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Thickened Perirenal Fat Predicts Poor Renal Outcome in Patients with Immunoglobulin A Nephropathy: A Population-Based Retrospective Cohort Study

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Keywords
Perirenal fat · Immunoglobulin A nephropathy · Renal prognosis

Abstract
Introduction: Perirenal fat is a pad that fills the retroperitoneal space outside the kidney, which affects kidney function in various ways. However, the association between perirenal fat and IgA nephropathy (IgAN) has not yet been elucidated. This study aimed to investigate the role of perirenal fat in predicting IgAN progression. ***Methods:*** A total of 473 patients with biopsy-proven IgAN and follow-up information were recruited, and perirenal fat thickness (PFT) was measured using color Doppler ultrasonography at renal biopsy. Patients were divided into two groups according to the median PFT: the low-PFT group (PFT ≤1.34 cm, $n = 239$) and the high PFT group (PFT >1.35 cm, $n = 234$). A total of 473 healthy participants were included in the control group. Basic clinical characteristics were assessed at the time of renal biopsy, and the relationship between PFT and combined endpoints was analyzed. The renal composite endpoints were defined as a two-fold increase in blood creatinine level, end-stage renal disease (dialysis over 3 months). Kaplan-Meier survival analysis was used to explore the role of PFT in the progression of IgAN. Three clinicopathological models of multivariate Cox regression analysis were established to evaluate the association between PFT and renal prognosis in patients with IgAN. ***Results:*** Compared to healthy subjects, patients with IgAN showed significantly higher PFT. After a median follow-up of 50 months, 75 of 473 patients (15.9%) with IgAN reached renal composite endpoints. Among those, 13 of 239 patients (5.4%) were in the low PFT group, and 62 of 234 patients (26.5%) were in the high PFT group ($p < 0.001$). The results of three Cox regression models (including demographics, pathological and clinical indicators, and PFT) demonstrated that a higher PFT was significantly associated with a higher risk of reaching renal composite endpoints in patients with IgAN. ***Conclusion:*** This study indicated a positive relationship between PFT at renal biopsy and renal progression in patients with IgAN, suggesting that perirenal fat might act as a marker of poor prognosis in patients with IgAN.

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Introduction

Immunoglobulin A nephropathy (IgAN) is a major cause of primary glomerulonephritis, and nearly 15–40% of patients with IgAN will progress to end-stage renal disease (ESRD) within 20 years [1]. However, the pathogenesis of IgAN remains controversial. The proposal of a four-hit hypothesis supporting that supports the autoimmune process is now widely accepted [2]. Several pharmacological therapeutic targets have emerged based on the autoimmune pathogenesis of IgAN, including the immune response, complement activation, mucosal immunity, and renal inflammation. However, few of them have well-established efficacy. Therefore, it is essential to identify superior risk factors to predict poor renal outcomes in IgAN.

Perirenal fat (PRF) is a fat pad that encapsulates the kidney and fills the space between the kidney and the adjacent retroperitoneal tissue, renal parenchyma, and adrenal glands [3]. It is surrounded by a complete renal fascia with a complete system of blood supply, lymphatic fluid drainage, and innervation. It is adjacent to the kidneys, active in metabolism and adipokine secretion, and shares the same developmental origin as typical visceral fat [4]. Composed of both brown adipose tissue and white adipose tissue, PRF is able to synthesize and secrete many adipokines, such as leptin, adiponectin, and so on [5]. PRF plays an essential role in various diseases such as hypertension [6], unilateral nephrolithiasis [7], renal cell carcinoma [8], metabolic syndrome, and atherosclerosis [9]. In addition, its role in various renal diseases has been previously proposed [10–12]. Our previous study showed that PRF is a simple and reliable tool for predicting the onset and progression of albuminuria in patients with diabetes [13]. It potentially affects renal function in several ways, including inflammation, direct pressure, and adipokine secretion [14]. As inflammation, hypertension, and immune responses are also important in the pathogenesis of IgAN, we speculate that PRF may also contribute to the progression of IgAN. Furthermore, it remains unclear whether the thickness of PRF could predict the progression of IgAN.

Patients and Methods

Study Population

As a retrospective study, a registered cohort of renal biopsy between January 2014 and May 2022 was included. The exclusion criteria of the present study were as follows: (1) patients with incomplete clinical and follow-up data, (2) patients younger than 18 years, (3) patients with secondary IgAN (such as diabetic nephropathy, lupus nephritis), and (4) patients with a history of malignancy or surgical trauma. A total of 659 patients had a renal biopsy confirmed IgAN, with a median age of onset of 38 years old. Among those, 121 patients with incomplete clinical or follow-up data and 65 patients with secondary IgAN were excluded. PRF was measured based on the ultrasound record of the kidneys at the time of renal biopsy. In order to find out the difference in PRF between patients with IgAN and individuals without renal disease, a cohort of healthy individuals at comparable ages with routine physical examination at our medical center was screened. The study was approved by the Ethics Committee of Renmin Hospital of Wuhan University (WDRY2021-KS036), and the study procedures complied with the ethical standards of the Committee for Human Experimentation. The flowchart is shown in Figure 1.

Subjects Grouping

Patients with IgAN were divided into two groups according to the median PFT: the low PFT (L-PFT) group (PFT ≤1.34 cm, n = 239) and the high PFT (H-PFT) group (PFT >1.35 cm, n = 234). Healthy individuals of comparable age (to IgAN patients) were included (control group).

Clinical Data

Medical history, including diabetes and hypertension, was reviewed. Demographic data, such as sex and age of the patients, were collected. All patients underwent a physical examination and anthropometric measurements including body weight, height, body mass index (BMI), neck circumference, waist circumference, hip circumference, and waist-to-hip ratio. Early morning fasting venous blood was collected for the measurement of hemoglobin (Hb), albumin (ALB), urea nitrogen (urea), blood creatinine (SCr), blood uric acid (UA), total cholesterol, total triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and 24-h urine protein (UTP). BMI was defined as the ratio of weight (kg) to the square of height (m^2). Estimated glomerular filtration rate (eGFR) was calculated using the modified diet test for renal disease formula: eGFR [mL/min/1.73 m^2] = 175 × (SCr [mg/dL])$^{-1.234}$ × (age)$^{-0.179}$ × (0.79 [female]). Ultrasound examinations were performed using a duplex Doppler instrument (Acuson Sequoia 512 Ultrasound System; Siemens, USA). Measurement of PFT was performed according to a previously reported method [15], and PFT was defined as the average of the maximum ultrasound-measured thickness values of the fat capsule from the renal fascia to the surface of the kidney. PFT was measured by three experienced technologists for each patient, and the average length was calculated. A schematic representation of the PFT measurements is shown in Figure 2.

Pathological Characteristics

Tissue from renal biopsies was examined by light microscopy and immunofluorescence. Pathology was graded according to the Oxford pathological staging criteria [16]. Briefly, mesangial score <0.5 or >0.5 (M0/M1); segmental glomerulosclerosis absent or present (S0/S1); endocapillary hypercellularity absent or present (E0/E1); tubular atrophy/interstitial fibrosis <25%, 26–50%, or >50% (T0/T1/T2); and cellular or fibrocellular crescents absent or present in at least one glomerulus or at least 25% of glomeruli (C0/C1/C2). The patients with changes of diabetic nephropathy in the presence of IgA deposit were excluded in the present cohort [17].

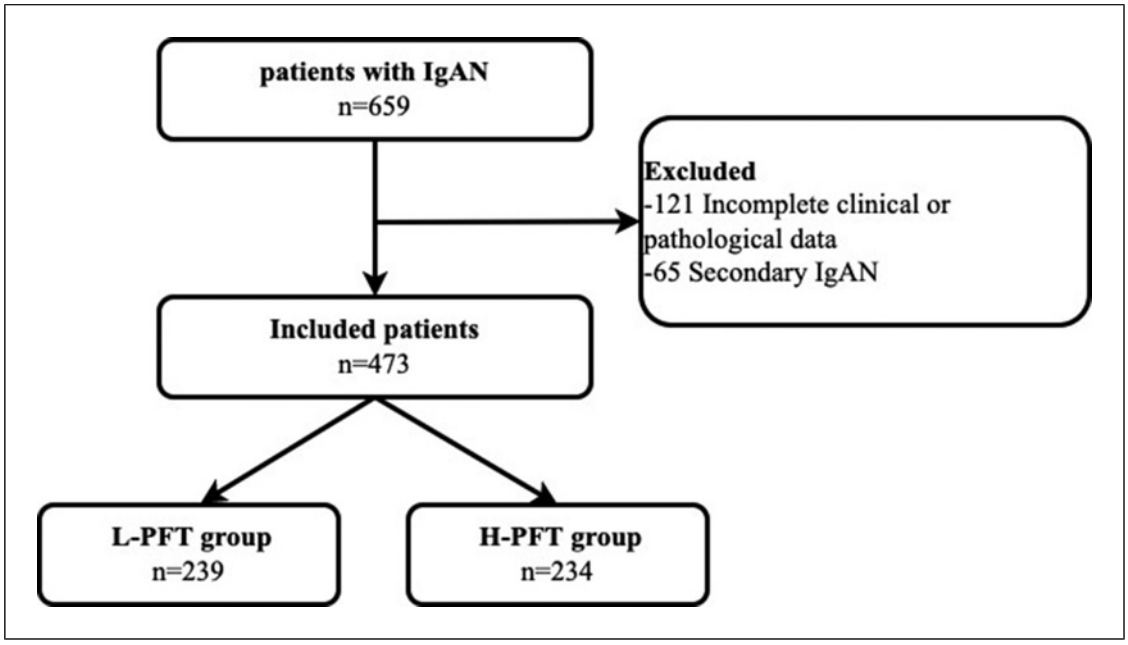

Fig. 1. Flowchart of the study. L-PFT: low PFT group; H-PFT: high PFT group.

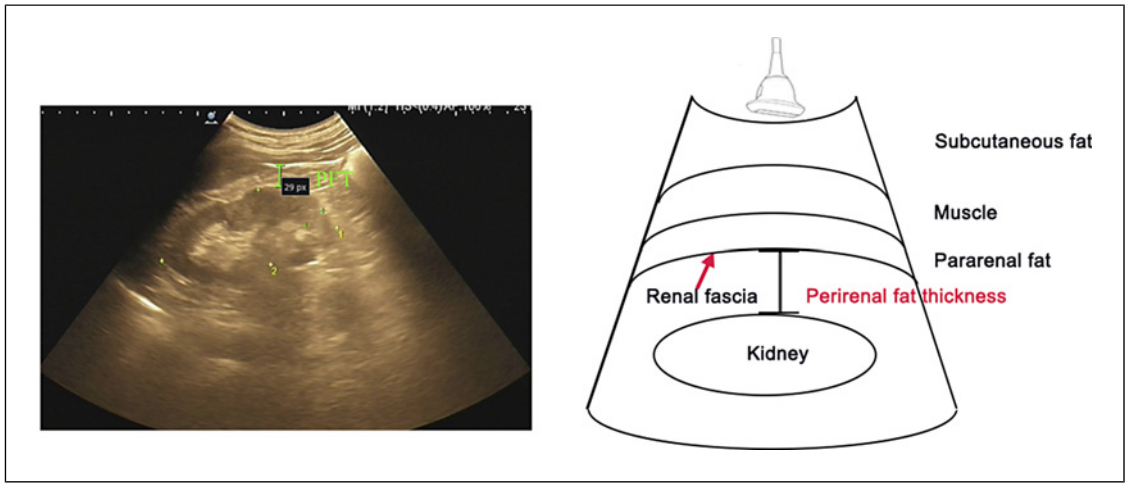

Fig. 2. Schematic diagram of PFT measurement.

Treatments

The treatment plan was decided by the patients and their physicians based on the patients' disease characteristics. All patients received optimal supportive treatment, including ACEI/ARB. Glucocorticoids were prescribed in patients with persistent proteinuria (>1 g/day) at initial dose of 0.4–0.6 mg/kg prednisone daily and tapered over 6–8 months. Immunosuppressants were used in patients with a rapidly progressive decline in renal function. Immunosuppressants included mycophenolate mofetil (1.0–1.5 g daily for 6–12 months) and cyclophosphamide (0.8 g monthly for 6 months).

Outcome Definitions

Composite endpoints for renal outcomes included a two-fold increase in blood creatinine level, ESRD (dialysis over 3 months).

Statistical and Graphical Methods

R (version 4.0.0; MathSoft, Inc.) was used for graphs, and the statistical software SPSS (version 17; SPSS, Inc.) was used for statistical analysis. Mean ± standard deviation was used for normally distributed variables, and quartiles were used for non-normally distributed variables. Independent samples *t* tests were used to compare normally distributed continuous variables. For differences between groups for non-normally

Table 1. Comparison of clinical characteristics and PFT in patients with IgAN and healthy individuals

Variable	Control (n = 473)	IgAN (n = 473)	p value
Age, years	38 (31–48)	36 (31–46)	0.561
Sex, F, n (%)	257 (54.3)	263 (41.4)	0.471
BMI, kg/m^2	20.81 (18.43, 22.56)	21.56 (18.70, 23.89)	0.258
PFT, cm	0.86 (0.65, 1.278)	1.34 (1.07, 1.65)	<**0.001**
ALB, g/L	47.60 (45.65, 49.60)	41.30 (36.90, 44.60)	<**0.001**
Urea, mmol/L	5.87 (4.90, 6.92)	5.75 (4.62, 7.57)	0.727
SCr, μmol/L	70.00 (57.00, 87.00)	51.00 (32.00, 73.00)	<**0.001**
UA, μmol/L	307.00 (247.50, 380.00)	420.00 (344.25, 508.75)	<**0.001**
TCh, mmol/L	4.44 (4.18, 5.56)	4.68 (4.06, 5.48)	**0.010**
TG, mmol/L	1.48 (1.00, 2.44)	1.58 (1.05, 2.68)	0.175
HDL, mmol/L	1.30 (1.09, 1.55)	1.19 (0.96, 1.50)	<**0.001**
LDL, mmol/L	2.41 (2.13, 2.90)	2.58 (2.00, 3.03)	<**0.001**
Hb, g/L	141.00 (129.00, 153.00)	128.00 (114.00, 140.50)	<**0.001**

PFT, perirenal fat thickness; BMI, body mass index; ALB, albumin; urea, urea nitrogen; SCr, blood creatinine; UA, blood uric acid; TCh, total cholesterol; TG, total triglycerides; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol.

distributed variables, the Mann-Whitney U test was used for analysis, and the χ^2 test was used to compare groups for count data. Kaplan-Meier survival analysis curves and log-rank tests were used to compare the differences in renal survival between the 2 groups of patients. Cox univariate and multifactorial regression were used to analyze the risk factors affecting renal survival in patients with IgAN, and $p < 0.05$ was considered statistically significant.

Results

Clinical Characteristics of IgAN Compared with the Control Group

A total of 473 patients with IgAN and follow-up data showed no statistically significant differences in demographics (sex and age) compared to the control group ($p > 0.05$). The PFT, SCr, UA, total cholesterol, and low-density lipoprotein cholesterol levels were significantly higher in the IgAN group. ALB, high-density lipoprotein cholesterol, and Hb levels were significantly lower than those in the control group, with statistically significant differences ($p < 0.05$), as shown in Table 1.

Baseline Characteristics of Patients with IgAN in L-PFT and H-PFT Group at Renal Biopsy

The median PFT of all patients with IgAN was 1.34 cm (1.07, 1.65). Patients in the H-PFT group had a higher PFT ($p < 0.001$), a higher proportion of hypertension (43.2%, $p = 0.030$), higher levels of UA ($p = 0.001$), SCr ($p < 0.001$), and UTP ($p = 0.033$), and lower levels of Hb ($p = 0.011$). In contrast, other indicators, such as age, male gender, BMI, and pathological characteristics, were not statistically significant ($p > 0.05$). The detailed baseline characteristics of the patients are shown in Table 2.

Long-Term Composite Renal Survival

The median follow-up of the 473 patients with IgAN was 50.3 (12, 91) months. During the follow-up period, 75 patients (75 of 473 patients, 15.9%) progressed to renal endpoints. Among those, 62 patients in the H-PFT group reached composite endpoint events, including 47 patients with ESRD, 15 patients with doubled serum creatinine levels. A total of 13 patients in the L-PFT group reached composite endpoint events, including 9 patients with ESRD, 2 patients with doubled serum creatinine. Notably, more patients in the H-PFT group (62 in 234 patients, 26.5%) achieved composite renal endpoints than those in the L-PFT group (13 in 239 patients, 5.4%). Kaplan-Meier survival curve analysis showed a significantly poor cumulative renal survival in the H-PFT group than that in the L-PFT group (log-rank test, $\chi^2 = 27.93$, $p < 0.001$), as shown in Figure 3.

Predictive Value of PFT for Renal Composite Endpoints

The receiver operating characteristic curve was used to determine the prognostic value of PFT. The cutoff value of PFT for predicting the new onset of composite endpoints was 1.48 cm (sensitivity, 76.0%; specificity, 68.6%;

Table 2. Clinical data and pathological data of the L-PFT group and the H-PFT group

Variable		L-PFT (n = 239)	H-PFT (n = 234)	p value
Age, years		38 (31, 47)	38 (32, 48)	0.279
Sex F, *n* (%)		134 (56.1)	123 (52.6)	0.766
PFT, cm		1.07 (0.92, 1.20)	1.66 (1.50, 1.87)	<**0.001**
Hypertension (N/Y, %)		159/80 (66.5/33.5)	133/101 (56.8/43.2)	**0.030**
Diabetes (N/Y, %)		214/25 (89.5/10.5)	220/14 (94.0/6.0)	0.077
BMI, kg/m^2		21.13 (18.59, 23.22)	21.89 (19.13, 24.01)	0.474
Neck circumference, cm		34.53 (27.52, 37.25)	33.42 (24.33, 35.21)	0.321
Waist circumference, cm		88.24±8.41	89.42±9.22	0.213
Hip circumference, cm		96.27±10.21	97.43±9.23	0.142
WHR		0.91±0.22	0.89±0.15	0.447
TCh, mmol/L		4.59 (4.06, 5.38)	4.73 (4.07, 5.68)	0.307
TG, mmol/L		1.44 (1.02, 2.68)	1.62 (1.10, 2.71)	0.198
HDL, mmol/L		1.19 (0.98, 1.47)	1.19 (0.95, 1.55)	0.912
LDL, mmol/L		2.55 (2.05, 3.02)	2.60 (1.92, 3.04)	0.715
UA, μmol/L		410.95±107.98	459.86±185.92	<**0.001**
FPG		6.12±1.24	6.25±2.11	0.254
HbA1c, %		5.2±1.11	5.43±1.47	0.313
eGFR, mL/min/1.73 m^2		54.00 (48.88, 74.10)	57.04 (45.50, 76.70)	0.307
ALB, g/L		40.90 (36.20, 44.50)	41.70 (37.10, 44.88)	0.202
Urea, mmol/L		5.84 (4.88, 7.41)	5.70 (4.55, 7.67)	0.307
SCr, μmol/L		66.00 (55.00, 82.00)	73.00 (59.00, 92.00)	<**0.001**
UTP, g/24 h		1.44 (0.76, 2.45)	1.90 (0.83, 3.50)	**0.033**
Hb, g/L		131.48±18.79	127.09±18.83	**0.011**
Glucocorticoids, *n* (%)		164 (68.50)	170 (72.40)	<**0.001**
M	0, *n* (%)	156 (65.3)	164 (70.1)	0.263
	1, *n* (%)	83 (%)	70 (29.9)	
E	0, *n* (%)	210 (87.9)	213 (91.0)	0.264
	1, *n* (%)	29 (12.1)	21 (9.0)	
S	0, *n* (%)	200 (83.7)	193 (82.5)	0.727
	1, *n* (%)	39 (16.3)	41 (17.5)	
T	0, *n* (%)	205 (85.8)	198 (84.6)	0.838
	1, *n* (%)	30 (12.5)	33 (14.1)	
	2, *n* (%)	4 (1.7)	3 (1.3)	
C	0, *n* (%)	207 (86.6)	198 (84.6)	0.256
	1, *n* (%)	28 (11.7)	35 (15.0)	
	2, *n* (%)	4 (1.7)	1 (0.4)	

PFT, perirenal fat thickness; BMI, body mass index; IFTA, interstitial fibrosis and tubular atrophy; WHR, waist-to-hip ratio; TCh, total cholesterol; TG, total triglycerides; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; UA, blood uric acid; eGFR, estimated glomerular filtration rate; ALB, albumin; urea, urea nitrogen; SCr, blood creatinine; UTP, 24-h urine protein; Hb, hemoglobin; M, mesangial hypercellularity; E, endocapillary hypercellularity; S, segmental glomerulosclerosis or adhesion; T, tubular atrophy/interstitial fibrosis; C, crescents.

and Youden index, 1.45). In addition, the area under the curve was 0.75, indicating that PFT had good efficiency in predicting the occurrence of the new onset of composite endpoints, as shown in Figure 4.

Risk Factors of Renal Endpoints

Univariate regression analysis showed that patients with hypertension, diabetes, glucocorticoid use, increased PFT, increased UA, increased UTP, decreased ALB, decreased eGFR, mesangial cell hyperplasia (M1), endothelial cell hyperplasia (E1), segmental sclerosis/adhesion (S1), tubular atrophy/interstitial fibrosis (T1–2), and crescentic lesions (C1–2) had an increased risk of developing renal endpoint events. These indicators were included in a multivariate regression model to analyze the risk factors affecting the prognosis of patients with IgAN. Models 1 (demographic + pathological indicators + PFT), 2 (demographic + clinical indicators + PFT),

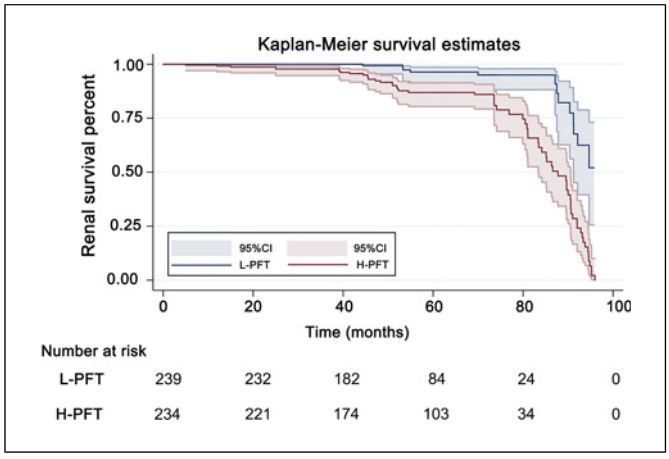

Fig. 3. Probability of renal survival between the L-PFT group and the H-PFT group.

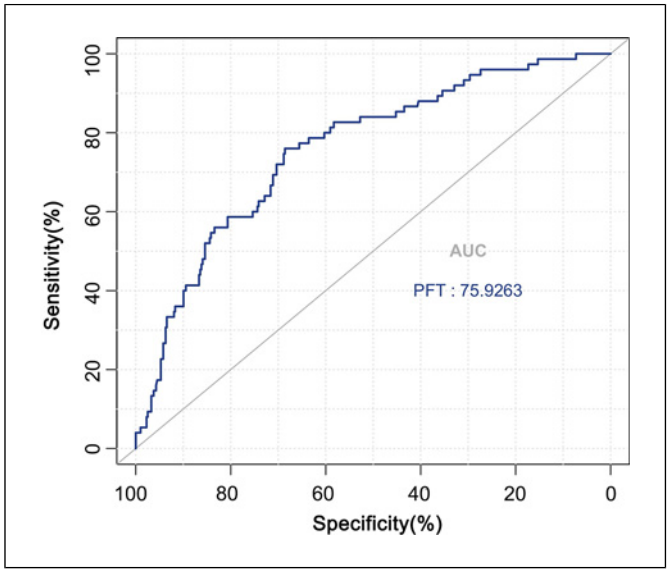

Fig. 4. Area under the receiver operating characteristic curve of PFT.

and 3 (demographic + clinical indicators + PFT) showed that increased PFT was a risk factor for renal endpoint events in patients with IgAN (model 1: HR: 2.20, 95% CI: 1.52, 3.19, $p < 0.001$; model 2: HR: 1.76, 95% CI: 1.22, 2.52, $p = 0.002$; model 3: HR: 1.77, 95% CI: 1.18, 2.66, $p = 0.006$) (Tables 3–5). In addition, we plotted Cox regression forest plots for the three models based on the HR values, as shown in Figure 5. Based on the above results, it is supposed that elevated PFT is an independent risk factor for poor long-term renal survival in patients with IgAN.

Table 3. Cox regression model 1 for risk factors associated with renal outcomes (demographic + pathological indicators + PFT)

Variable	HR	95% CI	*p* value
Sex (male/female)	1.017	0.626, 1.651	0.946
Age, years	1.000	0.979, 1.022	0.987
PFT, cm	2.201	1.521, 3.185	**<0.001**
M (M1/M0)	0.999	0.611, 1.634	0.998
E (E1/E0)	1.350	1.134, 1.542	**0.011**
S (S1/S0)	2.226	1.196, 4.141	**0.012**
T (T1–2/T0)	0.834	0.394, 1.769	0.637
C (C1–2/C0)	3.208	1.558, 6.602	**0.002**

PFT, perirenal fat thickness; M, mesangial hypercellularity; E, endocapillary hypercellularity; S, segmental glomerulosclerosis or adhesion; T, tubular atrophy/interstitial fibrosis.

Discussion

In the present cohort of 473 patients with biopsy-proven IgAN, 5.4% (13/239) patients in the low PFT group and 26.5% (62/234) patients in the high PFT group progressed to the renal endpoints ($p < 0.001$). Multivariate Cox regression analysis showed that PFT was an independent risk factor in all models. Therefore, PFT levels could be considered as a risk factor for the poor long-term prognosis of patients with IgAN.

PRF is a specific site of visceral fat deposition and is closely associated with several diseases such as cardiovascular disease, diabetes, and renal disease [7]. PRF has a higher predictive value for CKD than total, subcutaneous, or visceral fat in patients with type 2 diabetes mellitus patients [8, 18]. PFT is also positively associated with urinary ALB excretion rate in patients with type 2 diabetes mellitus [6]. Similarly, higher para-perirenal ultrasonographic fat thickness values have been observed in hypertensive patients with impaired renal function, independent of other indices of adiposity [19]. Interestingly, telmisartan improved nephropathy in metabolic syndrome by reducing leptin release from the perirenal adipose tissue [20]. The thickened perirenal adipose tissue may directly compress the renal tissue and blood vessels, leading to increased blood pressure. In addition, perirenal adipose afferent nerves were reported to involve in provoking pathological hypertension in rats [21], which gave us a new insight into this.

Abnormal glucose metabolism is common in patients with IgAN [22]. Elevated lipid levels have been reported as an independent risk factor for progression of

Table 4. Cox regression model 2 for risk factors associated with renal outcomes (demographic + clinical indicators + PFT)

Variable	HR	95% CI	*p* value
Sex (male/female)	0.872	0.524, 1.451	0.598
Age (years)	0.979	0.958, 1.001	0.058
PFT (cm)	1.759	1.224, 2.529	**0.002**
BMI (kg/m^2)	1.01	0.76, 1.30	0.914
Diabetes (N/Y)	4.995	1.950, 12.797	**0.001**
Hypertension (N/Y)	3.609	1.919, 6.787	<**0.001**
UA (μmol/L)	1.007	1.004, 1.010	<**0.001**
UTP (g/24 h)	1.258	1.092, 1.448	**0.001**
ALB (g/L)	0.992	0.963, 1.021	0.580
Glucocorticoids (Y/N)	0.87	0.521, 1.443	0.657
CKD stages (stage 1–3/4–5)	5.294	1.246, 22.494	**0.024**

PFT, perirenal fat thickness; BMI, body mass index; UA, blood uric acid; UTP, 24-h urine protein; ALB, albumin.

Table 5. Cox regression model 3 for risk factors associated with renal outcomes (demographic + pathological indicators + clinical indicators + PFT)

Variable	HR	95% CI	*p* value
Sex (male/female)	0.809	0.459, 1.427	0.464
Age (years)	0.978	0.956, 1.001	0.058
PFT (cm)	1.771	1.180, 2.659	**0.006**
Diabetes (N/Y)	4.927	1.800, 13.491	**0.002**
Hypertension (N/Y)	3.547	1.853, 6.790	<**0.001**
UA (μmol/L)	1.007	1.003, 1.010	<**0.001**
UTP (g/24 h)	1.244	1.070, 1.447	**0.005**
ALB (g/L)	0.988	0.954, 1.023	0.500
Glucocorticoids (Y/N)	0.894	0.534, 1.497	0.670
CKD stages (stage 1–3/4–5)	5.494	1.242, 24.311	**0.025**
M (M1/M0)	1.135	0.644, 1.999	0.661
E (E1/E0)	0.970	0.370, 2.544	0.950
S (S1/S0)	1.129	0.559, 2.281	0.735
T (T1–2/T0)	0.988	0.440, 2.218	0.977
C (C1–2/C0)	1.038	0.481, 2.239	0.925

PFT, perirenal fat thickness; UA, blood uric acid; UTP, 24-h urine protein; ALB, albumin; M, mesangial hypercellularity; E, endocapillary hypercellularity; S, segmental glomerulosclerosis or adhesion; T, tubular atrophy/interstitial fibrosis.

IgAN [23]. A recent study showed that IgAN patients with dyslipidemia had a worse prognosis than those in the non-dyslipidemia group [24]. Furthermore, imaging mass spectrometry analysis revealed an altered lipid distribution pattern in the tubular areas of hyper-IgA mouse kidneys [25]. In addition, a high BMI and interstitial fibrosis are associated with the progression of IgAN [26]. Interestingly, statins stabilize the renal function in IgAN patients, independent of their reduction of proteinuria [27]. These results suggest that lipid metabolism and PRF may be closely related to the progression and prognosis of IgAN. However, in this study, we did not find any association between PRF and BMI or blood lipid levels. As PRF is composed of both brown adipose tissue and white adipose tissue, the relationship between PRF and BMI or blood lipids is more than complex, but the underlying reason remains to be elucidated.

As a metabolic tissue located around the kidney, PFT might affect renal function in the following ways. First, the accumulation of PRF can directly compress the renal parenchyma and blood vessels, leading to increased intrarenal pressure, renal interstitial pressure, and decreased renal blood flow, which gradually leads to renal injury [28, 29]. Second, hypertrophic PRF can release proinflammatory adipokines and chemokines, such as leptin, lipocalin, vimentin, resistin, interleukin 6 (IL-6), IL-1β, and tumor necrosis factor-α (TNF-α) [30]. In addition, we randomly selected 6 patients with high PRF and 6 patients with low PRF from the cohort and performed immunohistochemical staining for TNF-α on their kidney tissue samples. The results showed that patients with high PRF had significantly higher expression of TNF-α than those with low PRF ($p < 0.001$) (online suppl. Fig. S1; for all online suppl. material, see https://doi.org/10.1159/000533507), which further confirmed our hypothesis. Of note, chronic inflammation is also involved in the pathogenesis of IgAN. Many adipokines are closely related to the immune and autoimmune systems [31]. Furthermore, PRF thickening can activate the RAS system by compressing the blood vessels, lymphatic system, and ureters, leading to hypertension, atherosclerosis, and renal dysfunction [32]. In addition, the activation of afferent signals in the PRF may increase renal sympathetic nerve activity and regulate local homeostasis, energy balance, and lipolysis in the kidney [33].

There were several limitations in the present study. First, this was a single-center study, so it was unclear whether our results had distinctive demographic or ethical characteristics, and a larger sample is needed to obtain more representative results and further validate the effect of PRF on IgAN. Second, the sample size was limited, which may introduce bias. Finally, PRF measurement was performed manually, which may have introduced some measurement error. Thus, despite its small size compared to the

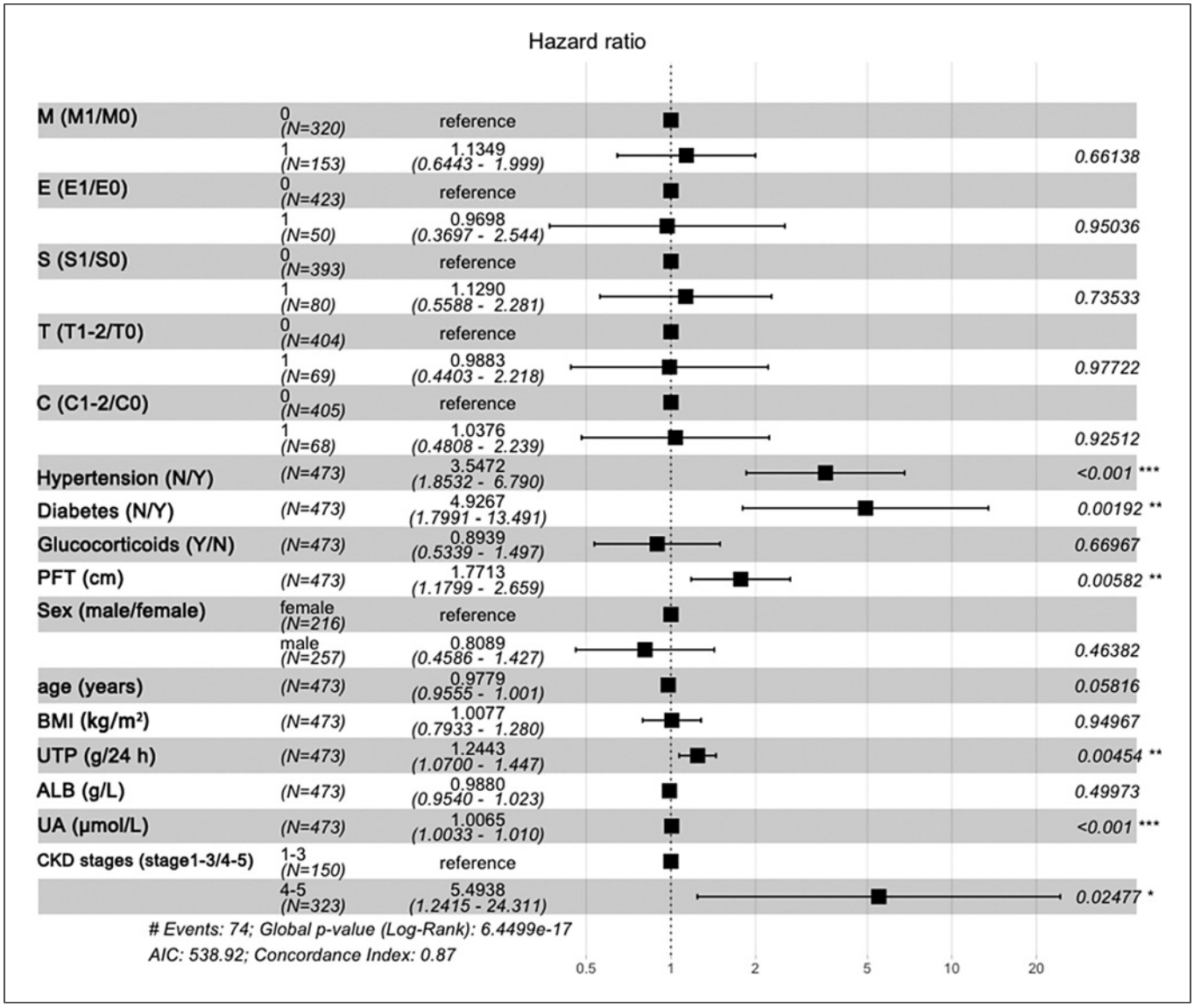

Fig. 5. Forest plot for Cox model 3.

subcutaneous and other sites of visceral fat deposition, the proximal location of the PRF to the kidney makes its specific anatomical and morphological features closely related to the development and progression of IgAN.

Conclusion

PFT levels may be positively associated with IgAN progression and could be used as a novel predictor of IgAN. Based on the importance of the pathophysiological functions of PFT, the development of PRF treatments may play an important role in delaying the progression of IgAN.

Statement of Ethics

All procedures performed in studies involving human subjects were in accordance with the ethical standards of the Institutional and/or National Research Committee and with the Helsinki Declarations of 1964 and its subsequent amendments or comparable ethical standards. The study was approved by the Ethics Committee of Renmin Hospital of Wuhan University (WDRY2021-KS036), and the study procedures complied with the

ethical standards of the committee responsible for human experimentation. Written informed consents were obtained from all participants to access clinical data for clinical research.

Conflict of Interest Statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Author Contributions

H.-T.H., Z.-W.Z., and W.L. participated in the research design; Z.-W.Z., H.-T.H., Z.-K.L., and F.C. performed the experiments; J.-L.R. performed data analysis and interpretation; Z.-W.Z. and H. -H.T. drafted the manuscript; Z.-W.Z. and W.L. designed and supervised the study; and all authors read and approved the final manuscript.

Data Availability Statement

Data are not publicly available due to ethical reasons. Further inquiries can be directed to the corresponding author.

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