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Perirenal fat thickness is an independent predictor for metabolic syndrome in steatotic liver disease

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The objective of our study is to measure perirenal fat thickness using MRI in individuals with steatotic liver disease and investigate the relationship between perirenal fat thickness and metabolic syndrome. This retrospective study included consecutive patients with steatotic liver disease who underwent magnetic resonance imaging-proton density fat fraction from October 2018 to February 2020. Among them, patients with crossed fused kidneys or who underwent nephrectomy were excluded. The metabolic abnormalities were reviewed; presence of hypertension, type 2 diabetes, abdominal circumference, triglyceride, and high-density lipoprotein. Perirenal fat was measured in four directions in both kidneys and the total sum of them was calculated. A total of 250 patients (140 males and 110 females) were included. Perirenal fat thickness showed a moderate correlation with waist circumference, creatinine, and hepatic fat fraction (all $p < 0.001$). Perirenal fat thickness was significantly higher in patients with metabolic syndrome than in patients without (76.8 mm vs. 65.1 mm, $p = 0.004$). In multivariable regression analysis, the group with high perirenal fat thickness had as significantly higher odd ratio of 2.71 compared to the low group. The perirenal fat thickness is independently associated with metabolic syndrome in patients with steatotic liver disease.

Keywords Steatotic liver disease, Metabolic syndrome, MRI, Perirenal fat

Metabolic syndrome encompasses a cluster of metabolic abnormalities that serve as predictors for diabetes and cardiovascular disease[1]. Visceral obesity has shown a stronger association with these conditions than overall or subcutaneous fat tissue[2]. Elevated visceral adipose tissue levels, independent of total body fat, are associated with reduced insulin sensitivity and increased cardiovascular risk[3]. Furthermore, visceral obesity is a key factor in the development and progression of steatotic liver disease[4]. This condition is both a cause and a consequence of metabolic syndrome[5]. These interconnected health issues significantly influence each other.

Within the part of visceral adipose tissue, perirenal fat, recognized as a metabolically active component, has emerged as an easily reproducible and indirect measure of visceral fat[6]. Favre et al. contributed to establishing a perirenal adipose tissue mass by the measurement of perirenal fat thickness with CT[7]. Studies by Yuxian et al. have established a correlation between perirenal fat thickness measured via ultrasound and the presence of fatty liver disease, as well as the risk of advanced fibrosis[8]. Li et al. have also suggested a potential association between perirenal fat thickness and a high risk of metabolic syndrome in adults with overweight and obesity[9]. Moreover, the accumulation of perirenal fat has been identified as an emerging cardiovascular risk factor, contributing to conditions such as hypertension and atherosclerosis[10,11].

Despite these findings and good correlation between ultrasound and computed tomography (CT), the ultrasound measurement methods for perirenal fat vary across studies, with potential interobserver variability when using ultrasound[12,13]. In particular, few studies have explored the connection between magnetic resonance imaging (MRI)-measured perirenal fat and metabolic abnormalities[9]. Additionally, it remains unclear whether perirenal fat can independently impact metabolic syndrome in steatotic liver disease and other metabolic abnormalities.

Given these gaps in knowledge, the objective of our study is to measure perirenal fat thickness using MRI in individuals with steatotic liver disease and investigate the relationship between perirenal fat thickness and metabolic syndrome.

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Materials and methods

Study population

This retrospective study included consecutive liver magnetic resonance imaging-proton density fat fraction (MRI-PDFF) at the time of initial diagnosis in adult patients with steatotic liver disease from October 2018 to February 2020. All images were identified retrospectively through a search of imaging records at our institution. All participants had a clinically suspected diagnosis of steatotic liver disease.

Baseline characteristics and biochemical test data were retrospectively reviewed. Data on age, gender, waist circumference (WC), and body mass index, were collected from the relevant medical records. Biochemical test data were also collected: leukocytes, hemoglobin, platelets, serum total protein concentration, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, triglycerides (TGs), and high-density lipoprotein (HDL), low-density lipoprotein (LDL), and cholesterol.

Definition of metabolic abnormality

Metabolic risk abnormalities, as defined as follows[14]; (1) central obesity: WC of ≥ 90 cm for men and ≥ 80 cm for women, (2) high blood pressure: blood pressure ≥ 130/85 mmHg and/or taking hypertension medication, (3) high TGs: serum triglyceride levels of ≥ 150 mg/dL, (4) low-HDL cholesterol: serum HDL cholesterol level, defined as < 40 mg/dL for men and < 50 mg/dL for women, and/or the use of dyslipidemia medication, and (5) prediabetes or diabetes: fasting glucose levels of ≥ 100 mg/dL, hemoglobin A1c levels ≥ 5.7%, and/or those taking diabetes medication.

MRI examination

All images were conducted utilizing a 3 Tesla MR scanner (Ingenia; Philips Healthcare, Best, Netherlands) with a torso coil. MRI included T2-weighted navigator-triggered turbo spin-echo imaging, MRI PDFF, and MR elastography (MRE).

For MRI-PDFF, a three-plane localization imaging gradient-echo (GRE) sequence was first obtained. Then, a 3D multi-echo GRE sequence based on mDIXON technology (mDixon-Quant, Philips Medical Systems, Best, The Netherlands) was performed in a single breath-hold. Three non-overlapping circular regions of interest (ROIs) of 100 mm^2 area were located within each Couinaud liver segment avoiding large vessels, ducts, focal liver lesions, and imaging artifacts. A total of 24 ROIs were obtained per patient across 8 segments, and the average of all measurements was defined as the average PDFF.

2D MRE is also performed. Images were processed automatically without manual intervention. The liver stiffness values are measured by placing four ROIs covering the largest liver, excluding artifacts, large vessels, and gallbladder. Mean values measured for the four ROIs were used.

Perirenal fat thickness

Perirenal fat thickness was measured at T2 weighted image. Perirenal fat was measured in four directions in both kidneys by two experienced radiologists who were blinded to all clinical outcomes and the total sum of them was calculated (Fig. 1). Patients with crossed fused kidneys or who underwent nephrectomy were excluded. If there were duplicate scans, only the first MRI scan was included. Measurements were performed two times for each patient by each radiologist, and values were averaged to minimize measurement error.

Statistical analysis

Baseline characteristics are presented as frequencies and percentages or means and standard deviations. The correlation between perirenal fat thickness and clinical parameters was determined using a Pearson correlation analysis and coefficient of determination. The agreement between observers for perirenal fat thickness was examined by the intraclass correlation coefficient. Perirenal fat thickness was compared according to metabolic abnormalities. The diagnostic performance of perirenal fat thickness for diagnosing metabolic syndrome was evaluated for men and women, respectively, using the receiver operating characteristic (ROC) plot method. Optimal cut-off values of perirenal fat in men and women were calculated via maximized Youden's index, and

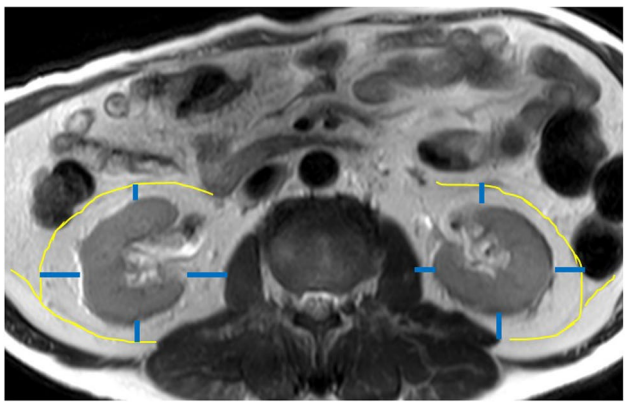

Figure 1. A representative case of measurement of perirenal fat thickness.

the cutoff value was used to divide the patients into high and low groups. To examine that groups of perirenal fat can affect metabolic syndrome independently of fatty infiltration of the liver and other metabolic abnormalities, we used univariate and multivariate linear regression analyses. Hayes Process Macro model 4 was used to analyze the indirect effects of high and low values of perirenal fat thickness on metabolic syndrome via other parameters[15]. A $p < 0.05$ was considered statistically significant. All statistical analyses were performed with a commercially available statistical package for the Social Sciences 25 software (SPSS Inc., Chicago, IL, USA).

Ethics approval

The Institutional Review Board of Hanyang University Hospital approved this study (IRB No. 2024-01-017). The informed consent has been waived by the approval committee "Institutional Review Board of Hanyang University Hospital". All methods were performed in accordance with the Declaration of Helsinki.

Results

Baseline characteristics

Among 358 consecutive patients, excluding 108 patients with missing clinical data, 1 patient with crossed fused kidney, and 1 patient who underwent nephrectomy, a total of 250 patients (140 males, 110 females) were enrolled, and their clinical characteristics are summarized in Table 1. The mean age of the patients was 54.8 ± 12.0 years. The proportion of hypertension, diabetes, high WC, high TG, and low HDL was 15.2%, 38.8%, 64.4%, 36.0%, and 42.0%, respectively. The mean hepatic fat fraction was 9.1 ± 8.2%. The mean of perirenal fat was 67.4 ± 34.9 mm. The mean of perirenal fat was 77.1 ± 36.8 mm in men and 55.1 ± 27.9 mm in women, respectively.

Peripheric fat thickness

Perirenal fat thickness showed a positive moderate correlation with hepatic fat fraction (γ = 0.426), waist circumference (γ = 0.568), body mass index (γ = 0.524), and creatinine (γ = 0.355, all $p < 0.001$) (Table 2). As

Clinical characteristics	Total ($N = 250$)
Age, years	54.8 ± 12.0
Sex	
Men (%)	140 (56.0)
Women (%)	110 (44.0)
Waist circumference, cm	90.8 ± 12.1
Body mass index, kg/m^2	26.0 ± 4.3
WBC, /μL	6184 ± 2033
Hemoglobin, g/dL	14.3 ± 1.6
Platelet, x10^9/L	214.2 ± 75.9
Total protein, g/dL	7.4 ± 0.5
Albumin, g/dL	4.3 ± 0.5
AST, U/L	46.2 ± 38.9
ALT, U/L	44.2 ± 46.2
Total bilirubin, mg/dL	1.05 ± 1.27
Creatinine,	0.78 ± 0.23
Triglyceride, mg/dL	151.5 ± 102.8
HDL, mg/dL	47.7 ± 17.2
LDL, mg/dL	103.6 ± 32.2
Cholesterol, mg/dL	181.7 ± 39.2
Metabolic abnormalities	
Hypertension (%)	38 (15.2)
Diabetes (%)	97 (38.8)
High WC (%)	161 (64.4)
High triglyceride (%)	90 (36.0)
Low HDL (%)	105 (42.0)
Hepatic fat fraction (%)	9.1 ± 8.3
MRE, kPa	3.03 ± 1.68
Perirenal fat, mm	67.4 ± 34.9
Men	77.1 ± 36.8
Women	55.1 ± 27.9

Table 1. Clinical characteristics. Note. Data are presented with mean ± standard deviation or number of subjects (percentage). Abbreviations: NAFLD, non-alcoholic fatty liver disease; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MRE, magnetic resonance elastography.

Parameters	γ	*p*-value	γ^2	*p*-value
Age, years	0.116	0.066	0.011	0.052
Waist circumference	0.568	< 0.001	0.248	< 0.001
Body mass index	0.524	< 0.001	0.193	< 0.001
WBC	0.284	< 0.001	0.027	0.006
Hemoglobin	0.328	< 0.001	0.078	< 0.001
Platelet	0.135	0.035	0.003	0.604
Total protein	-0.014	0.822	0.001	0.352
Albumin	0.142	0.025	0.011	0.052
AST	0.144	0.073	0.004	0.735
ALT	0.204	0.001	0.006	0.111
Total bilirubin	0	0.999	0.004	0.847
Creatinine	0.355	< 0.001	0.145	< 0.001
Triglyceride	0.211	0.001	0.002	0.230
HDL	-0.121	0.056	0.010	0.066
LDL	0.022	0.727	0.003	0.696
Cholesterol	-0.083	0.191	0.002	0.485
Fat fraction	0.426	< 0.001	0.110	< 0.001
MRE	0.024	0.709	0	0.319

Table 2. Correlation analysis between perirenal fat thickness and clinical parameters. Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma glutamyl transferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MRE, magnetic resonance elastography.

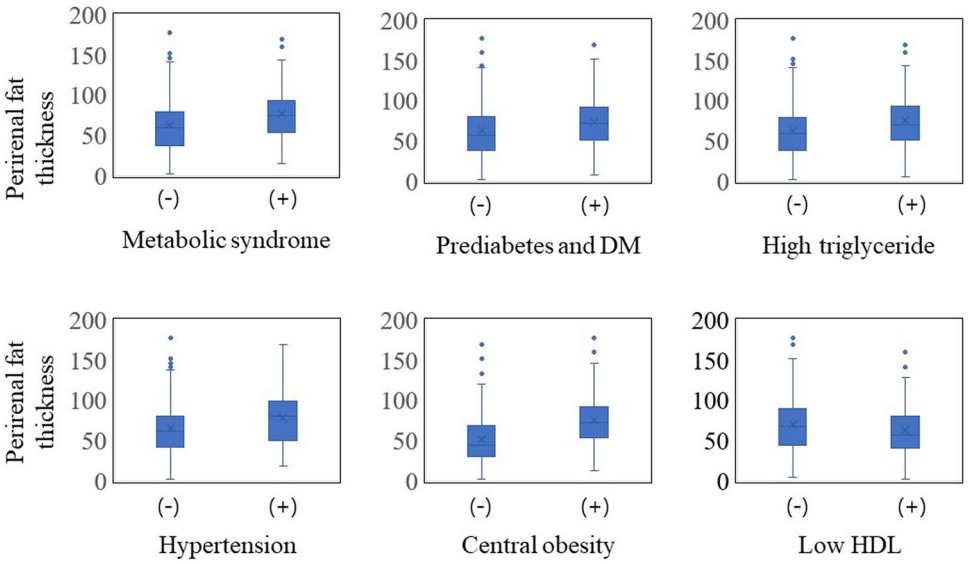

Figure 2. Perirenal fat thickness according to metabolic abnormalities. Abbreviations: DM, diabetes; HDL, high-density lipoprotein.

the thickness of perirenal fat increased, the degree of fatty liver also increased ($\gamma = 0.426$, $p < 0.001$), but hepatic fibrosis did not ($\gamma = 0.024$, $p = 0.709$). The intraclass correlation coefficient of perirenal fat thickness was excellent as 0.994 (95% confidence interval: 0.928–0.956, $p < 0.001$).

The perirenal fat thickness was significantly higher in patients with metabolic syndrome at 76.8 mm than in patients without at 65.1 mm ($p = 0.004$). The perirenal fat thickness was significantly higher in patients with diabetes, central obesity, and dyslipidemia (high triglyceride) than in patients without (all $p < 0.05$, Fig. 2; Table 3).

The area under the ROC of perirenal fat thickness to predict metabolic syndrome for men and women was 0.651 ($p = 0.004$) and 0.728 ($p < 0.001$), respectively (Fig. 3). In men, the sensitivity, and specificity of perirenal fat thickness were 62.9% and 66.7%, respectively with a cutoff of 80 mm. In women, the sensitivity, and specificity were 81.8% and 66.7%, respectively with a cutoff of 49.7 mm.

	Absence	Presence	*p*-value
Metabolic syndrome	65.1 ± 35.9	76.8 ± 30.8	0.004
Hypertension	65.4 ± 32.3	78.7 ± 36.4	0.030
Prediabetes or diabetes	63.4 ± 36.5	73.8 ± 31.3	0.022
Central obesity	51.6 ± 32.5	76.2 ± 33.1	< 0.001
High triglyceride	62.8 ± 32.2	75.6 ± 37.9	0.005
Low HDL	70.4 ± 38.1	63.4 ± 29.5	0.119

Table 3. Perirenal fat thickness according to metabolic abnormalities. Abbreviations: HDL, high-density lipoprotein.

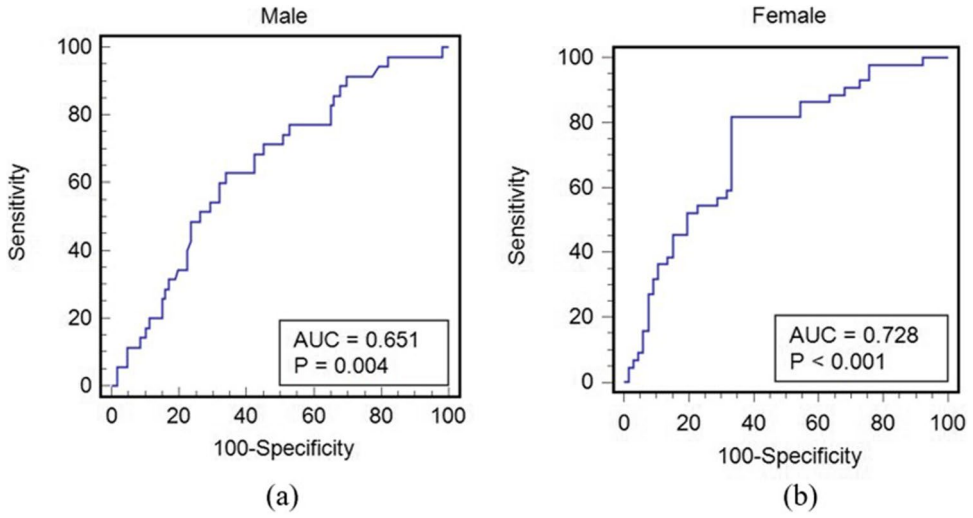

Figure 3. Receiver operating characteristic (ROC) curves for prediction of metabolic syndrome in men (**a**) and women (**b**). The AUC (area under the ROC curve) of perirenal fat thickness to predict metabolic syndrome was 0.651 and 0.728, respectively.

Perirenal fat for diagnosis of metabolic risk abnormalities

In the univariate logistic regression analysis, female sex, presence of hypertension, presence of diabetes, increased abdominal circumference, higher triglyceride, lower HDL, higher MRI-PDFF, and higher perirenal fat thickness were significantly associated with metabolic syndrome (all $p < 0.05$). In the subsequent multivariable analysis, the group with high perirenal fat thickness had a significantly higher odd ratio of 2.71 compared to the low perirenal fat thickness ($p < 0.05$) (Table 4).

To examine whether clinical characteristics mediates the relationship between perirenal fat thickness and metabolic syndrome, Hayes's Process Macro Model 4 was employed (Table 5). First, perirenal fat thickness was found to have a statistically significant effect on WC, TG, BMI, and MRI-PDFF ($p < 0.05$). WC, TG and BMI, in turn, had a statistically significant effect on metabolic syndrome ($p < 0.05$). Additionally, the direct effect of perirenal fat thickness on metabolic syndrome was significant ($p < 0.001$). The significance of the indirect effect was confirmed through bootstrapping (5,000 samples). The indirect effect of WC, TG and BMI in the relationship between perirenal fat thickness and metabolic syndrome was found to be 0.338, 0.331, and 0.378, respectively. The significance of this indirect effect was confirmed with a confidence interval that does not include 0.

Discussion

Our study revealed a correlation between increased perirenal fat thickness and a higher incidence of metabolic abnormalities, demonstrating perirenal fat thickness as a valuable predictor of metabolic syndrome in steatotic liver disease, in particular, by measuring perirenal fat simply and precisely using MRI. Consistent with earlier research, our study showed the thickness of perirenal fat increased in metabolic abnormalities that constitute metabolic syndrome, such as hypertension, diabetes, central obesity, and dyslipidemia[16].

In this study, the average waist circumference of 90.8 cm was relatively high, given that the metabolic syndrome standard is 90 cm for men and 80 cm for women[17]. Patients with a waist circumference that met the criteria for metabolic syndrome were 64.4% of the total number of patients. The average body mass index of 26.0 kg/m^2 was also elevated, considering Korea's obesity standard of 25.0 kg/m^{2}and AST/ALT levels were elevated on average, considering the normal value is below 40 U/L[18]. Additionally, the average triglyceride level was slightly higher than the normal value of 150 mg/dL and 36% of participants met the diagnostic criteria for triglyceride in metabolic syndrome. In our study's logistic regression, the impact of perirenal fat thickness on metabolic

	Univariate analysis			Multivariate analysis (Enter)			Multivariate analysis (Forward: conditional)		
	OR	95% C.I.	*P*-value	OR	95% C.I.	*P*-value	OR	95% C.I.	*P*-value
Age	1.01	0.99-1.04	0.313						
Female	2.00	1.17-3.43	0.012	16.76	4.88-57.60	<0.001	18.04	5.33-61.0	<0.001
Hypertension	6.50	3.07-13.78	<0.001	33.74	8.02-141.9	<0.001	33.73	8.26-137.76	<0.001
Diabetes	7.04	3.89-12.73	<0.001	28.98	8.89-94.44	<0.001	27.82	8.47-91.39	<0.001
Waist circumference	1.11	1.07-1.16	<0.001	1.01	1.01-1.18	0.022	1.11	1.06-1.17	<0.001
BMI	1.11	1.03-1.08	<0.001	1.09	0.88-1.35	0.435	…	…	…
WBC	1.00	1.00-1.00	0.532						
Hemoglobin	0.89	0.75-1.05	0.156						
Platelet	1.00	0.99-1.00	0.861						
Albumin	0.89	0.49-1.60	0.707						
ALT	1.00	0.99-1.01	0.120						
Triglyceride	1.01	1.01-1.02	<0.001	1.02	1.01-1.03	<0.001	1.02	1.01-1.03	<0.001
HDL	0.95	0.93-0.97	<0.001	0.91	0.87-0.95	<0.001	0.91	0.76-0.54	<0.001
Cholesterol	0.99	0.98-1.00	0.124						
Creatinine	0.86	0.23-3.27	0.827						
Hepatic fat fraction	1.05	1.02-1.08	0.002	0.98	0.92-1.05	0.560	…	…	…
Perirenal fat			<0.001			0.044			0.048
Low	…	…	…	…					
High	5.24	2.91-9.46	<0.001	2.72	1.05-7.09	0.040	2.71	1.05-7.00	0.039

Table 4. Univariate and multivariate logistic regression analysis for prediction of metabolic syndrome. Note. CI, confidence interval. Abbreviations: OR, odds ratio; BMI, body mass index; HDL, high-density lipoprotein.

syndrome was significant independent of fatty infiltration of the liver and other metabolic abnormalities, and the AUC for metabolic syndrome was found to be at a level of 0.651 and 0.728 in men and women, respectively.

Although perirenal fat thickness was expected to have a significant relationship with fatty infiltration in the liver in the study, it had no special relationship with hepatic fibrosis. The association between visceral adiposity and non-alcoholic fatty liver disease has been well-established in numerous studies and, it is widely recognized that non-alcoholic fatty liver disease can progress to hepatic fibrosis[19,20]. Several studies have postulated a correlation between visceral adiposity and the progression of liver fibrosis, suggesting potential mechanisms such as insulin resistance, lipotoxicity, and inflammation[21–23]. However, the precise pathophysiological mechanisms underlying this association remain elusive. The finding of our study allows us to speculate that the increase in perirenal fat and hepatic fibrosis proceeds through more different pathogenic mechanisms.

Obese individuals with visceral abdominal adipose tissue face elevated risks of cardiovascular mortality, insulin resistance, dyslipidemia, hypertension, and the development of diabetes[24]. Situated in the retroperitoneal space enveloping the kidney and wrapped together by Gerota fascia, perirenal fat emerges as a crucial classification of visceral adipose tissue, distinct from intraperitoneal visceral fat[25]. It offers both defense and structural supports to the kidneys and adrenal glands by maintaining their anatomical position[26]. Anatomical studies confirm perirenal fat's unique vascularization, innervation, and drainage into the lymphatic system, providing a structural basis for its regulatory role in cardiovascular and metabolic systems[27]. Some histological studies suggest that perirenal fat shares the same developmental origin as typical visceral adipose tissue, with emerging evidence indicating a more pronounced role in energy metabolism, adipokine biotransformation, and cytokine secretion compared to typical visceral adipose tissue[28]. These multifaceted studies indicate that perirenal fat may hold significant clinical relevance for patients with visceral obesity.

The study found significantly increased perirenal fat thickness in patients with metabolic syndrome, hypertension, diabetes, central obesity, and hypertriglyceridemia compared to those without these conditions. Increasing evidence indicates the involvement of perirenal fat in the development of metabolic dysfunctions, including hypertension, insulin resistance, dyslipidemia, and polycystic ovary syndrome[29–31]. Various studies have shown that perirenal fat thickness is not only associated with cardiometabolic risk but also related to nearby liver and kidney dysfunction[32–34]. The reported positive correlation between perirenal fat and the renal resistance index suggests potential direct compression on renal blood vessels, with associated lipotoxic effects on the kidneys, accelerating the progression to chronic kidney disease[35–37]. Consistent with previous research, our study validated the clinical value of using perirenal fat thickness measurement to predict the risk of metabolic syndrome.

Our study has several strengths, such as the straightforward measurement of perirenal fat thickness without the need for specialized programs. The renal fascia was discovered and the perirenal fat thickness could be measured on MRI. The correlation between peripheral fat thickness and metabolic indicators was suggested in other studies using ultrasound[12,13]. In previous studies, the thickness between the fibrous membrane and the renal fascia, or the lateral surface of the kidney and the inner edge of the lateral trunk muscles were measured for perirenal fat thickness. However, interobserver consistency was not confirmed. Our unique contribution lies

	Mediating parameters				Metabolic syndrome			
	B	SE	t	*p*	B	SE	Z	*p*
Perirenal fat	9.594	1.416	6.775	<0.001	1.378	0.317	4.343	<0.001
WC	-				0.035	0.014	2.581	0.010
Perirenal fat	3.761	0.484	7.764	<0.001	1.331	0.324	4.109	<0.001
BMI					0.100	0.040	2.506	0.012
Perirenal fat	-0.028	0.209	-0.134	0.894	1.675	0.309	5.419	<0.001
Hemoglobin					-0.139	0.093	-1.495	0.135
Perirenal fat	0.031	0.026	1.188	0.236	1.656	0.303	5.461	<0.001
Creatinine					-0.467	0.705	-0.663	0.507
Perirenal fat	30.337	12.913	2.349	0.020	1.690	0.333	5.070	<0.001
Triglyceride					0.011	0.002	5.095	<0.001
Perirenal fat	-3.778	2.165	-1.745	0.082	1.716	0.324	5.291	<0.001
HDL					-0.053	0.011	-4.597	<0.001
Perirenal fat	4.861	1.009	4.817	<0.001	1.537	0.310	4.963	<0.001
MRI-PDFF					0.028	0.018	1.594	0.111
Bootstrap results for indirect effect								
	Effect		BootSE		BootLLCI		BootULCI	
WC	0.338		0.142		0.089		0.643	
BMI	0.378		0.160		0.100		0.739	
Hemoglobin	0.004		0.035		-0.056		0.095	
Creatinine	-0.014		0.031		-0.084		0.045	
Triglyceride	0.331		0.184		0.057		0.775	
HDL	0.200		0.134		-0.022		0.497	
MRI-PDFF	0.136		0.096		-0.040		0.343	

Table 5. Process marco mediating effect (Model 4). Abbreviations: SE, standard error; WC, waist circumference; HDL, high-density lipoprotein; BMI, body mass index; PDFF, proton density fat fraction; BootLLCI, Bootstrap lower level confidence interval; BootULCI, bootstrap lower level confidence interval. Bootstrap sample size = 5,000.

in the utilization of MRI for measurement, offering high reproducibility between observers. Another strength of this study is that visceral obesity measured on MRI can be diagnosed without radiation exposure.

However, it is crucial to acknowledge the limitations of our study, including the relatively small sample size, and the observational, cross-sectional design. Future research should aim for larger, more diverse study populations and consider factors such as race and geographic distribution. The observational nature of our study limits its ability to establish a causal relationship between perirenal fat thickness and metabolic syndrome in steatotic liver disease.

In conclusion, our study established an association between metabolic syndrome and perirenal fat thickness precisely measured by MRI in individuals with steatotic liver disease. To further investigate this association, large-scale prospective cohort studies are essential.

Data availability

Data availability statement: The datasets generated or analyzed during the study are available from the corresponding authors upon reasonable request.

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Declarations

Competing interests
The authors declare no competing interests.

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