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Serum Lipidomic Profiles for Distinguishing Primary Focal Segmental Glomerulosclerosis from Minimal Change Disease in Patients with Nephrotic Syndrome

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Objectives : Primary focal segmental glomerulosclerosis (FSGS) and minimal change disease (MCD) are representative podocytopathies that often present with similar clinical features of nephrotic syndrome (NS), making differential diagnosis difficult without kidney biopsy. This study aimed to identify serum lipidomic biomarkers that could differentiate FSGS from MCD and to develop a diagnostic model.
Methods : Serum samples were obtained from patients with biopsy-proven primary FSGS (n=20) and MCD (n=66) presenting with nephrotic syndrome. Serum lipidomic profiling was performed using liquid chromatography–mass spectrometry (LC-MS). Differential lipid species were identified using partial least squares discriminant analysis (PLS-DA). Clinical variables and lipidomic markers were integrated to construct diagnostic models, and their discriminative performance was evaluated using receiver operating characteristic (ROC) curve analysis.
Results : Patients with FSGS had a higher prevalence of hypertension and significantly worse kidney function than those with MCD. Proteinuria and serum albumin levels were comparable between the groups. Total cholesterol and LDL cholesterol levels were significantly higher in patients with MCD. Lipidomic analysis revealed that several LDL-4–associated lipid markers—including LDL-4 apolipoprotein B (L4AB), LDL-4 particle number (L4PN), LDL-4 cholesterol (L4CH), LDL-4 phospholipids (L4PL), and LDL-4 free cholesterol (L4FC)—were significantly elevated in the MCD group. Incorporation of these lipidomic markers significantly improved the diagnostic performance for differentiating FSGS and MCD. The baseline clinical model showed an AUC of 0.757, which increased to 0.860 after adding LDL-4 lipidomic markers. The combined clinical–lipidomic model including kidney function variables achieved the highest discrimination (AUC 0.877, DeLong test p=0.047).
Conclusions : Serum lipidomic profiling identified multiple LDL-4–associated lipid markers that were significantly increased in patients with MCD compared with those with FSGS. A diagnostic model incorporating these lipidomic biomarkers improved disease discrimination and may provide a promising non-invasive approach for differentiating FSGS from MCD in patients with nephrotic syndrome.

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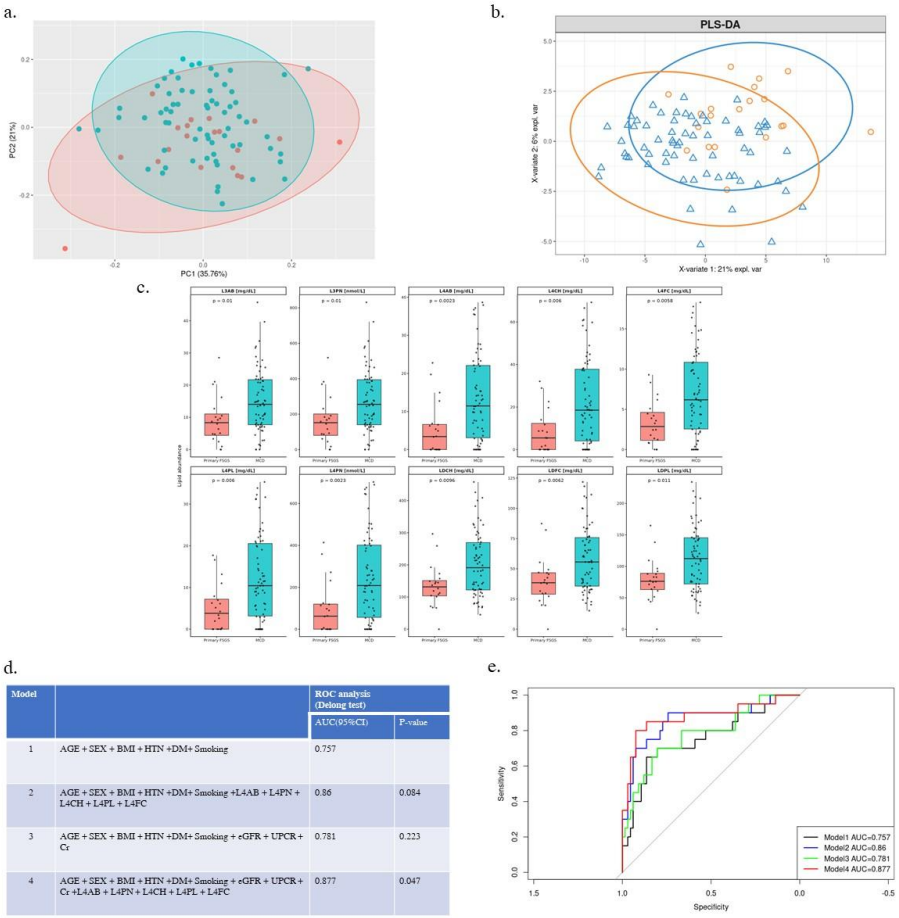

d.

Model		ROC analysis (Delong test)	
		AUC(95%CI)	P-value
1	AGE + SEX + BMI + HTN +DM+ Smoking	0.757	
2	AGE + SEX + BMI + HTN +DM+ Smoking +L4AB + L4PN + L4CH + L4PL + L4FC	0.86	0.084
3	AGE + SEX + BMI + HTN +DM+ Smoking + eGFR + UPCR + Cr	0.781	0.223
4	AGE + SEX + BMI + HTN +DM+ Smoking + eGFR + UPCR + Cr +L4AB + L4PN + L4CH + L4PL + L4FC	0.877	0.047

Figure1.Lipidomics profiling distinguishes Primary FSGS from MCD and improves the accuracy of diagnosis.

a. Principal component analysis (PCA) score plot shows the distribution of lipidomic profiles in patients of primary focal segmental glomerulosclerosis (Primary FSGS) and minimal change disease (MCD).
b. Partial least squares discriminant analysis (PLS-DA) demonstrates the separation between Primary FSGS and MCD based on serum lipid.
c. The significantly altered lipid compares Primary FSGS with MCD, presented as boxplot. Each dot represents an individual sample. Boxes represent the interquartile range (IQR) with the median indicated by the center line. L3AB, LDL-3 Apolipoprotein B; L3PN, LDL-3 Particle Number ; L4AB, LDL-4 Apolipoprotein B; L4CH, LDL-4 Cholesterol; L4FC, LDL-4 Free Cholesterol; L4PL, LDL-4 Phospholipids; L4PN, LDL-4 Particle Number; LDCH, Total LDL Cholesterol; LDFC, LDL Free Cholesterol; LDPL, Total LDL Phospholipids
d. Logistic regression models are constructed clinical variables and lipid markers to distinguish Primary FSGS from MCD. Model performance is analyzed by the area under the ROC curve (AUC) with corresponding p-values obtained from the DeLong test. ROC, receiver operating characteristic; BMI, body mass index; HTN, hypertension; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; UPCR, urine protein-to- creatinine ratio; Cr, creatine
e. The diagnostic performance of the four models are shown as receiver operating characteristic (ROC) curves.

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Table 1. Demographics and baseline characteristics of Primary FSGS and MCD .

	Total (n=86)	Primary FSGS (n=20)	MCD (n=66)	P_value
Male, n (%)	48 (55.8)	12 (60)	36 (54.5)	0.7987
Age, years	51 (35–64)	65 (50.2–70.2)	54 (37.2–67.5)	0.0552
Body mass index, kg/m²	24.9 (22.7–27.7)	25.6 (24.8–29.4)	25.2 (22.4–28.3)	0.1466
Systolic blood pressure, mm Hg	128 (113–140)	146 (127.8–152.2)	127 (113–140)	0.0091
Diastolic blood pressure, mm Hg	78 (71–86)	80.5 (71–91)	79 (72–86.8)	0.6675
Smoking, n (%)	14 (16.5)	7 (35)	7 (10.8)	0.0173
Hypertension, n (%)	35 (40.7)	13 (65)	22 (33.3)	0.0184
Diabetes mellitus, n (%)	10 (11.6)	5 (25)	5 (7.6)	0.0481
Serum creatinine, mg/L	1 (0.7–1.5)	1.4 (0.8–1.8)	0.8 (0.6–1.3)	0.0192
eGFR, mL/min/1.73 m²	81 (47.8–102.8)	44.8 (33–88.2)	91.9 (64.1–109.7)	0.0182
UPCR, mg/mg	3.9 (1–8.1)	8.9 (6.4–11.5)	8.9 (5.4–13.2)	0.6826
Blood urea nitrogen, mg/dL	18 (13–27)	21.5 (14.5–40.2)	17 (12–28)	0.3349
Uric acid, mg/dL	6.3 (5.2–7.3)	6.6 (4.6–7.6)	6.2 (5.2–7.8)	0.8254
Triglycerides, mg/dL	173.5 (118.2–265.5)	259 (194–279.5)	207 (153.2–283.5)	0.2884
Total cholesterol, mg/dL	224 (184–333)	294 (253–345)	381.5 (277–453.8)	0.0085
HDL cholesterol, mg/dL	53 (41–72)	51 (42.5–58)	69 (52–93)	0.0512
LDL cholesterol, mg/dL	147 (93.8–231)	197 (161.5–223.5)	264.5 (185.8–339.2)	0.1058
Total protein, g/dL	6.1 (4.8–6.9)	4.2 (3.8–4.9)	4.5 (4–4.8)	0.4935
Albumin, g/dL	3.3 (2.3–4.1)	2.2 (1.8–2.7)	2.2 (1.9–2.4)	0.4768
Hemoglobin, g/dL	13.3 (12–14.9)	12.1 (10.4–13.9)	13.9 (12.6–15)	0.0040
Glucose, mg/dL	98 (90–112)	107 (91.5–116.8)	95 (90–107.5)	0.0979
hsCRP, mg/dL	0.1 (0–0.2)	0.2 (0.1–0.4)	0.1 (0–0.1)	0.0639

Note: Categorical variables are presented as number (%), and continuous variables are shown as median (interquartile ranges)
Abbreviations: Primary FSGS, primary focal segmental glomerulosclerosis with nephrotic syndrome; MCD, minimal changed disease with nephrotic syndrome; eGFR, estimated glomerular filtration rate; UPCR, urine protein-to- creatinine ratio; hsCRP, high sensitivity C-reactive protein