Circulating FABP4 (Fatty Acid–Binding Protein 4) Is a Novel Prognostic Biomarker in Patients With Acute Ischemic Stroke

Wen-Jun Tu, PhD, MD; Xian-Wei Zeng, PhD, MD; Aijun Deng, PhD, MD; Sheng-Jie Zhao, PhD, MD; Ding-Zhen Luo, PhD, MD; Guo-Zhao Ma, MD; Hong Wang, PhD; Qiang Liu, PhD

Background and Purpose—FABP4 (fatty acid–binding protein 4) is an intracellular lipid chaperone involved in coordination of lipid transportation and atherogenesis. This study aimed at observing the effect of FABP4 on the 3-month outcomes in Chinese patients with acute ischemic stroke.

Methods—In a prospective multicenter observational study, serum concentrations of FABP4 were on admission measured in plasma of 737 consecutive patients with acute ischemic stroke. Serum concentrations of FABP4, National Institutes of Health Stroke Scale score, and conventional risk factors were evaluated to determine their value to predict functional outcome and mortality within 3 months.

Results—During follow-up, an unfavorable functional outcome was found in 260 patients (35.3%), and 94 patients (12.8%) died. In multivariate models comparing the third and fourth quartiles to the first quartile of FABP4, the concentrations of FABP4 were associated with poor functional outcome and mortality. Compared with the reference category (Q1–Q3), the concentrations of FABP4 in Q4 had a relative risk of 4.77 (95% confidence interval [CI], 2.02–8.15; $P<0.001$) for poor functional outcome and mortality (odds ratio, 6.15; 95% CI, 3.43–12.68) after adjusting for other significant outcome predictors in univariate logistic regression analysis. Receiver-operating characteristic curves to predict poor functional outcome and mortality demonstrated areas under the curve of FABP4 of 0.78 (95% CI, 0.75–0.82) and 0.83 (95% CI, 0.79–0.88), which improved the prognostic accuracy of National Institutes of Health Stroke Scale score with combined areas under the curve of 0.83 (95% CI, 0.76–0.89; $P<0.01$) and 0.86 (95% CI, 0.81–0.92), respectively.

Conclusions—Data show that FABP4 is a novel independent prognostic marker improving the currently used risk stratification of stroke patients. **(*Stroke*. 2017;48:1531-1538. DOI: 10.1161/STROKEAHA.117.017128.)**

Key Words: adipocytes ■ atherosclerosis ■ biomarker ■ patient outcome assessment ■ stroke

In China, the annual stroke mortality rate is ≈1.6 million, which has exceeded heart disease to become the leading cause of death and adult disability.[1] Furthermore, China has 2.5 million new stroke cases each year and 7.5 million stroke survivors.[2] Rapidly measurable biomarkers to predict illness development, outcome, and mortality are pivotal for the optimized care and allocation of healthcare resources.[3]

Fatty acid–binding proteins (FABPs) are a family of small cytoplasmic lipid-binding proteins. To date, at least 10 genes encoding FABPs have been identified in the human genome.[4] FABP expression is distributed through various tissues in highly specific manners with different levels. In adipocytes, for example, FABP4 (fatty acid–binding protein 4) and FABP5 are expressed at a high level and a trace of amount, respectively.[5] FABP4 is an intracellular lipid chaperone involved in the coordination of lipid transportation[6] and atherogenesis.[7] Previous studies have suggested that FABP4 was associated with insulin resistance,[8] obesity,[9] hypertension,[10] diabetes mellitus,[11] and atherosclerosis.[12]

FABP4 expression in atherosclerotic plaques of carotid arteries was previously found to predict cardiovascular outcome,[13] and naturally occurring genetic low expression variant of FABP4 was found to promote plaque stability and reduce the risk of cardiovascular events.[14] Data from previous investigations imply that FABP4 is a prognostic biomarker for cardiovascular disease.[15] Furthermore, Holm et al[16] suggested that FABP4 was linked to atherogenesis, plaque instability, and adverse outcome in patients with carotid atherosclerosis

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From the Institute of Radiation Medicine, China Academy of Medical Science and Peking Union Medical College, Tianjin, China (W.-J.T., Q.L.); Department of Neurology, China Rehabilitation Research Center, Beijing, China (W.-J.T., S.-J.Z.); School of Rehabilitation Medicine, Capital Medical University, Beijing, China (W.-J.T., H.W.); Department of Neurosurgery, Affiliated Hospital of Weifang Medical University, China (X.-W.Z., A.D.); and Department of Neurology, Provincial Hospital of Shandong University, Jinan, China (D.-Z.L., G.-Z.M.).

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Correspondence to Qiang Liu, PhD, Institute of Radiation Medicine, China Academy of Medical Science and Peking Union Medical College, No. 238, Baiti Road, Tianjin 300192, China. E-mail liuqiang_cams@163.com

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and acute ischemic stroke (AIS) in a small sample. In this study, we, therefore, evaluated the short-term prognostic value of early measurement of FABP4 concentration in Chinese patients with AIS from 3 stroke treatment centers.

Methods

Patients and Study Design

This study was conducted at 3 stroke centers from 3 cities (Beijing, Weifang, and Jinan) in China. Patients were eligible for inclusion if they were admitted to the emergency department with a first-ever AIS and with symptom onset within 24 hours. The number of AIS patients attended during the study period (from January 2015 to December 2015) determined the sample size. The patients or their relatives (patients unable to communicate) gave written informed consents before entering the study. This study was approved by the investigational review board of the Affiliated Hospital of Weifang Medical University.

The inclusion and exclusion criteria, clinical variables, and neuroimaging information were as described in our previous study.[17] Demographic data (age and sex), body mass index (BMI), and history of risk factors were obtained at admission. In addition, acute stroke treatment (IV thrombolysis and mechanical thrombectomy) was recorded. Magnetic resonance imaging with diffusion-weighted imaging was available in some patients. The infarct volume was calculated using the formula: 0.5×a×b×c.[18] Clinical severity was assessed at admission using the National Institutes of Health Stroke Scale (NIHSS) score. The primary end point was functional outcome on month 3, and functional outcome was assessed by the modified Rankin Scale.[19] A favorable functional outcome was defined as a modified Rankin Scale score of 0 to 2 points, whereas an unfavorable outcome was defined as a modified Rankin Scale score of >2 points.[20] Secondary end point was all-cause mortality within 3 months. Outcome assessment was performed by 2 trained staff members blinded to FABP4 concentrations with a structured follow-up telephone interview with the patient or, if not possible, with the closest relative or family physician.

Blood Collection and Quantification

For all patients, blood samples were drawn on the first morning (06:00 AM) after admission under fasting state and within 48 hours of stroke onset (within 0–6 hours [n=286], 6–12 hours [n=227], 12–24 hours [n=101], and 24–48 hours [n=123] from the symptom onset). Furthermore, blood samples from some patients (n=71) were collected on 12, 24, 48, 72, 96, and 120 hours after admission for FABP4 tested. Blood HbA1c (hemoglobin A1c) was measured with a normal range of 4% to 6% at admission. Routine serum biomarkers, including high-density lipoprotein, low-density lipoprotein, fasting insulin, creatinine, fasting blood glucose (FBG), and high-sensitivity C-reactive protein (Hs-CRP) were tested using standard detection methods. Serum concentrations of FABP4 were batch analyzed using a commercially available ELISA from R&D Systems (Minneapolis, MN). Interassay and intra-assay coefficients of variation were 7.0% and 3.6%, respectively. The homeostasis model assessment of insulin resistance index was calculated as follows: fasting serum insulin (μU/mL)×FBG (mmol/L)/22.5. Estimated glomerular filtration rate (eGFR) was calculated by an equation for Chinese: eGFR (mL/min/1.73 m^2)=175×creatinine-1.234age-0.179sex (male=1, female=0.19).

Statistical Analysis

Results are expressed as percentages for categorical variables and as means (SD) and medians (interquartile ranges [IQRs]) for continuous variables. Proportions were compared using the χ^2 test. A 2-group comparison was performed using the Mann–Whitney *U* test or a 2-tailed Student unpaired *t* test. Spearman rank correlation was used for bivariate correlations.

The relation of biomarkers with the 2 end points was investigated with the use of logistic regression models. We used crude models

Table 1. Basal Characteristic of Patients With Acute Ischemic Stroke

Baseline Characteristics	Stroke Patients
n	737
Median age, y (IQR)	58 (51–68)
Male sex, n (%)	400 (54.3)
BMI, kg/m^2 (IQR)	26.3 (24.8–27.3)
Median arterial pressure, mm Hg (IQR)	
Systolic	155 (135–170)
Diastolic	90 (80–105)
Previous vascular risk factors, n (%)	
Hypertension	496 (67.3)
Atrial fibrillation	101 (13.7)
Diabetes mellitus	221 (30.0)
Hypercholesterolemia	196 (26.6)
Coronary heart disease	175 (23.7)
Family history for stroke and myocardial infarction	192 (26.1)
Cigarette smoking	208 (28.2)
Alcohol drinking	183 (24.8)
Acute treatment, n (%)	
IV thrombolysis	156 (21.2)
Mechanical thrombectomy	102 (13.8)
IV thrombolysis and mechanical thrombectomy	215 (29.2)
Admission median NIHSS score (IQR)	7 (4–12)
Lesion volumes, mL (IQR)*	18 (12–25)
Time from onset to inclusion, h (IQR)	6.2 (2.8–14.9)
Stroke cause, n (%)	
Small-vessel occlusive	160 (21.7)
Large-vessel occlusive	166 (22.5)
Cardioembolism	265 (36.0)
Other cause	75 (10.2)
Unknown	71 (9.6)
Laboratory findings, median (IQR)	
Hs-CRP, mg/dL	0.75 (0.33–1.42)
FBG, mmol/L	5.77 (5.05–7.12)
HbA1c, %	7.5 (6.3–9.0)
Fasting insulin, μU/mL	8.07 (5.99–9.58)
HOMA-IR	1.68 (1.10–2.21)
Creatinine, mmol/L	85.5 (69.8–103.2)
eGFR, mL/min/1.73 m^2	83 (65–104)
FABP, ng/mL	18.8 (13.8–25.4)

Results are expressed as percentages or as medians (IQR). BMI indicates body mass index; eGFR, estimated glomerular filtration rate; FABP, fatty acid–binding protein; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; HOMA-IR, the homeostasis model assessment of insulin resistance; Hs-CRP, high-sensitivity C-reactive protein; MRI, magnetic resonance imaging; and NIHSS, National Institutes of Health Stroke Scale.

*In the subgroup of patients (n=440) in whom MRI evaluations were performed.

and multivariate models adjusted for all significant outcome predictors in univariate analysis and report odds ratios (ORs). For a more detailed exploration of FABP4 and end points' relationship, we also used multivariate analysis models to estimate the adjusted OR and 95% confidence interval (CI) of outcome (mortality) for FABP4 quartiles (with the lowest FABP4 quartile as reference). Furthermore, receiver-operating characteristic curves, integrated discrimination improvement, and net reclassification improvement were used to test the overall prognostic accuracy of FABP4.[21] Finally, we calculated Kaplan–Meier survival curves and stratified patients by FABP4 quartiles. All statistical analyses were performed with SPSS for Windows version 21.0 (SPSS, Chicago, IL) and the ROCR package (version 1.0–2), which is available from the CRAN repository (http://cran.r-project.org/). Statistical significance was defined as $P<0.05$.

Results

Descriptive Characteristics of Stroke Patients

From a total of 896 eligible patients, blood was collected in 767 patients. Of the original 767 stroke patients, 737 completed the 3-month follow-up and were available for analysis (Figure I in the online-only Data Supplement). At admission, the median NIHSS score was 7 (IQR, 4–12), and the median FABP4 concentration was 18.8 ng/mL (IQR, 13.8–25.4). The baseline characteristics of the patients are described in Table 1. Furthermore, the serum FABP4 concentration and baseline characteristics among the 3 stroke centers were comparable (Table I in the online-only Data Supplement).

Main Results

Stroke treatment was conservative in 655 patients (88.9%), and 215 patients (29.2%) underwent thrombolysis. During follow-up, an unfavorable functional outcome was found in 260 patients (35.3%). Ninety-four patients died, and the mortality rate was, thus, 12.8%. The distribution of the 3 stroke centers of outcome event is not significantly different ($P>0.05$; Table II in the online-only Data Supplement).

Daily blood samples were obtained for 5 days after admission in a subgroup of 71 patients, 31 of whom subsequently experienced unfavorable functional outcomes. The result illustrates the time course of serum FABP4, showing significant changes with day of sampling ($P<0.001$), with peak concentrations on day 1 ($P<0.001$, compared with days 0, 0.5, and 2–5, respectively), falling to a plateau by days 2 to 5 (Figure 1).

FABP4 and Severity of Stroke

There was a modest correlation between serum concentrations of FABP4 and NIHSS score ($r=0.446$; $P<0.001$; Figure IIA in the online-only Data Supplement). In the subgroup of patients (n=440) in whom magnetic resonance imaging was available, FABP4 concentrations paralleled lesion size ($r=0.206$; $P<0.001$; Figure IIB in the online-only Data Supplement). In addition, there were positive correlations between serum concentrations of FABP4 and BMI, FBG, Hs-CRP, HbA1c, and homeostasis model assessment of insulin resistance and negative correlations between serum concentrations of FABP4 and high-density lipoprotein and eGFR ($P<0.05$, all). Interestingly, the median FABP4 concentration was significantly greater for cardioembolic stroke than for the other stroke subtypes (22.4 ng/mL [IQR, 15.9–30.1] versus 16.1 ng/mL [IQR, 11.2–21.2]; $P<0.001$).

FABP4 and Functional Outcome After 3 Months

FABP4 concentrations in patients with an unfavorable outcome were significantly greater than those in patients with a favorable outcome (25.4 ng/mL [IQR, 19.0–32.1] versus 16.5 ng/mL [IQR, 12.1–21.4]; $P<0.001$; Figure IIIA in the online-only Data Supplement).

In univariate logistic regression analysis, we calculated the ORs of FABP4 concentrations compared with the NIHSS score and other risk factors as presented in Table 2. After adjusting for all other significant outcome predictors in univariate analysis, FABP4 remained an independent outcome predictor with an adjusted OR of 1.086 (95% CI,

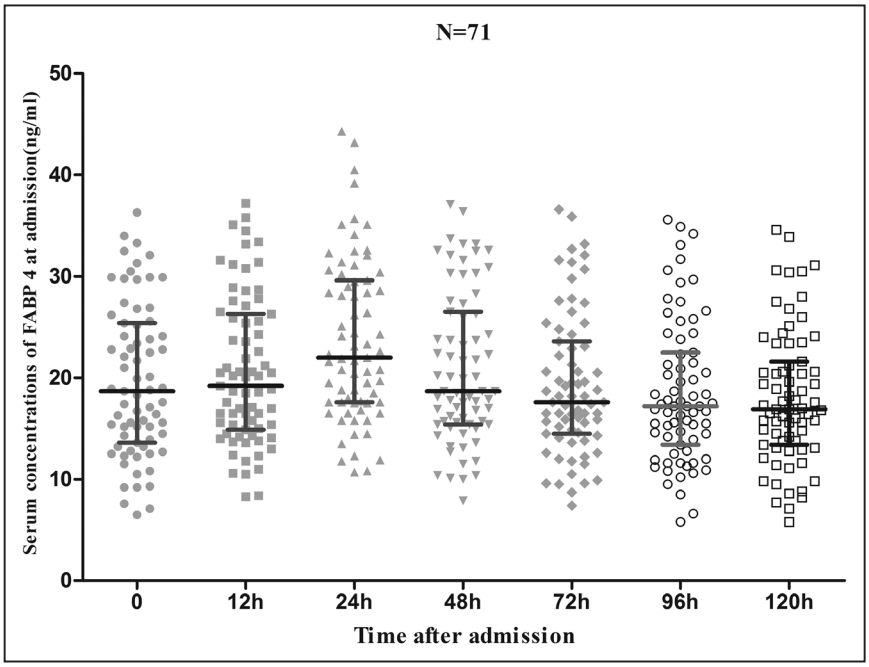


Figure 1. Scatter plots (median, interquartile ranges) of serum concentrations of FABP4 (fatty acid–binding protein 4) in the first 5 d after stroke (n=71).

Table 2. Univariate Logistic Regression Analysis for Outcome and Mortality

Predictors	Functional Outcome		Mortality	
	OR (95% CI)*	*P* Value	OR (95% CI)*	*P* Value
Age (increase per unit)	1.07 (1.04–1.10)	<0.001	1.10 (1.06–1.15)	<0.001
Female sex	1.55 (1.05–2.34)	0.07	1.44 (0.92–2.54)	0.20
BMI (increase per unit)	1.15 (0.93–1.37)	0.14	1.13 (1.02–1.22)	0.02
Systolic blood pressure (increase per unit)	1.02 (0.98–1.07)	0.52	1.05 (0.95–1.20)	0.83
NIHSS score (increase per unit)	1.13 (1.10–1.17)	<0.001	1.19 (1.07–1.28)	<0.001
Lesion volumes (increase per unit)†	1.01 (1.00–1.02)	0.01	1.02 (1.01–1.04)	0.009
Time from onset to inclusion (increase per unit)	1.17 (0.94–178)	0.32	1.22 (0.99–1.87)	0.28
Risk factors				
Hypertension	1.68 (1.04–2.55)	0.07	1.82 (0.93–2.76)	0.12
Atrial fibrillation	1.62 (1.14–2.05)	0.04	2.55 (1.14–4.03)	0.09
Diabetes mellitus	1.20 (0.90–1.96)	0.59	1.32 (0.77–2.31)	0.66
Hypercholesterolemia	0.85 (0.50–1.76)	0.33	0.98 (0.77–1.54)	0.25
Coronary heart disease	1.25 (0.75–1.87)	0.46	2.21 (1.05–4.63)	0.06
Family history for stroke or myocardial infarction	1.33 (0.96–1.77)	0.14	1.24 (0.87–1.98)	0.33
Cigarette smoking	1.62 (1.19–2.13)	0.04	1.82 (1.02–2.77)	0.09
Alcohol drinking	1.09 (0.95–1.21)	0.16	1.10 (0.99–1.24)	0.10
Stroke cause and syndrome				
Small-vessel occlusive	0.65 (0.50–0.90)	0.04	0.33 (0.13–0.58)	0.02
Large-vessel occlusive	0.92 (0.64–1.44)	0.55	0.76 (0.52–1.09)	0.19
Cardioembolic	1.28 (0.95–1.76)	0.29	1.35 (0.90–2.01)	0.42
Other cause	0.82 (0.20–1.82)	0.37	0.76 (0.16–1.99)	0.51
Unknown	1.55 (0.94–2.15)	0.10	1.67 (0.89–3.02)	0.62
TACS	3.12 (1.72–4.85)	0.008	4.42 (2.15–8.92)	<0.001
PACS	0.88 (0.67–1.32)	0.28	0.42 (0.12–1.08)	0.16
LACS	1.25 (0.64–3.04)	0.48	1.44 (0.90–2.15)	0.13
POCS	0.77 (0.54–0.92)	0.03	0.55 (0.20–1.27)	0.21
Laboratory findings				
Hs-CRP (increase per unit)	1.11 (1.02–1.25)	0.02	1.24 (1.03–1.35)	0.01
FBG (increase per unit)	1.08 (0.95–1.20)	0.19	1.05 (1.02–1.10)	0.009
HbA1c (increase per unit)	1.22 (1.04–1.39)	0.02	1.33 (1.21–1.52)	0.01
HOMA-IR (increase per unit)	1.09 (0.87–1.34)	0.46	1.15 (0.93–1.54)	0.38
eGFR, mL/min/1.73 m^2 (increase per unit)	1.06 (1.02–1.11)	0.03	0.97 (0.93–1.10)	0.43
FABP (increase per unit)	1.16 (1.13–1.19)	<0.001	1.29 (1.21–1.38)	<0.001

BMI indicates body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; FABP, fatty acid–binding protein; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; HOMA-IR, the homeostasis model assessment of insulin resistance; Hs-CRP, high-sensitivity C-reactive protein; LACS, lacunar syndrome; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; PACS, partial anterior circulation syndrome; POCS, posterior circulation syndrome; and TACS, total anterior circulation syndrome.

*Note that the odds ratio corresponds to a unit increase in the explanatory variable.

†In the subgroup of patients (n=440) in whom MRI evaluations were performed.

1.041–1.132). In the subgroup of patients (n=400) in whom magnetic resonance imaging evaluations were performed, FABP4 was an independent outcome predictor with an OR of 1.134 (*P*<0.001) after adjustment for both lesion size (OR, 1.011; *P*=0.013) and NIHSS score (OR, 1.076; *P*=0.007). We also used multivariate analysis models to estimate the adjusted OR and 95% CI of functional outcome for FABP4 quartiles (with the lowest FABP4 quartile as reference). In multivariate models comparing the third and fourth quartiles to the first quartile of FABP4 (Table 3), the concentrations of FABP4 were associated with functional outcome. Compared with the reference category (Q1–Q3), the concentrations of

Table 3. Multivariate Logistic Regression Analysis Models to Estimate Adjusted OR and 95% CIs of Stroke Functional Outcome or Mortality for FABP4 Quartiles

	Functional Outcome		Mortality	
Predictors	OR (95% CI)*	*P* Value	OR (95% CI)†	*P* Value
FABP Q2 VS Q1‡	1.46 (0.87–2.02)	0.21	1.35 (0.95–1.84)	0.13
FABP Q3 VS Q1‡	3.01 (1.85–5.72)	0.009	3.32 (1.94–5.94)	0.006
FABP Q4 VS Q1‡	9.88 (3.39–15.32)	<0.001	11.21 (4.12–20.44)	<0.001
FABP Q4 VS Q1-3‡	4.77 (2.02–8.15)	<0.001	6.15 (3.43–12.68)	<0.001

BMI indicates body mass index; CI, confidence interval; FABP, fatty acid–binding protein; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; Hs-CRP, high-sensitivity C-reactive protein; LACS, lacunar syndrome; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; PACS, partial anterior circulation syndrome; POCS, posterior circulation syndrome; and TACS, total anterior circulation syndrome.

*Adjust for significant confounding factors in univariate analysis, which including age, NIHSS score, atrial fibrillation, cigarette smoking, small-vessel occlusive, TACS, POCS, eGFR, Hs-CRP, and HbA1c.

†Adjust for significant confounding factors in univariate analysis, which including age, BMI, NIHSS score, small-vessel occlusive, TACS, POCS, Hs-CRP, FBG, and HbA1c.

‡Serum FABP concentrations in quartile 1 (<13.8 ng/mL), quartile 2 (13.8–18.8 ng/mL), quartile 3 (18.8–25.4 ng/mL), and quartile 4 (>25.4 ng/mL); Q1 as reference with OR=1.

FABP4 in Q4 had a relative risk of 4.77 (95% CI, 2.02–8.15; *P*<0.001) for functional outcome after adjusting for other significant outcome predictors in univariate logistic regression analysis (Table 3).

With an area under the curve (AUC) of 0.78 (95% CI, 0.75–0.82), FABP4 showed a significantly greater discriminatory ability compared with age, sex, BMI, presence of TACS (total anterior circulation syndrome), and NIHSS score (Table III in the online-only Data Supplement). In addition, FABP4 was superior to Hs-CRP (AUC, 0.65; *P*=0.001), FBG (AUC, 0.59; *P*<0.0001), and eGFR (AUC, 0.57; *P*<0.001). FABP4 improved the NIHSS score (AUC of the combined model=0.83; 95% CI, 0.76–0.89; *P*<0.001). Moreover, a model combining FABP4 concentration, age, sex, BMI, NIHSS score, Hs-CRP, FBG, and eGFR showed an AUC of 0.86 (95% CI, 0.82–0.90), which was greater than all predictors alone (*P*<0.001; Table III in the online-only Data Supplement). In addition, the net reclassification improvement and integrated discrimination improvement statistics showed that the addition of FABP4 to established risk factors significantly increased the correct reclassification of unfavorable and favorable outcomes (Table IV in the online-only Data Supplement).

FABP4 and Death Within 3 Months

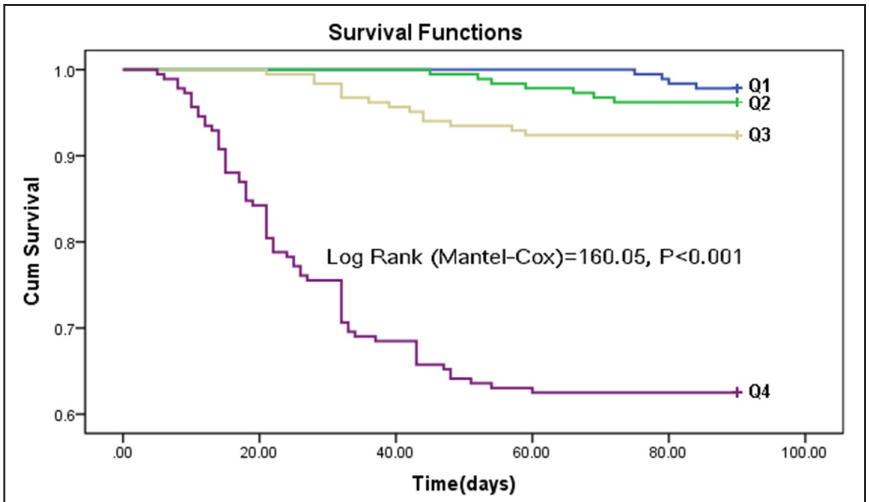
FABP4 concentrations in patients who died were higher than those patients who survived (30.2 ng/mL [IQR=25.4–35.3] versus 17.8 ng/mL [IQR=13.2–22.8]; *P*<0.001; Figure IIIB in the online-only Data Supplement). Univariate analysis identified FABP4 concentrations, age, Hs-CRP, and NIHSS score as the main predictors associated with death (Table 2). After adjustment for these parameters, FABP4 concentration remained an independent predictor for mortality with an OR of 1.192 (95% CI, 1.141–1.246). Similarly, we also used multivariate analysis models to estimate adjusted OR and 95% CI of mortality for FABP4 quartiles (with the lowest quartile as reference). In multivariate models comparing the third and fourth quartiles to the first quartile of FABP4 (Table 3), the concentrations of FABP4 were associated with mortality. Compared with the reference category (Q1–Q3), the concentrations of FABP4 in Q4 had a relative risk of 6.15 (95% CI, 3.43–12.68; *P*<0.001) for mortality after adjusting for other significant outcome predictors (Table 3).

Receiver-operating characteristic curve demonstrated the greatest discriminatory accuracies for FABP4 concentration (AUC=0.83) and NIHSS score (AUC=0.73). The combination of FABP4 concentration and NIHSS score had a higher discriminatory accuracy (AUC=0.86) than NIHSS score alone (*P*<0.001). In addition, the combination of age, FABP4, BMI, NIHSS score, Hs-CRP, FBG, and eGFR showed the greatest accuracy (AUC=0.92), greater than all individual parameters alone (*P*<0.01; Table III in the online-only Data Supplement). Again, the net reclassification improvement and integrated discrimination improvement statistics showed that the addition of FABP4 to established risk factors significantly increased the correct reclassification of mortality patients and survivors (Table IV in the online-only Data Supplement).

Kaplan–Meier analyses of all-cause mortality of the 4 quartiles of FABP4 concentrations are shown in Figure 2. Data show that the all-cause mortality is associated with different concentrations of FABP4 from a group with the lowest quartiles of plasma concentrations of FABP (group 1, 2.2%) to a group with the highest quartiles (group 4, 37.5%). Patients in the lowest and second quartiles had a minimal risk for death in contrast with patients with FABP4 concentrations in the third and fourth quartiles (*P*<0.0001).

Discussion

The NIHSS score is a standardized measure of stroke severity and is used to predict short-term outcome. However, it has some limitations that must be taken into account.[20] The present study is the first report to investigate the prognostic potential of FABP4 in a substantial cohort of stroke patients from a multicenter. Data confirm an important conclusion that FABP4 is a strong and independent prognostic marker of functional outcome and death in Chinese patients with AIS and adds significant additional predictive information to the clinical score of the NIHSS.



Q	Total N	N of Events	Censored	
			N	Percent
Q1	184	4	180	97.8%
Q2	185	7	178	96.2%
Q3	184	14	170	92.4%
Q4	184	69	115	62.5%
Overall	737	94	643	87.2%

Figure 2. Kaplan–Meier curves analysis for serum FABP4 (fatty acid–binding protein 4) concentrations according to quartiles to predict the end point of mortality in stroke patients. Patients in the lowest and second quartiles had a minimal risk for death, in contrast with patients with FABP concentrations in the third and fourth quartiles (P<0.0001).

Consistent with our finding, Holm et al[16] reported that FABP was linked to atherogenesis, plaque instability, and adverse outcome in patients with carotid atherosclerosis and AIS. Two previous studies have shown enhanced FABP expression within human carotid atherosclerotic lesions in association with poor prognosis.[13,22] Similarly, Chow et al[23] found that the circulating FABP4 concentration predicts the development of cardiovascular events after adjustment for traditional risk factors in a community-based cohort, whereas Furuhashi et al[24] reported that the FABP concentration, being related to adiposity and metabolic disorders, is a novel predictor of cardiovascular mortality in end-stage renal disease.

In our analysis, it is noteworthy that FABP4 seems to be a valid prognostic biomarker for stroke outcomes. Similarly, one study suggested that higher levels of FABP4 are associated with elevated cardiovascular mortality among men with type 2 diabetes mellitus.[25] Interesting, Zimmermann-Ivol et al[26] suggested that heart-type FABP3 is a valid serum biomarker for the early diagnosis of stroke. Another study showed that serum brain-type FABP7 and FABP3 are elevated early in AIS, indicating that especially FABP3 might have the potential to be a rapid marker of brain damage and clinical severity.[27] Furthermore, another study showed that urinary liver FABP (FABP1) level represented a sensitive and predictive early biomarker of acute kidney injury after cardiac surgery.[28]

The underlying mechanisms linking FABP with stroke outcome are not clearly illustrated in previous studies. However, some possible mechanisms may be speculated. First, CRP is an established prognostic marker in stroke.[29] We found a positive correlation between serum concentrations of FABP and Hs-CRP. However, after adjusting for Hs-CRP, FABP4 is still associated with functional outcomes, and it may be claimed that FABP is just another acute-phase protein. Second, a recent work has shown a pivotal role for FABP in macrophages in relation to cholesterol trafficking and inflammation[30] and atherosclerosis and plaque rupture.[31] Another study provides a mechanistic linkage between FABP and impaired endothelial function in diabetes mellitus, which leads to an increased cardiovascular risk.[32] Third, the natriuretic peptide system, including B-type natriuretic peptide and the N-terminal fragment of its prohormone NT-proBNP (N-terminal Pro-B-type natriuretic peptide), plays an important role in adipose tissue metabolism,[33] which might influence the secretion of adiponectin. Some studies demonstrated that NT-proBNP and adiponectin had a significantly positive correlation, and both could predict high mortality in participants with chronic heart failure or chronic kidney disease.[34]

Strengths and Limitations

Our study is the first analysis of serial serum measurements of FABP4 in Chinese patients with stroke in a multicenter. The result shows a significant change with day of samples collected. Furthermore, we collected data on a wide range of potentially confounding risk factors, allowing us to estimate the independent effect of FABP. Finally, we chose a different strategy using the fourth quartiles, because we have found this strategy to be more sensitive to other factors that might influence the relatively low concentrations.

The following limitations of our study must be taken into account. First, data on potential confounding factors, including other markers of FABPs, dietary intake, and outdoor physical activity, were not obtained. Thus, we could not determine

the association of those factors with serum FABP4 concentrations and outcomes of stroke. Second, our data came from Chinese only, which could have selection bias. Therefore, it is not clear that the results are generalizable outside of this population. Third, there is evidence that FABP4 may favorably influence stroke outcomes through multiple pathways, including hypertension, insulin resistance and secretion, diabetes mellitus, and chronic inflammation. The inclusion of those factors in the models could possibly lead to overadjustment, which tends to attenuate the associations. Finally, this observational study cannot determine the causal relationship between FABP4 and functional outcomes.

Conclusions

The present study is the first report showing the serum concentrations of FABP as a useful prognostic marker of functional outcomes or mortality in Chinese patients with stroke independent of established conventional risk factors.

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Disclosures

None.

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Circulating FABP4 (Fatty Acid–Binding Protein 4) Is a Novel Prognostic Biomarker in Patients With Acute Ischemic Stroke

Wen-Jun Tu, Xian-Wei Zeng, Aijun Deng, Sheng-Jie Zhao, Ding-Zhen Luo, Guo-Zhao Ma, Hong Wang and Qiang Liu

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Supplemental Data-online only

Supplemental Figure I: Study profile/flow sheet of the study

Supplemental Figure II. The correlation between serum FABP4 concentrations and other factors. (A) Correlation between serum FABP4 concentrations and the NIHSS score; (B) Correlation between serum FABP4 levels and Infarct volume (N=440). NIHSS=National Institutes of Health Stroke Scale; FABP4=Fatty acid-binding proteins 4.

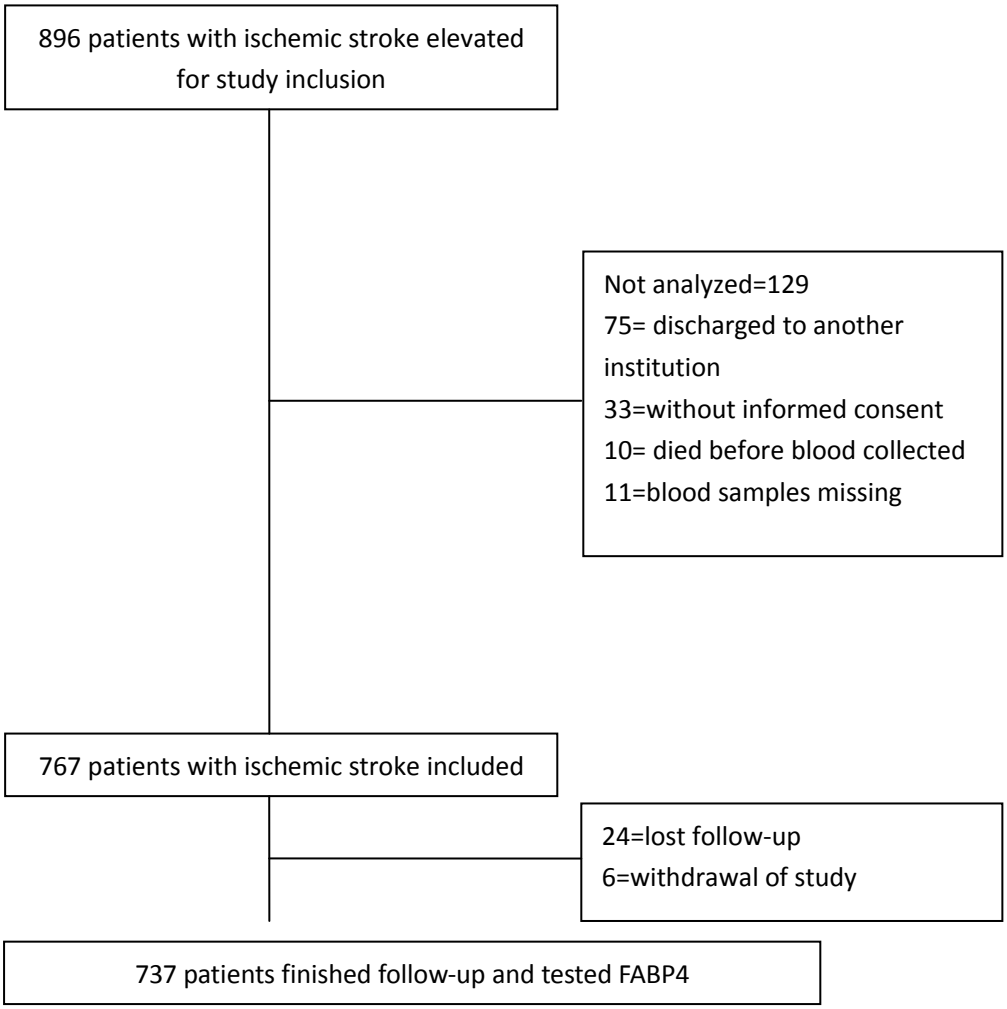
Supplemental Figure III. Serum concentrations of FABP4 in different groups. (A) Serum concentrations of FABP4 in stroke patients with favorable and unfavorable functional outcome; (B) Serum concentrations of FABP4 in survivors and nonsurvivors of stroke. Mann–Whitney U-test. All data are medians and interquartile ranges (IQR). FABP4=Fatty acid-binding proteins 4.

Supplemental Table I: The baseline characteristics of patients in different Stroke Centers

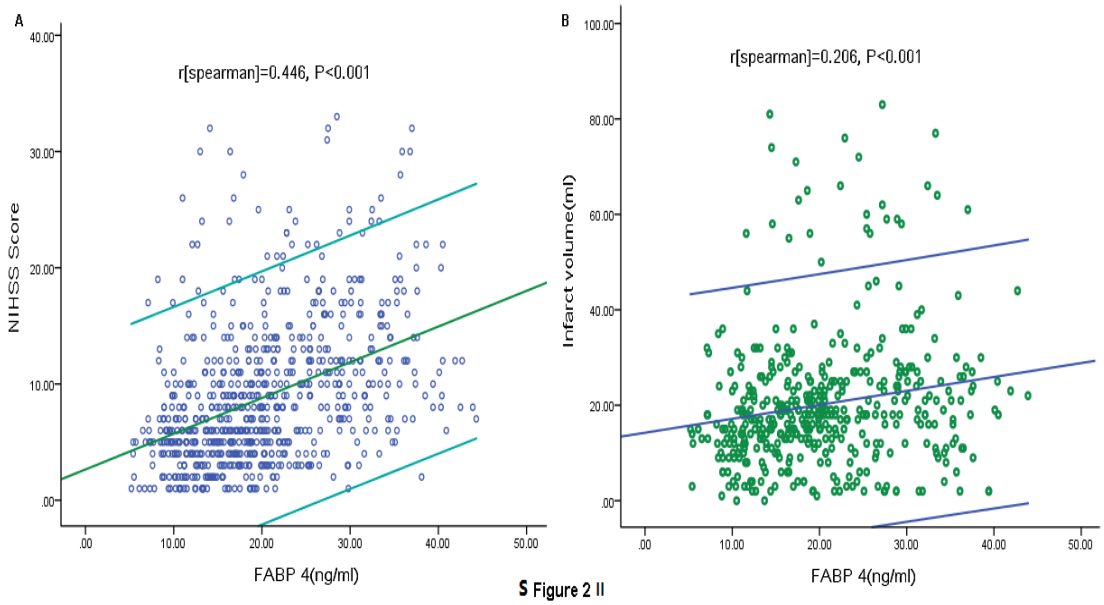
Supplemental Table II. Functional outcomes Risk in different Stroke Centers

Supplemental Table III Area under the curve for selected predictors of functional outcome or mortality

Supplemental Table IV Serum FABP4 concentrations at admission prediction of unfavorable outcome and mortality with AUROC, NRI, and IDI analyses



Supplemental Figure I: Study profile/flow sheet of the study



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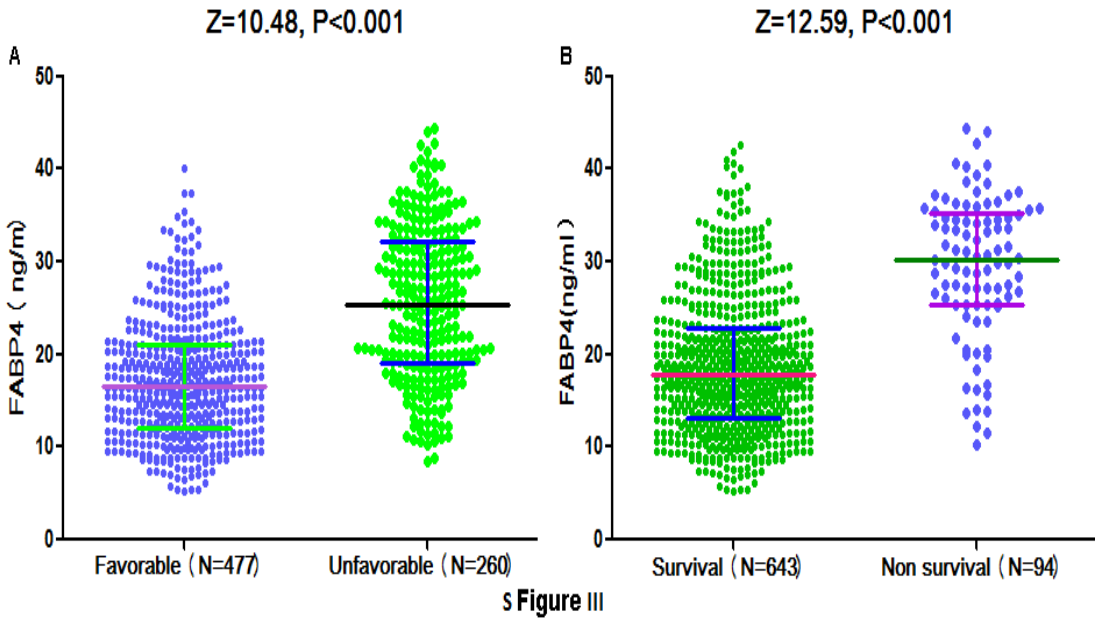

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Supplemental Table I**. The** baseline characteristics of patients in different Stroke Centers [‡]

Cohort	No	Age(IQR)	Sex, male (%)	NIHSS(IQR)	BMI(IQR)	FABP 4
Weifang	265	59(51-67)	52.8	7(4-13)	26.6(24.9-27.4)	19.0(14.1-25.6)
Jinan	232	58(50-68)	58.2	6(3-12)	26.3(24.6-27.3)	18.6(13.5-25.3)
Beijing	240	60(51-68)	52.1	7(4-12)	26.2(24.7-27.3)	18.8(13.8-25.3)
ALL	737	58(51-68)	54.3	7(4-12)	26.3(24.8-27.3)	18.8(13.8-25.4)

[‡] *p* value was assessed using Mann-Whitney *U* test or Chi-Square test between different groups. There is no significant different between those groups (P>0.05, all).

Results are expressed as percentages or as medians (IQR); FABP 4: Fatty acid-binding proteins; BMI, body mass index; NIHSS, National Institutes of Health Stroke Scale

Supplemental Table II. Functional outcomes Risk in different Stroke Centers

Cohort	No. of Patients	No. of unfavorable outcome	Risk % (95% CI) ‡	No. of Patients Who Died	Risk, % (95% CI) ‡
Weifang	265	90	34.0(28.3-39.7)	33	12.5(8.5-16.4)
Jinan	232	81	34.9(28.8-41.0)	30	12.9(8.6-17.2)
Beijing	240	89	37.1(31.0-43.2)	31	12.9(8.7-17.2)
ALL	737	260	35.3(31.8-38.7)	94	12.8(10.3-15.2)

‡ *p* value was assessed using Chi-Square test; there is no significant different between those groups (P>0.05, all)

CI; confidence interval

Supplemental Table III Area under the curve for selected predictors of functional outcome or mortality

Predictors	Functional outcome		Mortality	
	AUC (95%CI)	P	AUC (95%CI)	P
FABP4	0.78(0.75-0.82)		0.83(0.79-0.88)	
NIHSS	0.72(0.65-0.78)	0.01	0.73(0.68-0.77)	0.003
Age	0.70(0.63-0.75)	0.009	0.69(0.64-0.75)	<0.001
Sex	0.56(0.50-0.63)	<0.001	0.53(0.48-0.60)	<0.001
TACS	0.60(0.52-0.65)	<0.001	0.61(0.55-0.70)	<0.001
BMI	0.63(0.57-0.69)	<0.001	0.66(0.60-0.73)	<0.001
Hs-CRP	0.65(0.58-0.70)	0.001	0.70(0.64-0.78)	0.001
FBG	0.59(0.52-0.67)	<0.001	0.60(0.54-0.70)	<0.001
eGFR	0.57(0.52-0.64)	<0.001	0.62(0.57-0.71)	<0.001
Combined score (NIHSS/GABP4)	0.83(0.76-0.89)	0.02	0.86(0.81-0.92)	0.04
Combined score(all included)	0.86(0.82-0.90)	<0.01	0.92(0.87-0.95)	<0.01

CI, confidence interval; Hs-CRP: high-sensitivity C-reactive protein; FBG: fasting blood glucose; FABP 4: Fatty acid-binding proteins; BMI, body mass index; NIHSS, National Institutes of Health Stroke Scale; TACS, total anterior circulation syndrome; eGFR: estimated glomerular filtration rate.

Supplemental Table IV Serum FABP4 concentrations at admission prediction of unfavorable outcome and mortality with AUROC, NRI, and IDI analyses

	AUROC					
	FABP4 alone	Factors without FABP4‡	Factors with FABP4†	Incremental area (P)†	NRI(P)	IDI(P)
Outcomes	0.78	0.81	0.86	0.05(0.03)	0.11(0.01)	0.09(0.02)
Mortality	0.83	0.85	0.92	0.07(0.01)	0.17(<0.01)	0.14(<0.01)

‡ Risk factors including: age, sex, TACS, BMI, Hs-CRP, FBG, eGFR and NIHSS score

†Comparison of AUROCs: established risk factors without FABP4 vs. established risk factors with FABP4.

Hs-CRP: high-sensitivity C-reactive protein; FBG: fasting blood glucose; FABP 4: Fatty acid-binding proteins; BMI, body mass index; NIHSS, National Institutes of Health Stroke Scale; TACS, total anterior circulation syndrome; eGFR: estimated glomerular filtration rate; IDI, integrated discrimination improvement; NRI, net reclassification improvement; FABP 4: Fatty acid-binding proteins