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Serum lipoprotein-associated phospholipase A2 as a promising prognostic biomarker in association with 90-day outcome of acute intracerebral hemorrhage

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ABSTRACT

Background: Lipoprotein-associated phospholipase A2 (Lp-PLA2) is reflective of vascular inflammation and plays a role in the pathophysiology of cerebrovascular disease. We determine usefulness of serum Lp-PLA2 as a prognostic biomarker for intracerebral hemorrhage (ICH).

Methods: In this prospective, observational study, serum Lp-PLA2 concentrations were detected among 164 patients with acute spontaneous basal ganglia hemorrhage and 164 healthy controls. Using multivariate analysis, we analyzed its association with poor outcome (modified Rankin Scale > 2) at poststroke 90 days and hemorrhagic severity indicated by National Institutes of Health Stroke Scale (NIHSS) score and hematoma volume.

Results: Serum Lp-PLA2 concentrations were remarkably higher in patients than in controls. Lp-PLA2 concentrations were independently correlated with NIHSS score ($t = 5.095$, $P < .001$) and hematoma volume ($t = 2.850$, $P = .005$). At 90-day follow-up, 85 patients (51.8%) had poor outcome. Under receiver operating characteristic curve, serum Lp-PLA2 showed a significant prognostic discriminatory capability (AUC, 0.813; 95% CI, 0.744–0.869). Serum Lp-PLA2 concentrations ≥304 ng/ml was an independent predictor associated with poor outcome (OR 7.052; 95% CI 1.971–25.228).

Conclusions: Rising serum Lp-PLA2 concentrations are closely hemorrhagic severity and clinical outcomes after ICH, substantializing serum Lp-PLA2 as a potential prognostic biomarker of ICH.

1. Introduction

Intracerebral hemorrhage (ICH) is a type of severe cerebral disease that can result in a long-term disability or even death [1–5]. Clinical outcome after ICH remains to be poor and difficult to predict despite extensive studies and improvements in critical care [6–10]. Clinical rating scales, such as the National Institutes of Health Stroke Scale (NIHSS) and the hematoma volume are commonly utilized for prognostic prediction [11–16]. Currently, a growing body of data shows that neuroinflammation plays a crucial role in pathophysiological mechanisms contributing to hemorrhagic brain injury [17–20]. Lipoprotein-associated phospholipase A2 (Lp-PLA2) belongs to a type of serine lipase and is mainly derived from endothelium inflammatory cells [21–23]. Acting as a vascular inflammatory biomarker, it is widely implicated in the progression of atherosclerosis, such as plaque formation, development, and rupture, as well as has been described as an independent risk marker for recurrent events in ischemic stroke and myocardial infarction [24–30]. In acute ischemic stroke, the elevated Lp-PLA2 mass was associated with all cause-death independently of other risk factors within one year after acute ischemic stroke [31]. More recently, serum Lp-PLA2 concentrations were revealed to independently predict delay cerebral ischemia, vasospasm and 6-month unfavorable outcome in a group of aneurysmal subarachnoid hemorrhage patients [32,33]. Also, in a study with a very small sample size, Lp-PLA2 activity was associated with stroke volume of 14 patients with acute ICH [34]. Overall, it is postulated that serum Lp-PLA2 concentrations might be associated with hemorrhagic severity and clinical outcome of ICH.

Abbreviations: CT, computerized tomography; ICH, intracerebral hemorrhage; NIHSS, National Institutes of Health Stroke Scale; Lp-PLA2, Lipoprotein-associated phospholipase A2

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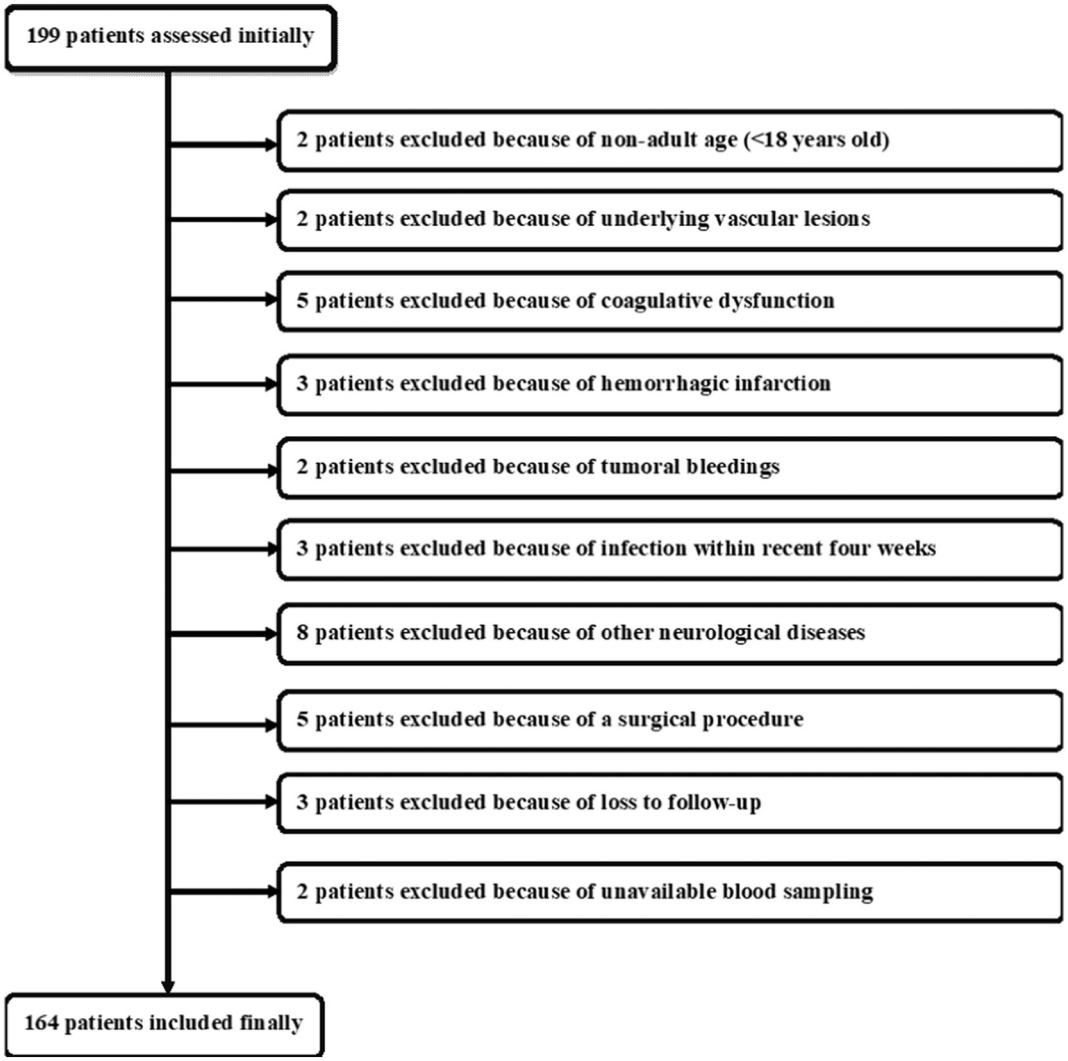

Fig. 1. Flow chart showing the exclusion criteria of patients with acute intracerebral hemorrhage in the current study.

2. Materials and methods

2.1. Study population

From January 2015 to January 2018, we performed a prospective, observational cohort study at our hospital. Initially, we consecutively acute spontaneous basal ganglia hemorrhage patients admitted within the first 24 h after stroke onset. Afterwards, we excluded those patients with non-adult age (< 18 y) underlying vascular lesions, coagulative dysfunction, hemorrhagic infarction, tumoral bleedings, infection within recent 4 weeks, other neurological diseases and a surgical procedure. Additionally, controls comprised a group of healthy volunteers. This study was designed in accordance with the guidelines outlined in the Declaration of Helsinki and approved by the local ethics committee at our hospital. Written informed consent for each patient was obtained from their authorized legal representative and controls' was signed by themselves.

2.2. Evaluation

The investigated materials in the current study included demographic data, vascular risk factors, concomitant medication and non-invasive blood pressure values. For the severity assessment, clinical and radiological rating scales were admission NIHSS and hematoma volume calculated based on ABC/2 method [35] respectively. The presence of intraventricular extension of hematoma was read too because it occurs commonly in acute basal ganglia hemorrhage [36–38]. Poststroke 90-day modified Rankin Scale score of > 2 was designated as a poor outcome.

2.3. Determination

Blood samples at admission of ICH patients and those at study entrance of controls were collected and then were centrifuged at 3000 xg for 10 min. Separated serum was preserve at −80 °C until measurements. Serum Lp-PLA2 concentrations were gauged in duplicate samples with the enzyme-linked immunosorbent assay using a commercial kit (Cloud-Clone Corp.), in accordance with the manufacturer's instructions. All quantifications were completed by the same laboratory technician inaccessible to all clinical data.

2.4. Statistical methods

The Statistical Package for the Social Sciences ver 19.0 and MedCalc 9.6.4.0 were utilized to analyze data statistically. Categorical variables, shown as count (percentage), were compared with the chi-square test or Fisher exact test as appropriate. For continuous variables, normal distributions were tested at first. Because all data in this study were verified with skewed distributions, they were presented as medians with interquartile range and were thereby compared with Mann-Whitney *U*

test. To clarify correlations of serum Lp-PLA2 concentrations with hemorrhagic severity assessed by NIHSS scores and hematoma volume, bivariate correlations were analyzed using Spearman correlation coefficients. Also, serum Lp-PLA2 concentrations were dichotomized based their median value and then some confounding factors were adjusted for confirming whether NIHSS score and hematoma volume were independently associated with high serum Lp-PLA2 concentrations. In addition, a multivariate linear regression model was configured to analyze the independent correlations of serum Lp-PLA2 concentrations with NIHSS score and hematoma volume. Area under receiver operating characteristics curve (AUC) and the corresponding 95% confidence interval (CI) values were calculated to assess the discriminatory capability and the optimal value was also chosen, which yielded the suitable sensitivity and specificity values for predicting 90-day poor outcome and distinguishing high serum Lp-PLA2 concentrations respectively. Intergroup comparison in AUC was done using Z test. We incorporated the significant variables in univariable analyses in a multivariable logistic regression model to identify variables independently associated with poor outcome. All associations were presented as odds ratios (ORs), with their corresponding 95% CIs. A 2-tailed $P < .05$ was considered significant for all test.

3. Results

3.1. Participant characteristics

In the current study, we at first assessed a total of 199 patients with acute spontaneous basal ganglia hemorrhage and then, we excluded thirty-five patients because of the reasons depicted in Fig. 1 and ultimately, 164 patients were evaluated. Simultaneously, 164 healthy controls were recruited. There were no significant differences in terms of age, gender percentage and body mass index between the patients and the controls.

This group of patients was aged at median value of 66 y (interquartile range, 56–76 y) as well as included 95 males and 69 females. Their median body mass index was 24.5 kg/m^2 (interquartile range, 22.8–25.8 kg/m^2). There were current smoking in 76 patients, moderate-heavy alcohol consumption in 63 patients, hypertension in 137 patients, diabetes mellitus in 46 patients, hyperlipidemia in 55 patients, congestive heart failure in 13 patients, coronary artery disease in 15 patients and chronic kidney disease in 11 patients. As regards pretreatment drug usage, there were antiplatelet pretreatment (28 cases), anticoagulant therapy (15 cases) and statin pretreatment (42 cases). The median admission NIHSS scores and hematoma volumes were 11 (interquartile range, 8–14) and 16 ml (interquartile range, 9–26 ml). In 47 patients, hematoma extended into intraventricular cavity. Via non-invasive measurement, there were 171 mm Hg (interquartile range, 158–190 mm Hg) at median systolic arterial pressure and 102 mm Hg (interquartile range, 98–108 mm Hg) at median diastolic arterial pressure. Patients were admitted at the median time of 9.7 h (interquartile range, 3.5–17.8 h) and their blood was acquired at the median time of 15.5 h (interquartile range, 9.0–23.0 h). At 90 days after hemorrhagic stroke, a poor outcome was found in 85 patients.

3.2. Serum Lp-PLA2 concentrations and its association with hemorrhagic severity

Shown in Fig. 2, as opposed to the controls, serum Lp-PLA2 concentrations were pronouncedly raised in the ICH patients. Moreover, serum Lp-PLA2 concentrations were dichotomized based on their median value (389 ng/ml). We designated serum Lp-PLA2 concentrations ≥389 ng/ml as a dependent variable and subsequently, conducted a multivariate binary logistic regression analysis. All significant variables in bivariate analyses in Table 1 (i.e., NIHSS score, hematoma volume, intraventricular extension of hematoma, systolic arterial pressure, blood glucose concentrations and serum C-reactive protein concentration) were incorporated into a multivariate model. It was revealed that NIHSS scores and hematoma volumes retained as the two factors independently associated with serum Lp-PLA2 concentrations ≥389 ng/ml (Table 2). Alternatively, NIHSS scores (Fig. 3), hematoma volumes (Fig. 4) and other variables in Table 3 (i.e., intraventricular extension of hematoma, systolic arterial pressure, blood glucose concentrations and serum C-reactive protein concentration) were intimately correlated with serum Lp-PLA2 concentrations using Spearman correlation coefficients. Also, we configured a multivariate linear regression model and thereby found that serum Lp-PLA2 concentrations were independently correlated with NIHSS scores ($t = 5.095$, $P < .001$) and hematoma volumes ($t = 2.850$, $P = .005$).

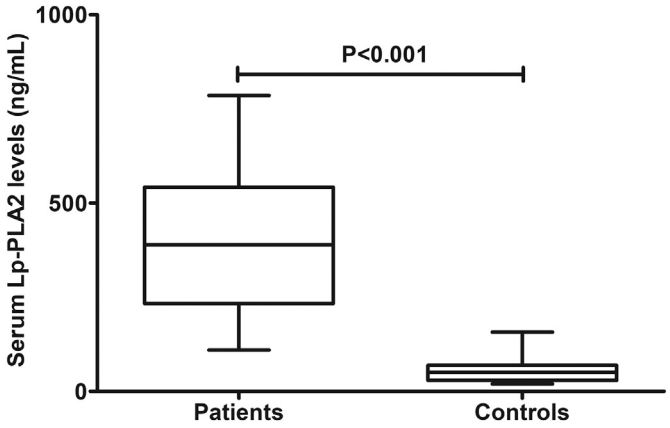

Fig. 2. Comparison of serum lipoprotein-associated phospholipase A2 concentrations between healthy controls and acute hemorrhagic stroke patients. Lp-PLA2 denotes lipoprotein-associated phospholipase A2.

3.3. Effect of serum Lp-PLA2 concentrations on 90-day prognosis

In Fig. 5, the patients with a poor outcome exhibited remarkably higher admission serum Lp-PLA2 concentrations than those experiencing a good outcome. Under ROC curve in Fig. 6, serum Lp-PLA2 concentrations distinguished the patients at risk of a poor outcome from those with a good outcome with predominantly high predictive ability reflected by AUC. In addition, a serum Lp-PLA2 concentration value of 304 ng/ml was chosen as an optimal cutoff point, which yielded a Youden index J value of 0.5117. In order to assess relationship between serum Lp-PLA2 concentration and prognosis, serum Lp-PLA2 concentrations ≥304 ng/ml was selected as a categorical variable. As a consequence, bivariate analyses in Table 4 showed that factors profoundly related to 90-day poor outcome were in the following: age, body mass index, diabetes mellitus, NIHSS score, hematoma volume, intraventricular extension of hematoma, systolic arterial pressure, blood glucose concentrations, serum C-reactive protein concentration and serum Lp-PLA2 concentrations ≥303.6 ng/ml. When the preceding significant variables were entered into the logistic regression model, it was revealed that age, NIHSS score, hematoma volume and serum Lp-PLA2 concentrations ≥304 ng/ml were the four independent predictors for 90-day poor outcome after ICH (Table 5). Furthermore, the predictive ability of serum Lp-PLA2 concentrations was similar to that of NIHSS score (AUC, 0.876; 95% CI, 0.816–0.922; $P = .111$), was equivalent to that of hematoma volume (AUC, 0.843; 95% CI, 0.778–0.895; $P = .414$) and substantially exceed that of age (AUC, 0.644; 95% CI, 0.566–0.717; $P = .004$).

4. Discussion

We conducted multivariate analysis to clarify this biomarker's association with stroke severity and prognosis in a group of ICH patients and thereby found some interesting results as follows: (1) there was an

Table 1
Parameters associated with high serum lipoprotein-associated phospholipase A2 levels in intracerebral hemorrhage patients.

Components	Lp-PLA2 levels ≥ 389 ng/ml	Lp-PLA2 levels < 389 ng/ml	*P* value	Odds ratio (95% confidence interval)	P value
	(*n* = 82)	(n = 82)			
Gender (male/female)	47/35	48/34	NS	0.951 (0.512–1.768)	NS
Age (y)	65 (58–76)	67 (57–76)	NS	1.001 (0.971–1.032)	NS
Body mass index (kg/m^2)	24.5 (23.4–26.2)	24.3 (21.7–25.8)	NS	1.098 (0.953–1.265)	NS
Current smoking	41 (50.0%)	35 (42.7%)	NS	1.343 (0.726–2.485)	NS
Moderate-heavy alcohol consumption	33 (40.2%)	30 (36.6%)	NS	1.167 (0.622–2.192)	NS
Hypertension	69 (84.1%)	68 (82.9%)	NS	1.093 (0.478–2.496)	NS
Diabetes mellitus	27 (32.9%)	19 (23.2%)	NS	1.628 (0.817–3.243)	NS
Hyperlipidemia	27 (32.9%)	28 (34.2%)	NS	0.947 (0.495–1.811)	NS
Antiplatelet pretreatment	17 (20.7%)	11 (13.4%)	NS	1.688 (0.736–3.870)	NS
Anticoagulant therapy	5 (6.1%)	10 (12.5%)	NS	0.468 (0.152–1.434)	NS
Congestive heart failure	5 (6.1%)	8 (9.8%)	NS	0.601 (0.188–1.920)	NS
Coronary artery disease	7 (8.5%)	8 (9.8%)	NS	0.863 (0.298–2.502)	NS
Chronic kidney disease	5 (6.1%)	6 (7.3%)	NS	0.823 (0.241–2.810)	NS
Statin pretreatment	21 (25.6%)	21 (25.6%)	1.000	1.000 (0.496–2.016)	NS
NIHSS score	14 (11–16)	9 (6–12)	< 0.001	1.286 (1.165–1.420)	< 0.001
Hematoma volume (ml)	22 (14–34)	10 (7–17)	< 0.001	1.090 (1.053–1.127)	< 0.001
Intraventricular extension of hematoma	31 (37.8%)	16 (19.5%)	0.010	2.507 (1.238–5.076)	0.011
Systolic arterial pressure (mm Hg)	176 (158–195)	170 (156–185)	0.043	1.017 (1.004–1.031)	0.011
Diastolic arterial pressure (mm Hg)	102 (97–109)	101 (98–106)	NS	1.015 (0.985–1.045)	NS
Blood glucose levels (mmol/l)	15.8 (12.9–19.4)	14.3 (12.1–16.3)	0.009	1.112 (1.036–1.193)	0.003
Serum C-reactive protein level (mg/l)	14.5 (11.9–18.2)	13.1 (11.7–14.8)	0.011	1.096 (1.019–1.180)	0.014
Blood white blood cell count ($\times 10^9$/l)	9.2 (7.2–11.8)	7.9 (6.5–11.4)	NS	1.050 (0.946–1.166)	NS
Admission time (h)	9.5 (3.4–17.6)	10.3 (3.4–18.9)	NS	0.986 (0.915–1.064)	NS
Blood-collecting time (h)	14.8 (8.6–22.7)	16.3 (10.4–23.4)	NS	0.957 (0.885–1.035)	NS

Categorical and continuous variables were shown as count (percentage) and median (interquartile range) respectively as well as were compared using the X^2 test, Fisher exact test or Mann-Whitney U test as appropriate. NIHSS represents National Institutes of Health Stroke Scale; Lp-PLA2, lipoprotein-associated phospholipase A2.

Table 2
Multivariate analysis for serum lipoprotein-associated phospholipase A2 levels ≥ 389.2 ng/ml in intracerebral hemorrhage patients.

Components	Odds ratio (95% confidence interval)	P value
NIHSS score	1.220 (1.093–1.361)	< 0.001
Hematoma volume (ml)	1.058 (1.018–1.099)	0.004
Intraventricular extension of hematoma	1.914 (0.819–4.473)	NS
Systolic arterial pressure (mm Hg)	1.010 (0.994–1.027)	NS
Blood glucose levels (mmol/l)	1.023 (0.933–1.122)	NS
Serum C-reactive protein level (mg/l)	0.993 (0.908–1.086)	NS

NIHSS indicates National Institutes of Health Stroke Scale; Lp-PLA2, lipoprotein-associated phospholipase A2. The significant variables in univariable analysis were included in a binary logistic regression model to yield variables independently associated with high serum Lp-PLA2 levels (> median value), with the associations reported as odds ratio (95% confidence interval).

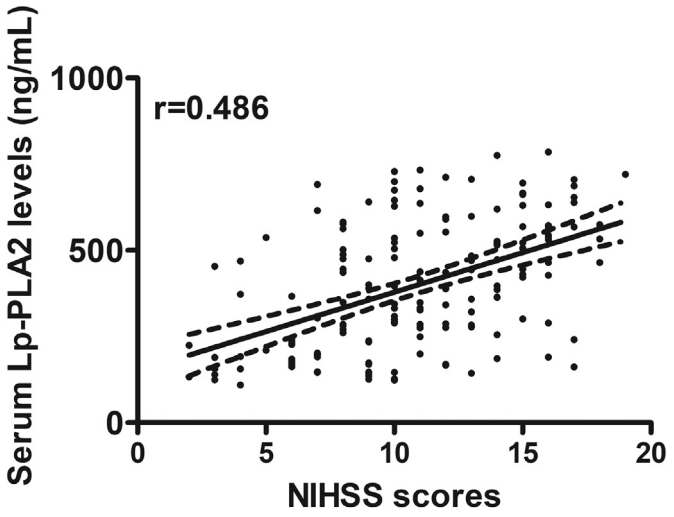

Fig. 3. . Correlative analysis of serum lipoprotein-associated phospholipase A2 concentrations with National Institutes of Health Stroke Scale scores after acute intracerebral hemorrhage. NIHSS indicates National Institutes of Health Stroke Scale. Lp-PLA2 denotes lipoprotein-associated phospholipase A2.

obvious elevation of serum Lp-PLA2 concentrations in the ICH patients, in comparison with the healthy controls; (2) serum Lp-PLA2 concentrations were positively correlated with NIHSS scores and hematoma volume, which was confirmed by multivariate analysis; (3) besides NIHSS scores, hematoma volume and age, serum Lp-PLA2 was a prognostic biomarker in independent association with 90-day poor outcome following hemorrhagic stroke; (4) serum Lp-PLA2 exhibited a high predictive capability for poor outcome at 90 days after acute ICH. The preceding data are supportive of the notions that serum Lp-PLA2 might be valuable to serve as a brain injury biomarker for reflecting ICH severity and predicting clinical outcome of hemorrhagic stroke.

Secretion of Lp-PLA2 from endothelium inflammatory cells has been verified in a great number of studies and thereby it can function as a proinflammatory cytokine, which is reflective of the extent of intravascular inflammatory response [21–23]. Specifically, the Lp-PLA2 concentration or activity is positively correlated with atherosclerosis, oxidative stress, and cardiovascular diseases in varieties of animal experiments and human epidemiology studies [24–30]. Nevertheless, it has been revealed that Lp-PLA2 mass was higher in ICH compared with ischemic stroke during the hyperacute stage [34]. Our study found the similar result that serum Lp-PLA2 concentrations were significantly elevated at the median time of 15.5 h after ICH, as compared with the healthy controls. Such data imply that Lp-PLA2 could present us with some different information in the hyperacute stage of stroke, especially ICH. Indeed, one of reasons why Lp-PLA2 concentrations were substantially raised among acute ICH patients could be secondary changes of the brain tissue surrounding hematoma [39,40]. Actually, within a short time following onset of hemorrhagic stroke, there are extravasated blood components around the hematoma and some associated

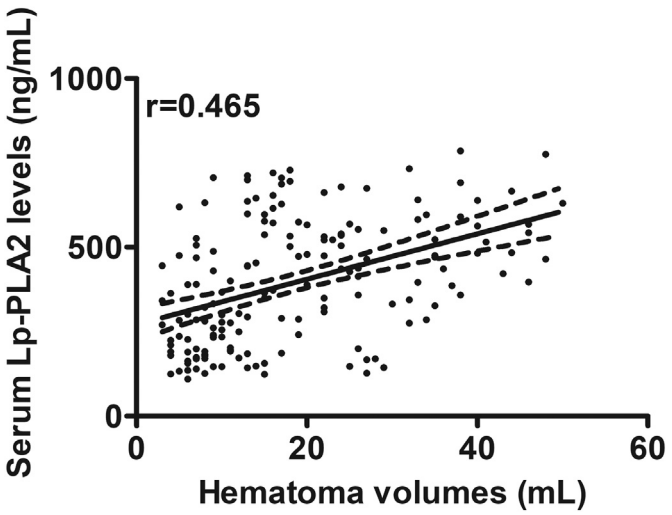

Fig. 4. . Analysis of relation of serum lipoprotein-associated phospholipase A2 concentrations to hematoma volume following acute intracerebral hemorrhage. Lp-PLA2 means lipoprotein-associated phospholipase A2.

Table 3
Parameters in association with serum lipoprotein-associated phospholipase A2 levels in intracerebral hemorrhage patients.

Components	r value	P value
Gender (male/female)	0.006	NS
Age (y)	0.038	NS
Body mass index (kg/m^2)	−0.022	NS
Current smoking	0.050	NS
Moderate-heavy alcohol consumption	0.042	NS
Hypertension	−0.065	NS
Diabetes mellitus	0.132	NS
Hyperlipidemia	0.041	NS
Antiplatelet pretreatment	0.093	NS
Anticoagulant therapy	−0.053	NS
Congestive heart failure	−0.027	NS
Coronary artery disease	0.043	NS
Chronic kidney disease	0.042	NS
Statin pretreatment	0.006	NS
NIHSS score	0.486	< 0.001
Hematoma volume (ml)	0.465	< 0.001
Intraventricular extension of hematoma	0.232	0.003
Systolic arterial pressure (mm Hg)	0.216	0.005
Diastolic arterial pressure (mm Hg)	0.064	NS
Blood glucose levels (mmol/l)	0.218	0.005
Serum C-reactive protein level (mg/l)	0.228	0.003
Blood white blood cell count ($\times 10^9$/l)	0.120	NS
Admission time (h)	−0.064	NS
Blood-collecting time (h)	−0.076	NS

Bivariate correlations were assessed by Spearman correlation coefficients, with correlations reported as r values. NIHSS means National Institutes of Health Stroke Scale; Lp-PLA2, lipoprotein-associated phospholipase A2.

molecular patterns released from necrotic and damaged tissue, whereby a strong proinflammatory reaction is activated in the adjacent viable brain cell [39,40]. Thus, it may be theorized that an increase in circulating Lp-PLA2 concentration after ICH may be due to the infiltration of white cells with a proinflammatory phenotype around the hematoma [39,40]. However, the mechanisms implicated in this sort of association remain unknown and must be specified.

There is few of data available with respect to the relationship between serum Lp-PLA2 concentrations and the severity of acute brain injury diseases. Only in a study regarding ICH, which enrolled a very small number of patients (14 patients with ICH of various locations), serum Lp-PLA2 mass or activity was correlated with stroke volume, but not NIHSS scores [34]. In our study, we included those patients solely with acute basal ganglia hemorrhage, the sample size was relatively

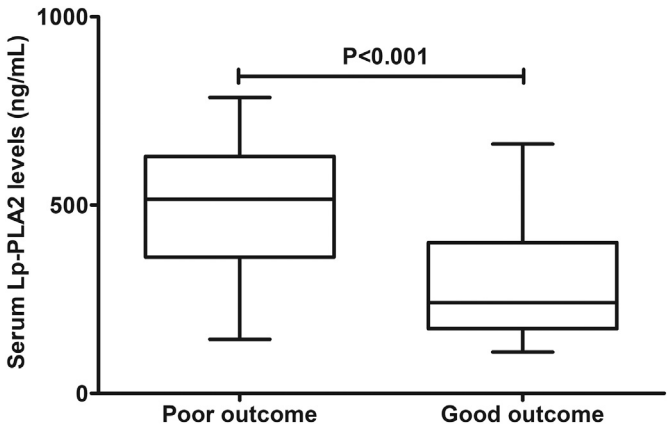

Fig. 5. Comparison of serum lipoprotein-associated phospholipase A2 concentrations by 90-day poor outcome among acute hemorrhagic stroke patients. Lp-PLA2 denotes lipoprotein-associated phospholipase A2.

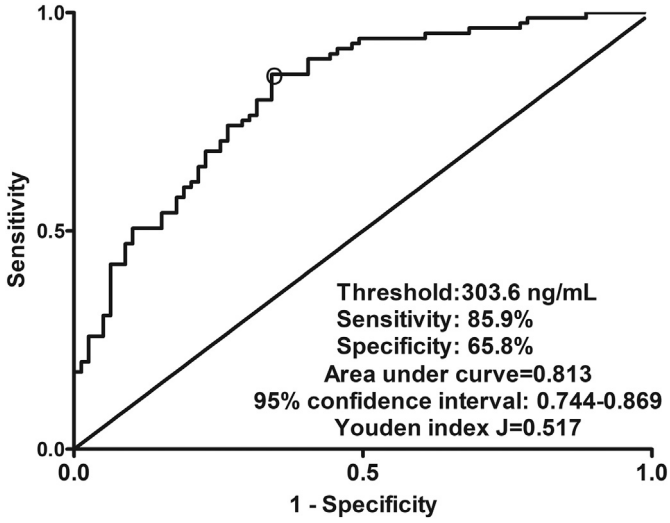

Fig. 6. Receiver operating characteristic curve analysis of serum lipoprotein-associated phospholipase A2 concentrations for discriminating acute intracerebral hemorrhage patients with development of 90-day poor outcome.

large (164 patients) and the results were ultimately validated by two multivariate models. The eventual results were that serum Lp-PLA2 concentrations were independently correlated with both hematoma volume and NIHSS scores among patients with acute hemorrhagic stroke. So, it is presumed that serum Lp-PLA2 concentrations should be able to reflect hemorrhagic severity after acute ICH.

There are two recent human epidemiological investigations showing that serum Lp-PLA2 was a predictor independently associated with vasospasm, delayed cerebral ischemia and 6-month unfavorable outcome (modified Rankin scale score of > 2) [32,33]. Also, the increasing Lp-PLA2 mass was associated with all cause-death independently within one year after acute ischemic stroke [31]. In the current study, we performed a 90-day follow-up for neurological function and also defined modified Rankin scale score of > 2 as a poor outcome. A total of 85 patients (51.8%) suffered from a poor outcome and this incidence was similar to the previous data [41,42]. Using a binary logistic regression model, serum Lp-PLA2, in addition to other conventional determinants, such as NIHSS score, hematoma and age [43–45], became the independent predictors for 90-day poor outcome after ICH. Moreover, AUC for serum Lp-PLA2 concentrations was 0.813, and a criterion value of 303.6 ng/ml was selected, which generated 85.9% sensitivity and 65.8% specificity. Furthermore, according to AUC, the predictive ability of serum Lp-PLA2 concentrations was similar to those of NIHSS

Table 4
Parameters related to 90-day poor outcome in intracerebral hemorrhage patients.

Components	Poor outcome	Good outcome	P value	Odds ratio (95% confidence interval)	P value
	(n = 85)	(n = 79)			
Gender (male/female)	50/35	45/34	NS	1.079 (0.580–2.007)	NS
Age (y)	72 (63–78)	64 (56–73)	0.001	1.051 (1.017–1.085)	0.003
Body mass index (kg/m^2)	24.9 (23.6–26.2)	24.0 (22.6–25.6)	0.030	1.172 (1.014–1.354)	0.031
Current smoking	38 (44.7%)	38 (48.1%)	NS	0.872 (0.472–1.613)	NS
Moderate-heavy alcohol consumption	37 (43.5%)	26 (32.9%)	NS	1.571 (0.832–2.967)	NS
Hypertension	68 (80.0%)	69 (87.3%)	NS	0.580 (0.248–1.356)	NS
Diabetes mellitus	30 (35.3%)	16 (20.3%)	0.032	2.148 (1.060–4.353)	0.034
Hyperlipidemia	27 (31.8%)	28 (35.4%)	NS	0.848 (0.443–1.622)	NS
Antiplatelet pretreatment	18 (21.2%)	10 (12.7%)	NS	1.854 (0.798–4.307)	NS
Anticoagulant therapy	8 (9.4%)	7 (8.9%)	NS	1.069 (0.369–3.097)	NS
Congestive heart failure	9 (10.6%)	4 (5.1%)	0.191	2.220 (0.655–7.523)	0.200
Coronary artery disease	9 (10.6%)	6 (7.6%)	NS	1.441 (0.448–4.250)	NS
Chronic kidney disease	7 (8.2%)	4 (5.1%)	NS	1.683 (0.473–5.984)	NS
Statin pretreatment	22 (25.9%)	20 (25.3%)	NS	1.030 (0.511–2.079)	NS
NIHSS score	13 (11–15)	8 (6–10)	< 0.001	1.672 (1.432–1.951)	< 0.001
Hematoma volume (ml)	22 (16–33)	9 (6–14)	< 0.001	1.139 (1.091–1.189)	< 0.001
Intraventricular extension of hematoma	32 (37.7%)	15 (19.0%)	0.008	2.576 (1.262–5.257)	0.009
Systolic arterial pressure (mm Hg)	176 (159–195)	165 (157–188)	0.048	1.014 (1.001–1.027)	0.037
Diastolic arterial pressure (mm Hg)	103 (96–109)	101 (98–107)	NS	1.030 (0.999–1.061)	NS
Blood glucose levels (mmol/l)	14.3 (11.9–19.4)	13.3 (11.0–16.3)	0.023	1.098 (1.024–1.177)	0.008
Serum C-reactive protein level (mg/l)	14.6 (12.0–17.8)	13.0 (10.8–14.6)	0.001	1.147 (1.057–1.244)	0.001
Blood white blood cell count ($\times 10^9$/l)	9.1 (7.3–11.7)	8.0 (6.3–10.4)	NS	1.091 (0.981–1.212)	NS
Admission time (h)	9.4 (3.5–17.5)	10.8 (3.8–17.6)	NS	0.968 (0.897–1.044)	NS
Blood-collecting time (h)	15.8 (10.4–23.4)	14.7 (8.6–23.2)	NS	1.023 (0.947–1.106)	NS
Serum Lp-PLA2 levels ≥ 303.6 ng/ml	73 (85.9%)	28 (35.4%)	< 0.001	11.080 (5.156–23.812)	< 0.001

Categorical and continuous variables were shown as count (percentage) and median (interquartile range) respectively as well as were compared using the x^2 test, Fisher exact test or Mann-Whitney U test as appropriate. NIHSS denotes National Institutes of Health Stroke Scale; Lp-PLA2, lipoprotein-associated phospholipase A2.

Table 5
Multivariable analysis for 90-day poor outcome in intracerebral hemorrhage patients.

Components	Odds ratio (95% confidence interval)	P value
Age (y)	1.080 (1.015–1.150)	0.016
Body mass index (kg/m^2)	0.850 (0.641–1.128)	NS
Diabetes mellitus	2.239 (0.476–10.530)	NS
NIHSS score	1.977 (1.483–2.635)	< 0.001
Hematoma volume (ml)	1.145 (1.067–1.228)	< 0.001
Intraventricular extension of hematoma	2.364 (0.639–8.746)	NS
Systolic arterial pressure (mm Hg)	0.983 (0.959–1.009)	NS
Blood glucose levels (mmol/l)	0.848 (0.716–1.003)	NS
Serum C-reactive protein level (mg/l)	1.083 (0.946–1.239)	NS
Serum Lp-PLA2 levels ≥ 303.6 ng/ml	7.052 (1.971–25.228)	0.003

NIHSS denotes National Institutes of Health Stroke Scale; Lp-PLA2, lipoprotein-associated phospholipase A2. The significant variables in univariable analysis were included in a binary logistic regression model to generate variables in an independent relation to 90-day poor outcome, with the associations presented as odds ratio (95% confidence interval) values.

score and hematoma volume, as well as was remarkably higher than that of age. Clearly, laboratory biomarker may be more objective than the clinical grades. Lp-PLA2 might be capable to be reflective of small changes in the physical condition of a patient that may not be found in the clinical grades. So, in this aspect, determination of serum Lp-PLA2 concentrations might be beneficial for treatment plan of acute stroke.

5. Conclusions

Increased serum Lp-PLA2 concentrations are strongly associated with NIHSS scores and hematoma volume, as well as independently predict 90-day poor outcome after acute ICH, indicating that serum Lp-PLA2 might have the potential to be utilized as a clinical biomarker for estimating hemorrhagic severity and assessing individual patient's risk of poor clinical outcome in acute ICH.

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