Original Article

Clinical application and comparison of serum lipoprotein (a) particle concentration and mass concentration in stroke patients and healthy adults: a prospective cohort study

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Background: Serum Lp(a) is routinely detected by mass concentration in clinical laboratory, but the results of which cannot be standardized. On the other hand, particle concentration detection has gained increasing popularity and facilitated the standardization of Lp(a) testing in clinical practice. This study aimed to compare the Lp(a) mass concentration and particle concentration between patients with stroke and healthy controls.

Methods: The participants admitted in the Third Hospital of Hebei Medical University between January 2021 and October 2021 were assigned to hemorrhagic stroke, cerebral infarction and healthy control group. Serum Lp(a) particle and mass concentration were detected by using the Shenzhen Mindray BS-2000I and Beckman AU5821 detection system, respectively. The primary study endpoint was the difference between Lp(a) mass concentration and particle concentration among the 3 groups.

Results: There was no statistically significant difference in age and gender among the 3 groups. Serum Lp(a) mass concentration [227.7 (113.1–447.1) mg/L *vs.* 117.1 (59.8–210.7) mg/L, P=0.001] and particle concentration [30.1 (12.9–72.3) nmol/L *vs.* 13.5 (6.8–29.9) nmol/L, P=0.001] in the cerebral infarction group were significantly higher than those in the healthy control group. The areas under the receiver operating characteristic (ROC) curve (AUC) of Lp(a) mass concentration and particle concentration for the diagnosis of cerebral infarction were 0.67 and 0.66, respectively, and the cut-off value was 181.1 mg/L and 15.6 nmol/L, respectively. There was no statistically significant difference in the efficacy of the two parameters for the diagnosis of cerebral infarction (Z=0.88, P=0.38). The conversion factors for the two concentrations were not significantly different between gender nor age subgroups, and decreased as mass concentrations increased. Compared with healthy control group, the positive rate of Lp(a) mass concentration (37.8% *vs.* 17.5%, P<0.01) and the positive rate of particle concentration (24.4% *vs.* 10.8%, P=0.005) were significantly increased in the cerebral infarction group.

Conclusions: The particle concentration detection of Lp(a) has significant clinical relevance in patients with ischemic stroke. The mass concentration test results may overestimate the actual serum Lp(a) content in stroke patients.

Keywords: Stroke; lipoprotein (a); mass concentration; particle concentration

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Introduction

Stroke is the second leading cause of death and the third leading cause of disability among adults worldwide (1). Global burden of disease data released in 2019 suggested that a quarter of the population will experience at least one stroke in their lifetime. It is estimated that 9.6 million new cases of ischemic stroke and 4.1 million cases of hemorrhagic stroke occur worldwide each year (2). Risk factors of stroke include hypertension, smoking, diabetes, dyslipidemia, and unhealthy lifestyle (3,4). Monitoring and control of blood lipid levels are a key measure in the primary prevention and disease management of stroke (5). Among the numerous components of blood lipids, serum lipoprotein (a) [lipoprotein (a), Lp(a)] is strongly associated with stroke. Several studies have shown that elevated serum Lp(a) levels are an independent risk factor for developing stroke (6-8). Lp(a) is similar to low-density lipoprotein (LDL) and consists of a LDL particle molecule containing apolipoprotein (apo)B-100 and a highly polymorphic glycoprotein molecule named apo(a) (9). Considering the polymorphism of the apo(a) molecule in Lp(a), and the fact that the molecular weight is not identical between individuals, it is difficult to perform standardized laboratory tests, which also leads to the limitation of the application of Lp(a) in clinical practice (10). At present, the detection method of serum Lp(a) in China and overseas is still based on the mass concentration. Moreover, its quality is determined by immunoturbidimetry or immunonephelometry, and its mass is measured in mg/dL or mg/L. The calibrators from different manufacturers cannot achieve metrological traceability, and there are also large differences between the detection results in different laboratories (11). The detected results of mass concentration may overestimate the actual content of Lp(a) in the samples (12).

In 2003, the World Health Organization (WHO) Committee on Biological Standardization approved the first WHO/IFCC international reference material for the determination of Lp(a), IFCC SRM 2B (13). It is used to detect the particle concentration of Lp(a) and realize the traceability of calibrator metrology in nmol/L, facilitating the standardization of Lp(a) testing in clinical practice. However, the commercial reagents that actually express test results in nmol/L have only emerged on the market recently, for which the results are traceable to WHO/IFCC SRM 2B (14-16). In recent years, Lp(a) particle concentration detection has been gradually promoted in clinical practice and has shown high accuracy in the fields of cardiovascular disease (17-19) and chronic kidney disease (20), with lower deviations in particle concentration compared with mass concentration (20). To date, few studies have compared the results of different detection methods for Lp(a) in stroke patients (12). The aim of the present study is to assess the accuracy and stability of mass and particle concentration of Lp(a) between patients with cerebral hemorrhage or cerebral infarction and healthy controls in an effort to further improve the clinical management of cardiovascular diseases (CVD). We present the following article in accordance with the STARD reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-22-1220/rc).

Highlight box

Key findings

- The particle concentration detection of Lp(a) has significant clinical relevance in patients with ischemic stroke.

What is known and what is new?

- Serum Lp(a) is routinely detected by mass concentration in clinical laboratory.
- Lp(a) mass concentration and particle concentration in the cerebral infarction group was significantly higher than those in the healthy control group. The mass concentration test results may overestimate the actual serum Lp(a) content in stroke patients.

What is the implication, and what should change now?

- In clinical practice, both particle concentration and mass concentration of Lp(a) can be applied to the management of stroke patients. More attention should be paid to particle concentration in future researches.

Methods

Study design

This is a prospective cohort study carried out in the Third Hospital of Hebei Medical University from January 2021 to October 2021. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the ethics committee of the Third Hospital of Hebei Medical University (No. W2021-095-1). Individual consent for this retrospective analysis was waived.

Study subjects

Patients who were diagnosed with stroke in the outpatient, emergency, and inpatient departments were consecutively enrolled. To further differentiate the subtype of stroke,

patients were divided into hemorrhagic stroke and ischemic stroke groups. The following inclusion criteria were applied to the case group: (I) age ≥18 years old; and (II) diagnosis of cerebral infarction or cerebral hemorrhage. The following exclusion criteria (at least 1 item) were applied: (I) patients with cerebral infarction and cerebral hemorrhage combined with other traumatic diseases; (II) patients presented with liver, kidney, or coagulation dysfunction; (III) co-presentation with malignant tumors; and (IV) patients with congenital abnormalities of lipid metabolism. Healthy subjects who came to the hospital for physical examination during the same period and had been excluded from hypertension, heart disease, diabetes, and chronic diseases by electrocardiogram, B-ultrasound, CT, and various other tests, were enrolled into the healthy control group.

Diagnostic criteria for cerebral infarction and cerebral hemorrhage were based on the Chinese Guidelines for Diagnosis and Treatment of Acute Ischemic Stroke 2018 (21) and the Chinese Guidelines for Diagnosis and Treatment of Cerebral Hemorrhage 2019 (22), respectively.

The following diagnostic criteria was applied for acute ischemic stroke: (I) acute onset; (II) focal neurological deficits (weakness or numbness of one side of the face or limbs, language impairment and others) or global neurological deficits; (III) imaging showed responsible lesions or symptoms/signs lasting more than 24 hours; (IV) non-vascular causes have been excluded; and (V) cerebral hemorrhage has been excluded by brain computed tomography (CT) or magnetic resonance imagining (MRI).

The diagnostic criteria for hemorrhagic stroke were as follows: (I) acute onset; (II) focal neurological deficit symptoms (a few are global neurological deficits), often accompanied by headache, vomiting, elevated blood, and various degrees of disturbance of consciousness; (III) cranial CT or MRI showed hemorrhagic lesions; and (IV) non-vascular brain causes have been excluded.

Laboratory testing

Instruments and reagents

Serum Lp(a) particle concentration was detected using the Shenzhen Mindray BS-2000I detection system and supporting reagents by latex immunoturbidimetry. Calibrators and controls were original reagents. Calibrators were traceable to IFCC reference material SRM 2B, Lot: 148421003, which was detected in nmol/L. Serum Lp(a) mass concentration was detected using the Beckman AU5821 detection system and Langfang Hengyi reagent, calibrators and controls matched with reagents (Lot: 20210725). Serum Lp(a) mass concentration passed the inter-laboratory quality evaluation at the National Clinical Laboratory Center participating each year, which was tested in mg/L.

Detection method

Two reagents were calibrated separately, and clinical samples were tested after quality control. The same sample was divided into two parts for the detection of particle concentration and mass concentration by using the Mindray BS2000I and Beckman AU5821 systems, respectively. Lp(a) concentration ≥75 nmol/L was defined as a positive particle concentration test, and mass concentration ≥300 mg/L was defined as a positive mass concentration test (11). The positive rate was the ratio of the number of positive cases to the total number in each group. The mass concentration overestimation rate was defined as the ratio of the number of cases with mass concentration ≥300 mg/L and particle concentration <75 nmol/L to the total number. The particle concentration overestimation rate was defined as the ratio of the number of cases with particle concentration ≥75 nmol/L and mass concentration <300 mg/L to the total number. The conversion factor was defined as the ratio of the mass concentration to particle concentration for the same specimen.

Study endpoints

The primary study end point was the difference in Lp(a) mass concentration and particle concentration among the cerebral infarction group, cerebral hemorrhage group, and the healthy control group. Secondary endpoints included the comparisons of clinical characteristics between different groups, as well as the differences among groups in the conversion factors and overestimation rates of the two concentrations.

Data collection

Detailed clinical data (Demographics and clinical symptoms) and laboratory data [particle concentration and mass concentration data for Lp(a)] were collated from the stroke patients and the healthy controls.

Statistical analysis

Continuous variables conforming to the normal distribution were presented as mean ± standard deviation (mean ± SD), otherwise it was presented as median [interquartile range (IQR)], and comparisons between the two groups were performed using the independent samples *t*-test and the nonparametric Mann-Whitney U test, respectively. Categorical variables were presented as values and

Table 1 The demographic characteristics, lipoprotein (a) mass concentration, and particle concentration of the patients

Parameter	Cerebral hemorrhage group (n=51)	Cerebral infarction group (n=127)	Control group (n=120)
Age	56.4±13.2[#]	66.2±13.8[#]	61.6±13.7
Male	33 (64.7)[#]	77 (60.6)[#]	74 (61.7)
Mass concentration (mg/L)	180.3 (68.4–332.7)[#]	227.7 (113.1–447.1)*	117.1 (59.8–210.7)
Particle concentration (nmol/L)	24.0 (8.5–58.0)[#]	30.1 (12.9–72.3)*	13.5 (6.8–29.9)

Data are presented as mean ± standard deviation, median (IQR), or n (%). [#], indicates no statistical difference between the cerebral hemorrhage group or the cerebral infarction group and the healthy control group; *, indicates statistical difference between the cerebral infarction group and the healthy control group.

percentages, and comparisons between groups were performed using the Chi-square test or Fisher exact probability test. All statistical analyses were performed using two-sided tests with MedCalc 20.0 software. P<0.05 was considered statistically significant.

Results

Comparison of Lp(a) mass concentrations and particle concentrations among groups

A total of 298 patients were included in the study, including 51 patients with cerebral hemorrhage, 127 patients with cerebral infarction, and 120 healthy control subjects. Compared with the healthy control group, there was no statistically significant difference in age and gender between the cerebral hemorrhage group and the cerebral infarction group. Compared with the healthy control group, there was no statistically significant difference in serum Lp(a) mass concentration [180.3 (68.4–332.7) mg/L *vs.* 117.1 (59.8–210.7) mg/L, P=0.12] nor particle concentration [24.0 (8.5–58.0) nmol/L *vs.* 13.5 (6.8–29.9) nmol/L, P=0.10] in the cerebral hemorrhage group. The serum Lp(a) mass concentration [227.7 (113.1–447.1) mg/L *vs.* 117.1 (59.8–210.7) mg/L, P<0.01] and particle concentration [30.1 (12.9–72.3) nmol/L *vs.* 13.5 (6.8–29.9) nmol/L, P<0.01] in the cerebral infarction group were significantly higher than that in the healthy control group (*Table 1*).

The differential analysis of the conversion factors between the Lp(a) mass concentration and particle concentration in each group

The conversion factors between the mass concentration and particle concentration were 7.02±1.42, 7.26±1.71, and 7.72±1.31 in the cerebral hemorrhage group, the cerebral infarction group, and the healthy control group, respectively. While there were no significant differences between the cerebral hemorrhage group and cerebral infarction group, the conversion factors in these groups were significantly lower than those in the healthy control group. Subgroup analysis of the conversion factors stratified by gender, age, and mass concentration showed no significant differences in the conversion factors by gender and age. However, as the mass concentration increases, the conversion factor decreases (*Table 2*).

Analysis of the positive rate and overestimation rate of Lp(a) mass concentration and particle concentration in each group

There were no significant within-group differences regarding the positive rate of mass and particle concentration in the healthy control group (17.5% *vs.* 10.8%, P=0.14) and the cerebral hemorrhage group (31.4% *vs.* 17.7%, P=0.11). The positive rate of mass concentration in the cerebral infarction group was significantly higher than that of particle concentration (37.8% *vs.* 24.4%, P=0.02). Compared with the healthy control group, the positive rate of mass concentration in the cerebral hemorrhage group was significantly increased (31.4% *vs.* 17.5%, P=0.04), but there was no statistically significant difference in the positive rate of particle concentration (17.7% *vs.* 10.8%, P=0.23). The positive rate of mass concentration in the cerebral infarction group was significantly higher than that of particle concentration (37.8% *vs.* 24.4%, P=0.02). Compared with the healthy control group, the positive rate of mass concentration (37.8% *vs.* 17.5%, P<0.01) and the positive rate of particle concentration (24.4% *vs.* 10.8%, P=0.005) were significantly increased in the cerebral infarction group (*Table 3*).

There were no significant differences in the mass

Table 2 Conversion factor subgroup analysis of lipoprotein (a) mass concentration and particle concentration

Group	Conversion factor	$P_{trend\ value}$
Healthy control group (120 cases)	7.72±1.31	
Mass concentration (mg/L)		<0.01
≤100 (n=50)	8.18±0.88	
≤200 (n=39)	8.44±0.68	
≤300 (n=10)	7.16±0.58	
≤400 (n=7)	5.94±0.80	
>400 (n=14)	5.34±0.74	
Age (years old)		0.49
≤40 (n=3)	7.12±2.35	
≤50 (n=22)	7.74±1.23	
≤60 (n=34)	8.02±1.13	
≤70 (n=31)	7.44±1.40	
≤80 (n=19)	7.84±1.42	
>80 (n=11)	7.46±1.32	
Gender		
Male (n=74)	7.44±1.48	0.08
Female (n=46)	7.88±1.18	
Stroke group (n=178)*	7.19±1.63	<0.01*
Cerebral hemorrhage group (n=51)	7.02±1.42	0.01*
Cerebral infarction group (n=127)	7.26±1.71	0.02*
Mass concentration (mg/L)		<0.01
≤100 (n=45)	7.60±1.98	
≤200 (n=41)	8.58±0.75	
≤300 (n=28)	7.31±0.84	
≤500 (n=27)	6.55±0.56	
≤700 (n=5)	5.71±1.08	
>700 (n=13)	5.42±1.15	
Age (years old)		0.89
≤40 (n=10)	7.05±1.24	
≤50 (n=20)	7.44±1.51	
≤60 (n=51)	6.98±1.83	
≤70 (n=44)	7.32±1.72	
≤80 (n=27)	7.25±1.62	
>80 (n=26)	7.19±1.34	
Gender		
Male (n=110)	7.21±1.61	0.80
Female (n=68)	7.15±1.67	

Data are presented as mean ± standard deviation or (numeric). *, indicates a statistically significant difference in the related conversion factors between the cerebral hemorrhage or cerebral infarction group and the healthy control group.

Table 3 The positive rate and overestimation rate of lipoprotein (a) test results in included patients

Positive/overestimated rate	Cerebral hemorrhage group (n=51)	Cerebral infarction group (n=127)	Healthy control group (n=120)
Positive mass concentration (%)	31.4 (16/51)*	37.8 (48/127)*	17.5 (21/120)
Particle concentration positive rate (%)	17.7 (9/51)#	24.4 (31/127)*	10.8 (13/120)
Mass concentration overestimation (%)	13.7 (7/51)#	13.4 (17/127)#	6.7 (8/120)
Particle concentration overestimation (%)	0 (0/51)	0 (0/127)	0 (0/120)

*, indicates statistical difference between cerebral hemorrhage and cerebral infarction group and healthy control. #, indicates no statistical difference among cerebral hemorrhage group and cerebral infarction group and healthy control group.

concentration overestimation rates between the cerebral hemorrhage group (13.7% *vs.* 6.7%, P=0.14) nor the cerebral infarction group (13.4% *vs.* 6.7%, P=0.08) compared with the healthy control group (*Table 3*).

Discussion

The serum Lp(a) mass concentration and particle concentration were measured in 151 patients with cerebral hemorrhage, 127 patients with cerebral infarction, and 120 healthy subjects. There were no statistical differences in the Lp(a) mass concentration nor particle concentration between the cerebral hemorrhage group and the healthy control group. However, both the mass concentration and the particle concentration were significantly higher in the cerebral infarction group compared to the healthy control group. The Lp(a) mass concentration and particle concentration in patients with cerebral infarction were significantly higher than those in healthy control group. The conversion factor between the Lp(a) mass concentration and particle concentration decreased with the increment of mass concentration, regardless of age and gender.

Jia *et al.* (12) examined 124 stroke patients and 150 healthy control subjects in a 2017 study and showed that serum Lp(a) mass concentration [25.4 (7.3–66.6) *vs.* 10.0 (5.9–28.0) nmol/L, P<0.01] and particle concentration {148 [45–344] *vs.* 59 [33–149] mg/L, P<0.01} in the stroke group were significantly higher than that in the healthy control group. The positive rates of particle concentration (21.3% *vs.* 9.6%) and mass concentration (28.7% *vs.* 10.8%) in the stroke group were significantly higher than those in the healthy control group. However, the positive rate of mass concentration was significantly higher than that of particle concentration (36.2% *vs.* 25.4%, P<0.01). The overestimation of Lp(a) mass concentration related to particle concentration ranged from 11.8% to 13.7% in this latter study. This is consistent with our results herein, where particle concentration detection methods were not overestimated, while mass concentrations were overestimated by 6% to 13%. This indicates that Lp(a) detected by mass concentration is prone to bias results compared with particle concentration, and this may have a significant impact on the clinical decision-making.

Zhao *et al.* (23) measured the serum Lp(a) concentration in 147 patients with acute cerebral infarction using two different methods. The ROC analysis showed that the optimal cut-off values of Lp(a) mass concentration and particle concentration in the diagnosis of cerebral infarction were 168 mg/L and 19 nmol/L, respectively, with sensitivity of 71.1% and 78.7%, respectively, and specificity of 61.9% and 95.2%, respectively. A large study of the Chinese Han population published by Cui *et al.* (24) in 2018 suggested that the upper reference limit of Lp(a) should be set at 170 mg/L instead of the 300 mg/L that is currently used by most laboratories in China. The above evidence suggests that there is likely to be no significant difference in the diagnostic efficacy of Lp(a) mass concentration and particle concentration for cerebral infarction. Future prospective, large sample size studies should be conducted to further validated these findings.

Due to the inaccuracy of test results for Lp(a) mass concentration, a previous study attempted to convert particle concentrations to mass concentrations (25). Generally, the measured particle concentration results of Lp(a) are transformed into the results of mass concentration according to the conversion factor provided by the reagent vendor. However, it was found that there is a statistical difference between the conversion results and the actual measured Lp(a) mass concentration results. Therefore, a simple conversion of Lp(a) concentration between different detection methods using the conversion factor is not recommended, and may mislead the clinical evaluation. The

conversion error may be caused by the fact that the apoA molecule in Lp(a) is polymorphic with a different molecular weight and particle number among individuals (9), which are calculated by a unified conversion factor.

There were several limitations in the study. First, as a retrospective study, this report may lead to bias and confounding factors. However, consecutive patients were included, and strict inclusion and exclusion criteria were developed. Second, the sample size was small and multivariate regression analysis was lacking, which may have affected statistical power. However, subgroup analysis was performed in accordance with the different detection methods, gender, and age, which is helpful to evaluate the accuracy and pertinence of the diagnostic efficacy of the index. Third, most stroke patients have metabolic related diseases, such as diabetes and hyperlipidemia, which can directly or indirectly affect the levels of Lp(a). The contributory factors of these complications were not considered in this study, and subgroup analysis or adjustment in the multivariate analysis should be performed in future studies.

Conclusions

While there was no statistical difference in the Lp(a) mass concentration and particle concentration between patients with cerebral hemorrhage and healthy control subjects, the Lp(a) mass concentration and particle concentration in the cerebral infarction group was significantly higher than those in the healthy control group. The mass concentration test results may overestimate the actual serum Lp(a) content in stroke patients. The conversion factor between Lp(a) mass concentration and particle concentration decreased with the increment of mass concentration, regardless of age and gender.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-22-1220/rc

Data Sharing Statement: Available at https://apm.amegroups.com/article/view/10.21037/apm-22-1220/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-22-1220/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the ethics committee of the Third Hospital of Hebei Medical University (No. W2021-095-1). Individual consent for this retrospective analysis was waived.

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