Research article

Elevated plasma intestinal fatty acid binding protein and aberrant lipid metabolism predict post-stroke depression

Jiaju Zhong [a,1], Jianjun Chen [b,1], Maolin Cao [c,1], Liang Fang [c,d,e], Zhenyu Wang [a], Juan Liao [c], Dan Chen [c], Xiaoli Zhang [f], Jiaxun Guo [a], Libo Zhao [d,e,**], Chanjuan Zhou [c,d,e,*]

[a] Department of Rehabilitation Medicine, Yongchuan Hospital of Chongqing Medical University, Chongqing, China
[b] Institute of Life Sciences, Chongqing Medical University, Chongqing, China
[c] Chongqing Clinical Research Center for Geriatric Disease, Chongqing, China
[d] Department of Neurology, Yongchuan Hospital of Chongqing Medical University, Chongqing, China
[e] Chongqing Key Laboratory of Cerebrovascular Disease Research, Chongqing, China
[f] Department of Microbiology, Yongchuan Hospital of Chongqing Medical University, Chongqing, China

ABSTRACT

Post-stroke depression (PSD) is the most common mood disorder caused by stroke. Stroke might bring about increased intestinal permeability accompanied by gut microbiota changes. According to the "gut-brain" axis hypothesis, increased intestinal permeability may contribute to PSD. Therefore, we investigated the association between increased intestinal permeability and the occurrence of PSD. Intestinal fatty acid binding protein (iFABP) is responsible for intestinal fatty acid absorption and transport and is often considered a biomarker of gut hyperpermeability, also known as leaky gut. We enrolled 48 healthy controls (HCs), 48 stroke patients without depression, and 48 PSD patients in this study. Plasma iFABP was measured in the three groups. CRP, LBP, and sCD14 were quantified for bacterial infection assessment. In addition, clinical laboratory indicators of lipid metabolism were assessed. The PSD patients exhibited higher iFABP levels compared with HCs and non-depressed stroke patients. Using OPLS discriminant analysis, four proteins (ApoA1, HDL-C, iFABP, and Lp(a)) were identified as potential biomarkers for distinguishing PSD patients from non-depression stroke patients. Our study discovered that elevated plasma iFABP levels in PSD patients correlated with the degree of depression, along with disturbed lipid metabolism. These findings also suggested the need to consider the role of a leaky gut in depression after stroke.

1. Introduction

The neuropsychiatric disorders associated with cerebrovascular disease are of considerable clinical importance. Post-stroke depression (PSD) is the most common mood disorder caused by stroke. Meta-analyses estimated that the prevalence of depression in patients who experienced a stroke was as high as 33% (Mitchell, 2017), resulting in increased disability, morbidity, and mortality in stroke survivors (Bartoli, 2018). Current evidence has identified several similarities in molecular mechanisms between PSD and major depression (Robinson and Jorge, 2016). Nonetheless, additional reliable and specific pathophysiological alterations need to be identified in studies of PSD diagnosis and treatment.

The pathophysiology of PSD is closely linked to stroke. Research has demonstrated that stroke may cause damage to the brain (Pan, 2021) and influence the gastrointestinal (GI) tract, including causing increased intestinal permeability (IP). Increased IP frequently results from intestinal barrier dysfunction. Ye et al. (Ye, 2021) reported that acute stroke led to leucocyte accumulation in the intestinal mucosa, which impaired the intestinal barrier and increased IP. Ischemic stroke also can induce intestinal apoptosis (Ye, 2021) and activate the inflammasome in the intestinal tissues (Kerr, 2022), which might exacerbate gut integrity impairment. Due to stroke-induced IP, the gut microbiota composition

has been shown to be altered, and intestinal microbial translocation was observed in other organs (Stanley, 2016; Wei, 2021), which could initiate a systemic immune response following a stroke (Huang and Xia, 2021).

Intestinal fatty acid binding protein (iFABP), also known as FABP2, is specifically expressed throughout the intestine. IFABP is responsible for intestinal fatty acid absorption and metabolism and might influence circulating triglyceride levels (Furuhashi and Hotamisligil, 2008; Gajda and Storch, 2015). On the other hand, iFABP has been associated with intestinal dysfunction and has been reported to be a biomarker for the presence of a leaky gut in intestinal diseases (Wiercinska-Drapalo, 2008; Funaoka, 2010; Sarikaya, 2015) and extra-intestinal disorders. Serum iFABP was significantly elevated in subjects with biliary tract infections and accompanied by elevated high-sensitivity C-reactive protein (CRP) (Weng, 2021). Increased expression of iFABP was observed in patients with Graves' disease compared to healthy controls (Zheng, 2021). Interestingly, recent studies reported that subjects with major depressive disorder (MDD) displayed higher iFABP levels (Stevens, 2018; Ohlsson, 2019).

Therefore, in this study, we measured iFABP levels to determine the presence of a leaky gut in subjects with stroke and PSD. We also assessed CRP, lipopolysaccharide binding protein (LBP) and soluble cluster of differentiation 14 (sCD14) levels as indicators for intestinal bacterial imbalance and translocation. Clinical laboratory assessments that evaluated lipid metabolism also were compared to explore lipid metabolism changes related to the presence of a leaky gut in PSD.

2. Materials and methods

2.1. Study subjects and clinical data collection

All procedures were approved by the Ethics Committee of Yongchuan Hospital of Chongqing Medical University. The participants in this study were enrolled in the Yongchuan Hospital of Chongqing Medical University from May 2020 to December 2021. This study enrolled 144 subjects, including 48 stroke survivors without depression characteristics, 48 antidepressant drug-naïve PSD subjects, and 48 healthy controls (HCs). This study was conducted according to the Declaration of Helsinki for the protection of human participants in medical research. All participants provided written informed consent.

The inclusion criteria for the stroke participants were as follows: (1) diagnosed as either ischemic or hemorrhagic stroke patients who were 18 years or older; (2) a stroke was diagnosed using cranial computed tomography (CT) or magnetic resonance imaging (MRI) within 24h of admission; (3) the patients exhibited clear consciousness and were able to cooperate with the relevant examinations. Patients with the following clinical characteristics were excluded: (1) transient ischemic attack; (2) had neurological diseases other than stroke; (3) exhibited renal, hepatic, or heart failure.

The 24-item Hamilton Depression Rating Scale (HAMD) score was used to assess the depressive symptoms of stroke survivors after stroke onset. Depression severity was categorized as follows: a score of 7 or less indicated the absence of depression, a score between 8 and 19 indicated mild depression, and a score of 20 or higher indicated severe depression. The inclusion criteria for PSD patients were as follows: (1) met the inclusion and exclusion criteria for stroke; (2) had a 24-item HRSD score of 8 or higher; (3) did not have a previous history of psychiatric disorders before the stroke; (4) did not have another mental illness or a cognitive disorder; (5) had not received any antidepressant medication treatment before blood sample collection. The patients' demographic characteristics were collected within seven days of admission and included age, gender, height, weight, stroke type, smoking and drinking history, as well as the presence of diabetes mellitus, hypertension, or coronary heart disease (CHD).

2.2. Blood sample collection and measurement

Blood samples were collected and processed according to Nikolac's recommendation (Nikolac, 2013). In brief, blood was collected in the morning for all participants using vacutainer tubes containing the chelating agent ethylenediaminetetraacetic acid (EDTA) according to. Plasma was obtained by centrifuging the blood at 3,000rpm for 10min, and iFABP was measured in the three groups. Because a leaky gut is likely to cause bacterial translocation or inflammation, LPS-binding protein (LBP), soluble cluster of differentiation 14 (sCD14), and high-sensitivity C-reactive protein (CRP) also were assessed. The plasma levels of iFABP, LBP, and sCD14 were measured using a solid-phase sandwich enzyme-linked immunosorbent assay (ELISA) kit (MeiMian, Jiangsu, China) according to the manufacturer's specifications. Because iFABP is also related to fatty acid absorption that might influence lipid metabolism, we tested the levels of lipoprotein(a) (Lp(a)), apolipoprotein B (ApoB), apolipoprotein E (ApoE), apolipoprotein A1 (ApoA1), free fatty acid (FFA), total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL) and glucose, which are commonly used laboratory lipid indicators.

2.3. Statistical analysis

A one-way ANOVA and chi-square test were used to determine significant differences in the demographic data. The stroke and PSD patients were randomly assigned to a training set or testing set at a ratio of 2:1. First, an orthogonal projections to latent structures (OPLS) model was constructed using the training set, and a 399-item permutation test was used to validate the OPLS model. Second, the testing set and HCs were used to assess the model's accuracy in predicting independent and blind samples. Third, key molecules responsible for discrimination between stroke and PSD patients were selected based on a combination of a correlation coefficient of $|r| > 0.349$ from the OPLS model and $P < 0.05$ from the one-way ANOVA. Fourth, the Pearson correlation method was used to identify molecules that were significantly correlated with anxiety or depressive symptoms. Finally, binary logistic regression analysis was used to construct a discriminative model using the identified molecules, and receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of the model.

3. Results

3.1. Baseline characteristics

This study included 48 non-depressed patients after stroke (stroke group), 48 PSD patients (PSD group), and 48 age- and sex-matched healthy controls (HCs group). The general clinical characteristics of all subjects are shown in Table 1. No significant differences in sex, age, and body mass index (BMI) values were observed among the three groups ($P > 0.05$). However, a significant difference was observed in the HAMD scores among the groups. The PSD patients displayed mild or moderate depressive symptoms with an average 24-HAMD score of 16.7, while the average 24-HAMD scores were 1.91 and 4.52 in the HCs and stroke patients, respectively. There were no significant differences in the medical therapy (statins, antiplatelet aggregation drugs, anticoagulants) between stroke and PSD groups. Stroke and PSD subjects had no differences in preexisting comorbidities related to depression, including diabetes mellitus (Bădescu, 2016), coronary heart disease (Carney, 2017), hypertension (Li, 2015) and previous stroke. Moreover, the incidences of severe neurological deficits (NIHSS and modified Rankin scores) were higher in the PSD group than in the stroke group. It meant that the PSD group had worse stroke-related neurological status, which implied that stroke symptomatology might be an important indicator in the development of leaky gut in PSD.

3.2. The OPLS model

There were 32 stroke and 32 PSD patients included in the training set, which was used to construct the OPLS model. As shown in Figure 1A, the OPLS model demonstrated that the PSD patients were clearly

distinguished from the stroke patients. 90.6% of the stroke patients and 84.4% of the PSD patients were correctly recognized in the OPLS model. Furthermore, we used a 399-item permutation test to validate the OPLS model. The results demonstrated that the OPLS model was valid and not over-fitting, as all of the corresponding permutated R2 and Q2 values from the permutation test were significantly lower than the original R2 and Q2 values (Figure 1B).

3.3. OPLS model validation

The testing set included 16 stroke and 16 PSD patients that were used to validate the discriminative power of the OPLS model independently. The T-predicted scatter plot from the OPLS model demonstrated that 87.5% of the stroke patients and 81.3% of the PSD patients were correctly predicted by the OPLS model, yielding a predictive accuracy of 84.4% (Figure 2A). In addition, the 48 HCs were used as a blind set to validate whether the OPLS model was specific to patients with stroke versus HCs, and only six HCs were incorrectly identified as PSD patients (Figure 2B). These results indicated that this OPLS model was promising as an objective diagnostic method for PSD.

3.4. Potential biomarkers for PSD

The results of the one-way ANOVA indicated that seven molecules were significantly changed ($P < 0.05$) between stroke and PSD patients: iFABP, Lp(a), ApoB, TC, ApoA1, HDL-C, and LDL-C. By analyzing the OPLS loading coefficient plots, five molecules with an $|r|>0.349$ were identified: ApoA1, FFA, HDL-C, iFABP, and Lp(a). Thus, four key molecules responsible for discrimination between stroke and PSD patients were identified and were potential biomarkers for PSD: ApoA1, HDL-C, iFABP, and Lp(a) (Figure 3A-D). When compared to stroke patients and HCs, PSD patients were characterized by lower levels of ApoA1 and HDL-C and higher levels of iFABP and Lp(a). We also found that the ApoA1 ($P = 0.042$) and HDL-C ($P = 0.019$) levels were significantly lower in stroke patients than HCs. The detailed information on the assessed molecules is presented in Table 2.

3.5. Correlation analysis

We used the Pearson correlation method to assess significant correlations between the identified molecules and the HAMD and HAMA scores. Two correlation networks were observed. First, seven molecules

(ApoA1, HDL-C, TC, Lp(a), iFABP, LDL-C, and ApoB) were significantly correlated with the HAMD score (Figure 4A), and five molecules (ApoA1, HDL-C, TC, iFABP, and Lp(a)) were significantly correlated with the HAMA score (Figure 4B). All four identified potential biomarkers for PSD were significantly correlated with the HAMD and HAMA scores.

3.6. Diagnostic performance assessment

A discriminative model was identified using binary logistic regression analysis: P(Y = 1) = 1/(1 + EXP (-0.001675*iFABP -0.003169*Lp(a) +10.070161*ApoA1+1.219721*HDL-C -3.600708)). Using this model, we calculated the probability of illness in each patient. Then, the probability of illness in each patient was used to build the ROC curve. The results indicated that this discriminatory model effectively distinguished PSD patients from stroke patients with an area under the ROC curve (AUC) of 0.94 in the training set (Figure 5A). This model also effectively identified PSD patients in the testing set (AUC = 0.93) (Figure 5B) and displayed excellent discriminative power in separating PSD patients from HCs (AUC = 0.96) (Figure 5C). These results suggested that this model might be an excellent method to classify PSD and stroke patients.

4. Discussion

In clinical assessments, PSD is considered a specific type of depression that occurs after a stroke. One consequence of stroke are changes in the gastrointestinal structure and function, including a leaky gut (Arya and Hu, 2018). IFABP is a protein primarily expressed in the small intestine and helps to maintain intestinal integrity (Furuhashi and Hotamisligil, 2008). When the intestinal barrier is impaired, iFABP is released into the circulation. Camara Lemarroy et al. reported that patients with acute ischemic stroke had significantly higher serum iFABP concentrations compared to controls (Camara-Lemarroy, 2021). At the beginning of this study, we measured the level of iFABP, and it was significantly elevated in all stroke patients (with and without PSD) compared to controls (data not shown). Interestingly, we also found that the PSD patients had significantly higher plasma iFABP levels compared to HCs and stroke patients without depression. Thus, our study indicated that a leaky gut was potentially involved in PSD, and the level of iFABP in plasma was positively correlated with the HAMD scores.

In our study, the "gut-brain" axis is the most likely mechanism to explain how increased iFABP and the related IP are linked to depression after stroke. First, altered gut microbiota in PSD (Ling, 2020; Kang, 2021)

Table 1. Demographic data of the included subjects.[a]

	HCs	Stroke	PSD	p value (HCs vs. Stroke)	p value (HCs vs. PSD)	p value (PSD vs. Stroke)
Number	48	48	48	-	-	-
Age	63.4 ± 16.3	66.0 ± 9.3	63.0 ± 10.0	0.70	0.99	0.35
F/M	26/22	35/13	31/17	0.09	0.41	0.51
BMI(kg/m^2)	25.58 ± 2.72	26.26 ± 2.46	26.65 ± 2.61	0.61	0.14	0.99
24-HAMD	1.92 ± 1.54	4.52 ± 1.68	16.71 ± 6.56	<0.00001	<0.00001	<0.00001
14-HAMA	1.23 ± 1.29	3.06 ± 1.24	12.54 ± 4.41	<0.00001	<0.00001	<0.00001
NIHSS	-	9 (4,15)	13 (5.5,19)			0.026
GCS	-	15 (12,15)	13 (9,15)			0.10
mRS	-	4 (3,4)	4 (3,5)			0.007
Hypertension (%)	-	34 (70.8)	31 (64.6)			0.616
Diabetes mellitus (%)	-	7 (14.5)	10 (20.8)			0.344
History of stroke (%)	-	1 (2.1)	2 (4.1)			1.000
Coronary heart disease (%)	-	3 (6.25)	5 (10.4)			0.208
Statins (%)	-	26 (54.2)	27 (56.3)			0.99
Antiplatelet aggregation drugs (%)	-	26 (54.2)	23 (47.9)			0.13
Anticoagulants (%)	-	10 (20.6)	12 (25)			0.07
Antidepressants (%)	-	0 (0.0)	0 (0.0)			-

[a] one-way ANOVA or chi-square test was used to obtain p-values.
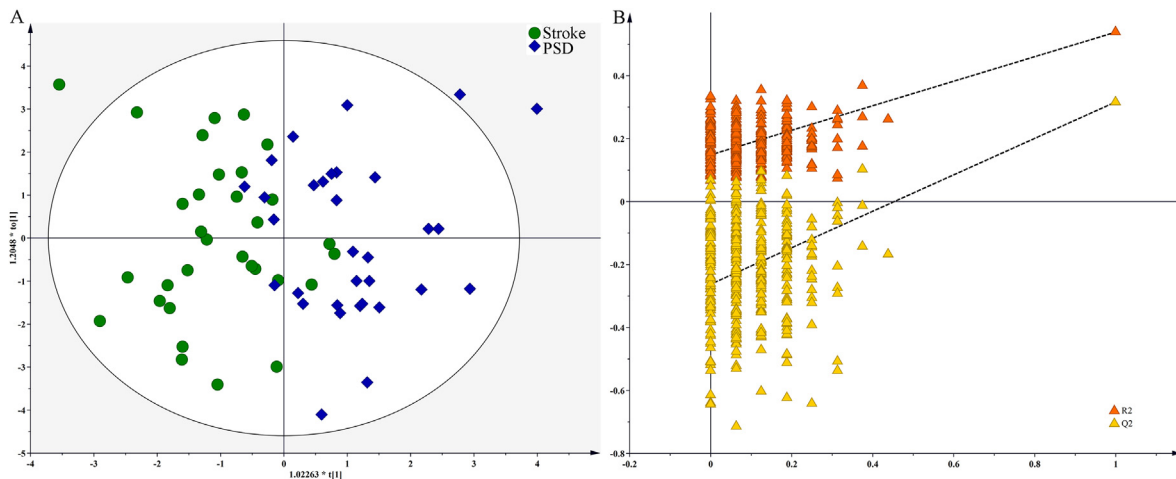
Figure 1. OPLS model built using Stroke and PSD patients in training set: A) Stroke (green dot) and PSD (blue diamond) patients were obviously separated with little overlap; B) this model was valid, as the original R2 and Q2 values (top right) were higher than their values from permutation test (bottom left).

together with metabolite alterations could get involved under increased IP condition. Mice that are null for iFABP have increased intestinal permeability, and iFABP ablation results in changes in gut motility and morphology (Lackey, 2021). Moreover, intestinal motility and structure alterations could influence the composition and function of gut microbiota. The microbiota abnormalities could influence emotional behavior by regulating the host metabolism. Several studies have reported that different forms of metabolism, such as amino acid, lipid, and energy metabolism, were significantly disturbed in mice that exhibited microbiota-mediated depressive-like behaviors (Zheng, 2016; Tian, 2021; Liu, 2021). Metabolic disorders associated with plasma and urine of PSD patients have been reported (Hu, 2019; Xie, 2020; Chen, 2020), and fecal metabolism was disturbed in PSD rat models as well (Jiang, 2021) For example, reduced fecal concentrations of short chain fatty acids (SCFAs) have been observed in stroke and PSD animal models (Jiang, 2021). Studies have reported that bacteria-derived SCFAs, such as acetate, butyrate, and propionate may help alleviate depressive symptoms in PSD (Dalile, 2019).

Second, increased immune system activation has been associated with depression (Bai, 2022). The homeostasis of the intestinal barrier immune defenses is critical in preventing the host from undergoing mood and cognitive changes due to bacterial influences (Leclercq, 2012; Maes, 2012). In ischemic stroke rat models, increased T lymphocytes were observed in Peyer's patches, and the IgA and IgM-mediated intestinal

immunity was activated (Liu, 2017). Inflammatory cytokines are released into the circulation in large amounts after stroke resulting in "off-site" effects causing increased IP (Ferrara, 2020). As a result, increased inflammatory cytokines such as IL-1 and TNF-α and lipopolysaccharide (LPS) could evoke inflammatory processes in the body, including neuroinflammation in PSD (Mass, 2008; Wijeratne, 2021). LBP is a response to elevated LPS and interacts with CD14 at the cell surface. In our study, we analyzed the plasma levels of LBP and sCD14, and they did not differ significantly among the groups. sCD14 is considered a non-specific monocyte activation marker and does not necessarily indicate increased gut permeability, which could explain why this marker did not show similar changes.

Recent metabolomics studies have reported alterations in fatty acids in PSD patients (Hu, 2019; Xie, 2020; Chen, 2020). We used traditional laboratory indicators to assess the relationship between lipid metabolism and PSD. Lp(a), ApoB, TC, Apo A1, HDL-C, and LDL-C levels were significantly changed in PSD patients. On the one hand, iFABP has long been thought to be involved in the uptake and transport of dietary fatty acids (FAs) in the small intestine (Gajda and Storch, 2015). IFABP can bind more FAs after apical absorption and transport them for TG synthesis and chylomicron formation. Vassileva et al. (Vassileva, 2000) observed that plasma triacylglycerol concentrations in male iFabp−/− mice were 1.3–1.5 fold higher than controls. However, the lipoprotein particles and glucose in the plasma of iFabp−/−mice were not altered.
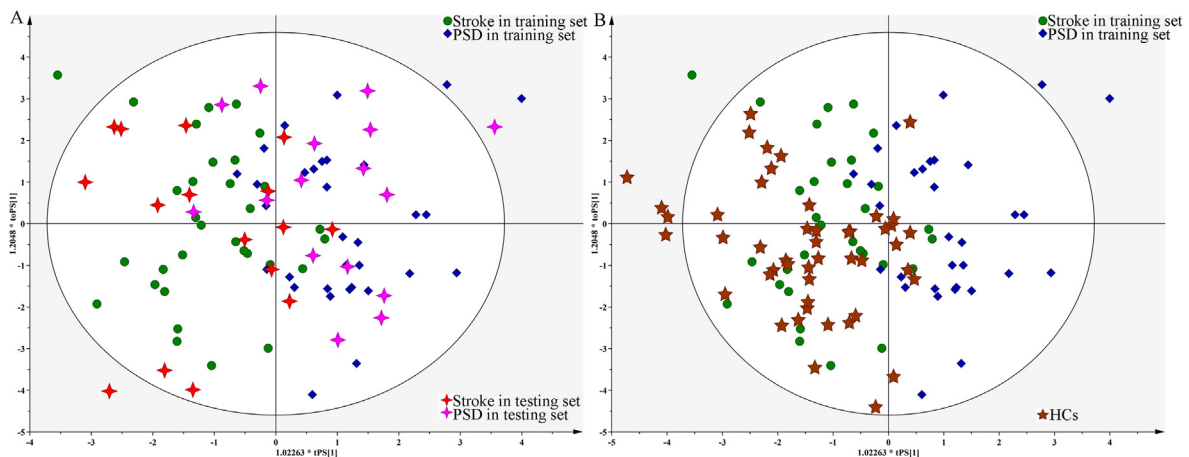

Figure 2. T-predicted scatter plot from OPLS model: A) both Stroke (red cross) and PSD (purple cross) patients in testing set were correctly predicted; B) this OPLS model could also effectively separate HCs (brown five-pointed star) from PSD patients.
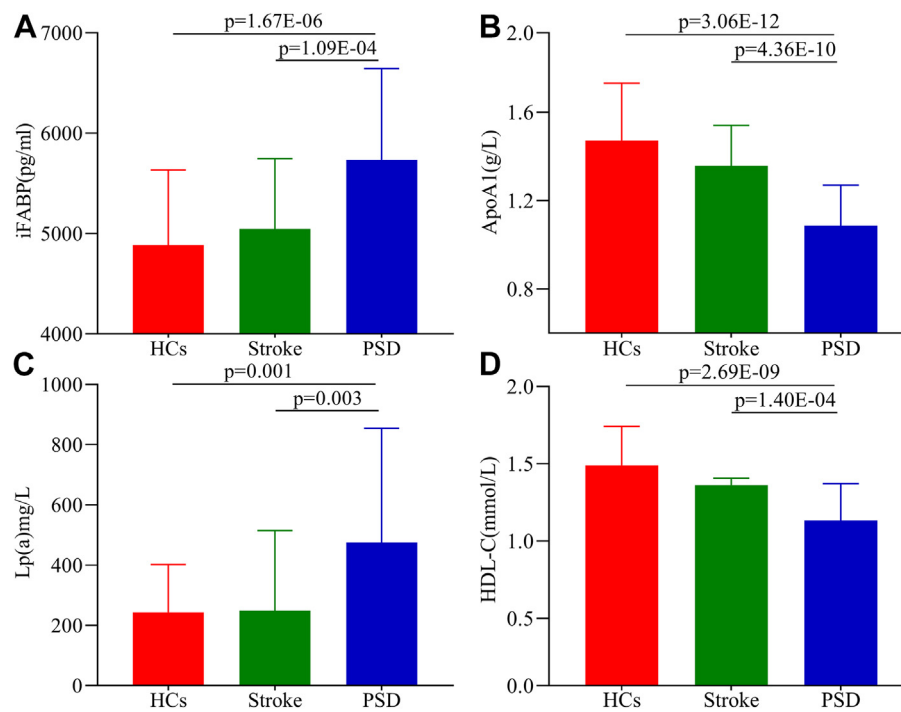
Figure 3. Potential biomarkers responsible for discrimination between Stroke and PSD patients. Plasma expression levels of A) iFABP and C) Lp (a) in PSD patients were significantly higher than those in HCs and stroke subjects without depression; B) ApopA1 and D) HDL-C displayed a significantly decreased plasma level in PSD patients compared to in HCs and stroke subjects without depression.

Notably, the iFabp−/− mice had down-regulated the FA levels in the blood, which may explain why the FFA was significantly higher in stroke patients without depression than PSD patients. On the other hand, a leaky gut could affect lipid absorption and delivery across the intestinal barrier. Mice with an impaired intestinal barrier exhibited altered levels of total cholesterol, HDL, and LDL (Wang, 2019). Thus, increased IP is one possible cause of the lipid metabolic disorder observed in PSD. However, additional evidence is needed for validation.

Finally, our findings indicated the presence of leaky gut in PSD patients. In the clinic, several methods might be available for the evaluation of leaky gut. For example, the measurement of urinary lactulose mannitol excretion ratio (LMR) after oral 13C-mannitol or other saccharides (Khoshbin, 2021; Nicholas, 2022) would be helpful to detect for possible leaky gut. Kinds of evidence have provided some gut-directed therapies to improve intestinal barrier impairment. Enteral glutamine could normalize the urinary LMR, although the biological significance of these

Table 2. Detailed information of the detected molecules.[a]

Indicators	HCs	Stroke	PSD	p value (HCs vs. Stroke)	p value (HCs vs. PSD)	p value (PSD vs. Stroke)	R[b]
iFABP (pg/ml)	4887.13	5045.08	5733.85	0.98	1.67E-06	1.09E-04	0.74
sCD14 (ng/ml)	464.68	413.56	422.08	0.13	0.28	0.99	0.06
LBP (μmol/L)	290.16	254.88	268.59	0.26	0.87	0.99	0.15
CRP (mg/L)	3.66	7.57	15.12	0.33	0.06	0.41	0.19
Lp(a) (mg/L)	244.08	249.71	475.17	0.99	0.001	0.003	0.78
ApoB (g/L)	0.95	0.94	0.82	0.98	0.028	0.038	0.06
FFA (μmol/L)	444.88	604.65	522.35	0.002	0.15	0.29	-0.44
TC (mmol/L)	5.15	4.72	3.75	0.069	7.79E-12	3.94E-05	-0.2
Apo A1 (g/L)	1.47	1.36	1.09	0.042	3.06E-12	4.36E-10	-0.96
HDL-C (mmol/L)	1.49	1.36	1.13	0.019	2.69E-09	1.40E-04	-0.43
LDL-C (mmol/L)	2.99	2.6	2.07	0.069	8.16E-07	0.007	-0.03
TG (mmol/L)	1.45	1.3	1.41	0.802	0.99	0.99	0.25
HDL/LDL	0.52	0.57	0.6	0.686	0.182	0.99	-0.31
ApoE (mg/L)	31.69	38	36.46	0.068	0.251	0.99	0.15
Glucose (mmol/L)	6.19	6.43	5.85	0.927	0.623	0.384	-0.22
Creatinine (μmol/L)	69.44	70.67	70.13	0.984	0.99	0.99	-0.28

iFABP, intestinal fatty acid binding protein; sCD14, soluble cluster of differentiation 14; LBP, lipopolysaccharide binding protein; CRP, high-sensitivity C-reactive protein; Lp(a), lipoprotein (a); ApoB, apolipoprotein B; FFA, free fatty acid; TC, total cholesterol; Apo A1, apolipoprotein A1; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TG, triglyceride; ApoE, apolipoprotein E.
[a] one-way ANOVA or chi-square test was used to obtain p-values.
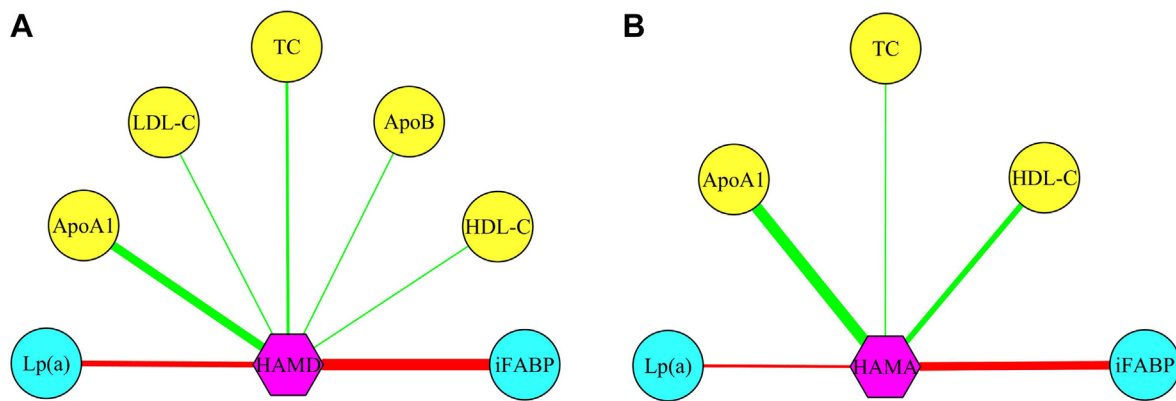[b] correlation coefficient from OPLS loading coefficient plots resulted.

Figure 4. Molecules significantly correlated with anxiety or depressive symptoms. A) ApoA1, HDL-C, TC, Lp(a), iFABP, LDL-C, and ApoB were significantly correlated with the HAMD score; and B) ApoA1, HDL-C, TC, iFABP, and Lp(a) were significantly correlated with the HAMA score. Red and green lines represented positive and negative correlations, respectively. Yellow and cyan circles represented lower and higher levels, respectively, in PSD patients compared to Stroke patients.
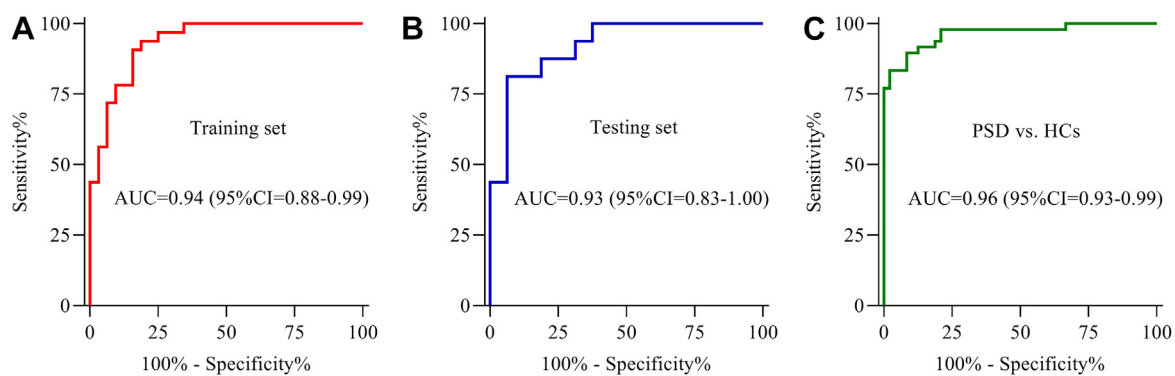

Figure 5. Diagnostic performances of potential biomarkers in diagnosing PSD from Stroke. The panel consisting of iFABP, Lp(a), ApoA1 and HDL-C had excellent diagnostic performances in both A) training and B) testing sets, and C) it was also very effective in separating PSD patients from HCs.

modifications has not been elucidated (Xi, 2004; Zhou, 2019). Glutamine metabolism is disturbed in subjects with post-stroke cognitive impairment (Liu, 2015); meanwhile, glutamine could protect the brain from ischemic injury (Luo, 2019). Besides, the Western diet with high-fat may increase gut permeability (Leech, 2019). As a result, a high-fiber diet or oral glutamine as a supplement is recommended for stroke patients to avoid gut barrier dysfunction (Agapova, 2018; Krawczyk, 2018). More clinical trials are needed to validate the effects of these methods in PSD in the future.

Several limitations are associated with this study. First, we did not evaluate the plasma iFABP response to antidepressant medications taken by PSD patients. The antidepressant medications could directly affect gut microbiota and the metabolomics profiles. However, whether these medications could affect the intestinal barrier and improve the gut leaky is not clear. Hence, longitudinal studies are needed to provide additional validation of this possibility. We only analyzed plasma iFABP levels as a biological indicator of an increased leaky gut in PSD patients. Additional testing methods using orally administered probe molecules such as sugars (Khoshbin, 2021) could demonstrate the presence of an increased leaky gut in PSD patients. Finally, although we identified several lipid indicators in PSD patients that could be measured clinically, the effects of iFABP on lipid metabolism require additional analysis to find more specific iFABP-related metabolites associated with PSD.

5. Conclusion

In summary, our results suggested that ApoA1, HDL-C, iFABP, and Lp(a) might be predictive blood biomarkers for PSD. We demonstrated that intestinal permeability is increased after stroke and is specifically associated with PSD. Thus, increased intestinal permeability might participate in PSD and affect the lipid metabolism in PSD patients.

Data availability statement

Data included in article/supp. material/referenced in article.

Declaration of interest's statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

Acknowledgements

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