms of cardiovascular risk[40-43]; it is better to perform an analysis in stratifying participants by gender. We did not stratify participants by gender because of our comparatively small sample size and the relatively low number of strokes, but we adjusted gender as an important confounding variable in multivariable analysis. Therefore, the associations between hypertension, LAP, and stroke incidence were independent of gender effect. Finally, 889 people in the investigation field did not participate in the cohort, which may have introduced some selection bias. We believe that this bias is minimal because it is unlikely that participants did not participate because of their blood pressure, WC, or TG concentration.

Conclusion

Our study found that high LAP was associated with an increased risk of future stroke, and hypertensives with high LAP had the highest risk of stroke among Inner Mongolians. These findings indicate that LAP and hypertension may be valuable to predict and prevent stroke incidence.

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The authors declare no conflict of interest.

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