

Analysis of Clinical Characteristics, Radiological Predictors, Pathological Features and Perioperative Outcomes Associated With Perinephric Fat Adhesion Degree

Junqiang Liu

First Affiliated Hospital of Dalian Medical University

Hongwei Huang

First Affiliated Hospital of Dalian Medical University

Yiheng Jiang

First Affiliated Hospital of Dalian Medical University

Dikuan Liu

First Affiliated Hospital of Dalian Medical University

Zheng Zhu

University of California, Davis

Jing Chen

First Affiliated Hospital of Dalian Medical University

Lina Wang

First Affiliated Hospital of Dalian Medical University

Huafeng Zong

Dalian Friendship Hospital

Xishuang Song

First Affiliated Hospital of Dalian Medical University

Xuejian Wang

First Affiliated Hospital of Dalian Medical University

Xinqing Zhu

First Affiliated Hospital of Dalian Medical University

Qiwei Chen

First Affiliated Hospital of Dalian Medical University

Sony Nahayo

First Affiliated Hospital of Dalian Medical University

Jianbo Wang

First Affiliated Hospital of Dalian Medical University

Deyong Yang (✉ yangdeyong@dlmedu.edu.cn)

First Affiliated Hospital of Dalian Medical University

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Abstract

Background: To assess the clinical characteristics, radiological predictors and pathological features of perinephric fat adhesion degree (PFAD) graded based on fixed criteria and to determine the impact of adherent perinephric fat (APF) on retroperitoneal laparoscopic partial nephrectomy (RLPN) outcomes.

Methods: 84 patients undergoing RLPN were included and graded into 4 groups based on PFAD. Univariate and multivariate analysis were performed for clinical characteristics and radiological predictors of PFAD. Perioperative data was compared between APF groups and non-APF groups. Masson staining determined collagen fibers. Immunohistochemistry detected CD45 immune cells and CD34 vessels.

Results: 20, 28, 18 and 18 patients were graded as normal perinephric fat (NPF), mild adherent perinephric fat (MiPF), moderate adherent perinephric fat (MoPF) and severe adherent perinephric fat (SPF), respectively. Multivariate analysis revealed that gender ($p < 0.001$), age ($p = 0.003$) and hypertension ($p = 0.006$) were significant clinical risk factors of PFAD, while radiological predictors included perinephric stranding ($p = 0.001$), posterior perinephric fat thickness ($p = 0.009$) and perinephric fat density ($p = 0.02$). APF was associated with drain output ($P = 0.012$) and accompanied by immune cells gathering in renal cortex near thickened renal capsule with many vessels.

Conclusions: Clinical characteristics and radiological predictors can evaluate PFAD and may assist guide preoperative surgical option. Pathological features of APF reflect decapsulation and bleeding during kidney mobilization at RLPN.

Introduction

For T1 stage renal cell carcinoma, especially for T1a tumors, partial nephrectomy is recognized as the standard operation whenever technically feasible.^{1–3} In RLPN, multiple radiological scores that may anticipate tumor complexity are proposed to describe the tumor-specific characteristics, but they neglect other factors. One of the potential patient-specific factors for surgical complexity is APF characterized by thickening and adhesion fat surrounding the kidneys.⁴

Due to lack of consensus objective grading criteria for the definition of APF, the incidence of APF varies greatly, ranging from 10.6–55.2% according to the previous studies.^{4,5} Most authors conducted a retrospective analysis based on the surgical records that whether adhesion.^{6–8} Zheng et al.⁹ graded APF according to the operative time for renal mobilization. Darane et al.¹⁰ graded APF based on the subjective surgical score for decapsulation during dissection. Despite these attempts to improve objectivity, there appears to be no clear criteria to grade PFAD.

So far, the pathogenesis of APF remains unclear. At present, the mainstream argues the APF has a positive correlation with chronic inflammation. And previous studies showed interleukins and adipocyte size were increase in APF.^{10,11} But these findings failed to reflect the clinical, radiological and surgical characteristics of APF.

Therefore, our study established objective criteria after multiple surgical videos were reviewed. The present study is to prospectively assess patients' clinical characteristics and radiological predictors for PFAD graded according to objective criteria, and to analyze the impact of APF on RLPN outcomes and pathological features of APF. Moreover, we explored the relationship between clinical characteristics, imaging findings, and pathology of APF.

Methods

Patients and data collection

We performed a prospective study of patients who underwent RLPN for suspicious renal mass between March 2017 and March 2018 at the First Affiliated Hospital of Dalian Medical University. The study was conducted the guidelines of the Declaration of Helsinki after approval from our hospital's institutional ethical committee (First Affiliated Hospital of Dalian Medical University). The clinical variables (age, gender, body mass index (BMI), preoperative eGFR, hypertension, diabetes, active smoking, and alcoholism), perioperative outcomes (operative time(OT), warm ischemia time (WIT), estimated blood loss (EBL), Transfusions, Clavien-Dindo classification (CDC), length of stay, drain output, postoperative gastrointestinal recovery time, postoperative fever, gastrointestinal discomfort and Change dressing frequency) and postoperative pathology results (Fuhrman Grade) were collected.

Criteria for PFAD grading

PFAD is divided into four grades (Fig. 1). Normal perinephric fat (NPF): easily blunt dissect perinephric fat from kidney, less fibers connect renal capsule and fat; mild adherent perinephric fat (MiPF): easily blunt dissect, more fibers connect renal capsule and fat, and scattered flaky fat remains on the renal capsule after blunt dissection; moderate adherent perinephric fat (MoPF): part of perinephric fat adheres to the kidney and need sharp dissection; severe adherent perinephric fat (SPF): All parts of perinephric fat adhere to the kidney and need sharp dissection or subcapsular dissection. NPF and MiPF were defined as non-APF, which did not complicate kidney mobilization while the latter two grades were APF.

Radiological data

All patients underwent preoperative abdominal computed tomographic (CT) imaging. The thickness of the medial, lateral, posterior and poster lateral perinephric fat were measured at the level of the renal vena cava according to the method described by Eisner et al.¹² Perinephric fat density was a manually selected area close to the renal capsule, and Hounsfield units (HU) in this area were calculated automatically. Perinephric fat area was defined as the area between the medial and posterior renal fat thickness measurement line. Perinephric stranding was determined as Kim *et al.*¹³ described (Fig. 2).

The preoperative CT was assessed by two urologists (J.L. and H.H.) blinded to patient PFAD status independently. If any differences between the two observers, the corresponding image was assigned to another highly qualified urologist (D.Y.) for final results.

Histological analysis

The isolated perinephric fat and adjacent kidney were taken from the NPF and the SPF, fixed in 4% formalin buffer, embedded in paraffin and cut into 4 mm thick serial sections. The slices were stained by Masson method. The primary antibodies against CD45 (1:200) and CD34 (1:200) were from Proteintech (CHINA). After staining, the samples were observed under the microscope. Light yellow, brown yellow or dark brown was supposed as the positive expression.

Statistical analysis

Continuous variables were reported as median (minimum and maximum) and qualitative variables as ratio (percentage). Univariate and ordered multivariate logistic regression analysis were performed to assess clinical characteristics and radiological predictors of PFAD. Chi-square test was used to compare categorical data and Mann–Whitney U test was used to compare non-normally distributed continuous variables and ordered-qualitative variables for perioperative outcomes or pathological grading of renal cell carcinoma (RCC) between the patients with APF and non-APF. A P values < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 20.0.

Results

Patients' clinical and radiographic characteristics

The clinical and radiographic characteristics in our study are summarized in Table 1. The PFAD was graded as none, mild, moderate and severe in 23.8%, 33.3%, 21.4% and 21.4% of our patient cohort, respectively. Of these, fifty-seven percent of the patients were over 55 years. The majority of patients were male (61.9%) and had malignant tumors (61.9%). The proportion of patients with malignant tumors and hypertension increases with the PFAD, as well as the median perinephric fat area and perinephric fat thickness. Only 2 patients had a history of chronic nephritis and both were in the SPF group. Proportion of patients with none, mild to moderate and severe perinephric stranding were 61.9%, 28.6% and 9.5%, respectively.

Table 1 Clinical and radiographic characteristics stratified by adhesiveness of perinephric fat

Characteristics	NPF(n=20)	MiPF(n=28)	MoPF(n=18)	SPF(n=18)	Total(n=84)
Age(yr)					
≤55	12(60)	13(46)	7(39)	4(22)	36 (43)
>55	8(40)	15(54)	11(61)	14(78)	48 (57)
Male gender	6(30)	14(50)	15(83.3)	17(94.4)	52 (61.9)
BMI kg/m ²					
≤25	8(40)	15(53.6)	6(33.3)	4(22.2)	33 (39.3)
25~30	10(50)	9(32.1)	10(55.6)	9(50)	38 (45.2)
≥30	2(10)	4(14.3)	2(11.1)	5(27.8)	13 (15.5)
Diabetes	5(25)	6(21.4)	4(22.2)	6(33.3)	19 (22.6)
Hypertension	5(25)	12(42.9)	9(50)	12(66.7)	38 (45.2)
Cardiovascular disease	3(15)	2(7.1)	3(16.7)	2(11.1)	10 (11.9)
Preoperative eGFR(<60 ml/min)	0(0)	0(0)	0(0)	2(11.1)	2 (2.4)
Active smoking	7(35)	9(32.1)	7(38.9)	8(44.4)	31 (36.9)
Alcoholism	7(35)	11(39.3)	6(33.3)	8(44.4)	32 (38.1)
malignancy	10(50)	16(57.1)	12(66.7)	14(77.8)	52 (61.9)
Preoperative creatinine(>ULN)	4(20)	3(10.7)	3(16.7)	4(22.2)	14 (16.7)
HU of perinephric fat	-103 (-112, -87)	-101 (-132-84)	-95-110-83)	-88 (-98-49)	-98 (-132, -49)
Perinephric fat area (cm ²)	0.69 (0-3.65)	2.81(1.21-8.34)	5.44(0.97,14.74)	8.61(2.40,20.72)	3.05(0,20.72)
Perinephric fat thickness (mm)					
Medial	1 (0,7)	5.9 (0,19.8)	7.5 (0,17.1)	9.6(3.1,27.2)	5.8 (0,27.2)
Lateral	1.1 (0,30)	10.1 (0,30)	17.5 (0,37)	22.5(3.4,40)	11.2 (0,40)
Posterior	3.5 (0,9.8)	7.8(2.4,17.4)	12.7(6.2,25.4)	19.4(10.2,57.7)	9.7 (0,57.7)
Posterolateral	8.8(2.4,23.4)	13.8(1.9,26.3)	15.7(8.8,26.5)	24(12.6,43)	15.1(1.9,43)
Stranding					
None	20(100)	26(92.8)	6(33.3)	0(0)	52 (61.9)
Type 1	0(0)	2(7.2)	11(61.1)	11(61.1)	24 (28.6)
Type 2	0(0)	0(0)	1(5.6)	7(39.9)	8 (9.5)

Clinical characteristics for PFAD

Table 2 highlights the clinical characteristics of PFAD. PFAD was significantly associated with clinical parameters including increasing age (OR 3.76, P = 0.003), male gender (OR 13.14, P < 0.001), and hypertension (OR 3.28, P = 0.006) on multivariable analysis, whereas other clinical variables were not associated with PFAD.

Table 2 Univariate and multivariable analysis clinical characteristics of PFAD

Characteristics	Univariate		Multivariate	
	OR	p value	OR	p value
Age	2.61(1.17,5.82)	0.019	3.76(1.57,8.97)	0.003
Male gender	8.39(3.32,21.24)	< 0.001	13.14(4.87,35.46)	<0.001
BMI				
≥30	2.65(0.82,8.54)	0.103		
25~30	1.58(0.68,3.68)	0.375		
Diabetes	1.83(0.73,4.62)	0.200		
Hypertension	2.85(1.28,6.33)	0.010	3.28(1.40,7.65)	0.006
Cardiovascular disease	0.99(0.30,3.25)	0.988		
Active smoking	1.34(0.60,2.98)	0.475		
Alcoholism	1.18(0.53,2.60)	0.685		
malignancy	2.14(0.95,4.80)	0.065		
Preoperative creatinine	0.84(0.30,2.37)	0.747		

Radiological predictors for PFAD

As shown in Table 3, all of radiological variables were found to be predictive of PFAD (all $P < 0.001$) on univariable analysis. However, multivariate analysis showed that perinephric stranding (Type 1 OR 25.05, $P = 0.001$, Type 2 OR 35.21, $P = 0.033$), posterior fat thickness (OR 11.46, $P = 0.009$) and perinephric fat density (OR 1.08, $P = 0.02$) appeared to be most predictive of PFAD.

Table 3 Univariate and multivariable analysis of predicting factors of PFAD

Characteristics	Univariate		Multivariate	
	OR	p value	OR	p value
Perinephric fat thickness				
Medial	12.48(4.79,32.55)	< 0.001		
Lateral	3.18(2.01,5.04)	< 0.001		
Posterior	31.09(10.62,91.02)	< 0.001	11.46(1.86,70.60)	0.009
Posterolateral	6.68(3.43,13.01)	< 0.001		
Perinephric fat area	1.91(1.55,2.35)	< 0.001		
HU of perinephric fat	1.14(1.08,1.20)	< 0.001	1.08(1.01,1.14)	0.020
Stranding				
Type 1	113.44(21.08,610.32)	< 0.001	25.05(3.76,167.00)	0.001
Type 2	986.26(68.87,14123.33)	< 0.001	35.21(1.32,937.66)	0.033

Impact of APF on Perioperative outcomes and pathological grading

The 84 cases comprised 36 with APF (MoPF or SPF) and 48 with non-APF (NPF or MiPF). Drain output is significantly higher in the APF group (169 vs 125.5 ml, $P = 0.012$, see Table 4). Other intraoperative variables (OT, WIT, EBL and transfusions), postoperative variables (postoperative gastrointestinal recovery time, length of stay, postoperative fever, postoperative gastrointestinal discomfort, change dressing frequency and CDC), and Fuhrman grading were similar between the two groups ($P > 0.05$).

Table 4 Correlation between APF and Perioperative outcomes and pathological grading of RCC

Variable	APF	Control group with no APF	p value
Operative time (OT) (min)	110.50(45,212)	89(45,222)	0.141
Warm ischaemia time [WIT] (min)	20.50(15,48)	21(15,45)	0.986
drain output (ml)	169(60,403)	125.5(63,355)	0.012
Postoperative gastrointestinal recovery time(days)	5(1,8)	4(1,8)	0.611
Length of stay (days)	15(9,36)	14(5,35)	0.091
Transfusions	2(5.6%)	3(6.3%)	0.894
Estimated blood loss [EBL] (ml)	240(107,664)	215(107,736)	0.249
Postoperative fever ($\geq 38.0^{\circ}\text{C}$)	1(2.8%)	4(8.3%)	0.287
Postoperative gastrointestinal discomfort	11(30.6%)	10(20.8%)	0.309
Change dressing frequency	4.5(1,28)	3(1,19)	0.052
Clavien-Dindo classification [CDC]	18(50%)	18(37.5%)	0.265
Clavien 1	15(41.7%)	15(31.3%)	
Clavien 2	3(8.3%)	3(6.3%)	
Fuhrman Grade	26(72%)	26(54%)	0.106
I	10(27.8%)	10(20.8%)	
II	10(27.8%)	11(22.9%)	
III	2(5.6%)	4(8.3%)	
IV	4(11.1%)	1(2.1%)	

Histological analysis

Masson staining showed that renal capsule was thin and had two layers in non-APF group. Our study defined the outer membrane-like structure as extracapsular fascia. Patients with APF lack of extracapsular fascia and the thickness of the renal capsule increased significantly (Fig. 3. A). Immunohistochemistry showed that CD45 + immune cells accumulate in the renal cortex and infiltrate into renal capsule in the APF group (Fig. 3. B). In patients with APF, the CD34 + vascular endothelial cells were significantly increased and arranged into a vascular like structure (Fig. 3. C).

Discussion

APF is one of potential tumor-specific factors that can complicate partial nephrectomy (PN) and is associated with decreased progression-free survival in patients with localized renal cancer.^{6, 10, 14-16} Previous studies on the association of APF with clinical, radiological features, or perioperative outcomes are summarized in Table 5. Due to lack of objective criteria for APF, the incidence of APF varies greatly. Therefore, our study established objective criteria after multiple surgical videos were reviewed. In this study, the incidence of APF was 42.8%, which was between the documented incidence.^{6, 8, 10}

Table 5 summary of previous studies on APF

Author Year	Patient	Surgery	APF grading	APF rate	Included factors	Significant variables
Bylund et al. (2013)	29	RPN, OPN or Laparoscopic cryoablation	Operative records	55.2%	Clinical, Imaging, Pathological, Outcome	Male gender, Tumor size, Stranding, Tumor >50% exophytic, Thickness of perinephric fat, OT
Zheng et al. (2014)	41	OPN	Time of perinephric fat dissection on	53.7%	Clinical, Imaging, Pathological, Outcome	Male gender, PnFSD
Davidiuk et al. (2014)	100	RPN	Described by Kim et al.	30%	Clinical, Imaging, Pathological, Outcome	Male gender, BMI, Posterolateral and Posterior perinephric fat, Stranding
Davidiuk et al. (2015)	100	RPN	Described by Kim et al.	30%	Outcome	
Kobayashi et al. (2016)	47	LPN or RALPN	Operative records	14.9%	Clinical, Imaging, Outcome	OT, Hypertension, FSPA on CT
Martin et al. (2016)	86	OPN	Operative records	50.0%	Clinical, Imaging, Outcome	Age, MAPscore
Kocher et al. (2016)	245	LPN or RPN	Operative records	10.6%	Clinical, Imaging, Pathological, Outcome	Age, Male gender, Stranding, Posterior fat thickness, MAP score, Malignant renal histology, Operating time, EBL
Darlane et al. (2016)	125	RPN or OPN	Described by Kim et al.	40.8%	Clinical, Imaging, Pathological, Outcome, Histologically	OT, EBL, Male gender, Age, Waist circumference, Fat density on CT, MAP score, Larger adipocytes
Shintaro et al. (2017)	92	Laparoscopic donor nephrectomy	Intraoperative videos	55.4%	Clinical, Imaging, Outcome, IHC	Perinephric fat area, Stranding, sIL-6R, OT
Khene et al. (2017)	202	RPN	Operative records	39.6%	Clinical, Imaging, Outcome	Male gender, Obesity, Hypertension, MAP score, OT, EBL, Transfusion, Conversion to open surgery or radical nephrectomy

Most literatures have confirmed that APF is associated with advanced age and common in males,^{4-6, 8-10, 14} which is correspond with our study. Male patients have more perinephric fat, whereas women have more subcutaneous fat.^{12, 17} However, in the age, adipose tissue redistribute from subcutaneous to visceral and ectopic fat, especially along the kidneys, liver and bone marrow. Adipose tissue is an endocrine organ which produces hormones such as cytokines especially in tumor necrosis factor- α (TNF α) and interleukin (IL-6). They can increase with aging and excessive accumulation of fat.¹⁸ It was confirmed that APF group solely increased the expression of sIL-6R, suggesting that APF may be a pathological procedure caused by systemic chronic inflammation.^{11, 19-21} Therefore, both age and gender can affect the distribution of visceral and subcutaneous fat, and also be the risk factors of APF.

In addition, our study also confirmed hypertension is the risk factor of PFAD, as previous studies reported.^{22, 23} Immune system play an important role in the development of hypertension and renal immune cell infiltration has been demonstrated in both experimental and clinical hypertension.²⁴ In SPF group, we first found that a large number of CD45 + immune cells accumulate in the renal cortex near renal capsule. There are also scattered immune cells, increased blood vessel distribution and thickening of the renal capsule near renal cortex. Hypertension may affect the adhesion of the renal capsule to the perinephric fat by inducing renal immune cell infiltration. Two patients with previous nephritis were in the SPF group, adding weight to the theory that chronic inflammation of the kidney can affect fat adhesion.^{11, 25, 26}

Perinephric stranding and thickness of posterior perinephric fat are important radiological predictor for APF in this study. Perinephric stranding represents a chronic inflammatory reaction which is considered as an important factor for formation of APF. The posterior perinephric fat thickness represents excessive and dysfunctional adipose tissue. Based on the two variables, Mayo Adhesive Probability (MAP) Score was established to predict APF⁵, which has been validated in different surgical methods for renal cancer.^{6, 8, 10, 14, 23}

However, predictive value for perinephric fat density is still controversial. Bylund et al⁴ found that the renal hilum level fat density had no significant effect on APF. Zheng et al⁹ pointed out that perinephric fat surface density can predict the difficulty of renal peritoneal fat separation. The above differences may be related to the measurement method of perinephric fat density. During surgery, we found that perinephric fat only adhered to the surface of the kidney and not to the posterior peritoneum or posterior abdominal wall, suggesting that the adhesion or inflammatory area may be closed to the kidney surface. So, we measure perinephric fat density in a high-density area adjacent to the renal capsule, we found that some patients with SPF had significantly increased perinephric fat HU value on enhanced CT. Our results suggest that perinephric fat density may be a complement to the MAP score.

Several authors considered that APF can increase the risk of OT and bleeding during PN.^{6,10,14} However, our results only find that drain output was associated with APF. The OT and intraoperative EBL may be more affected by surgeon's surgical experience and other reasons, such as location of the tumor, damage of variant renal blood vessels and adjacent organs, and suture cutting off the renal parenchyma. Senior surgeons can speed up the surgical process, reduce damage and intraoperative bleeding, suggesting that whether APF can affect the OT and EBL needs further verification.

In this study, we found another new layer of fascia on the lateral side of renal capsule in NPF group for the first time. This fascia was defined as extracapsular fascia. During PN, perinephric fat can be easily blunt dissected along the gap between renal capsule and extracapsular fascia. However, due to chronic inflammation for SPF group, extracapsular fascia was taken place by thickening and fusion of renal capsule with many vessels, which will cause decapsulation and increasing hemorrhage in the process of kidney mobilization.

In conclusion, APF is more prevalent in ageing and male populations, particularly those with hypertension. Radiological factors such as perinephric stranding, posterior perinephric fat thickness and perinephric fat density can be used to predict PFAD. APF was associated with drain output and accompanied by immune cells gathering in renal cortex near thickened renal capsule with many vessels.

Declarations

Author contributions

In this research, J.L., H.H and Y.J. designed and performed the experiment. D.L., Z.Z., J.C. and L.W. optimized algorithm flow. H.H and Y.J. wrote the paper and were responsible for the writing, revision, and finalization of the article. J.W. and D.Y. reviewed and edited the manuscript. H.Z. and X.S. collected and collated figures, X.W., X.Z., Q.C. and S.N. summarized the statistical data. All authors read and approved the manuscript.

Acknowledgements

Ethical approval

Ethical approval was given by the medical ethics committee of Chinese Clinical Trial Registry with the following reference number: ChiCTR-POC-15006412.

Informed Consent

Informed consent was obtained from all subjects or, if subjects are under 18, from a parent and/or legal guardian.

Additional Information

We declare no conflict of interest.

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Figures

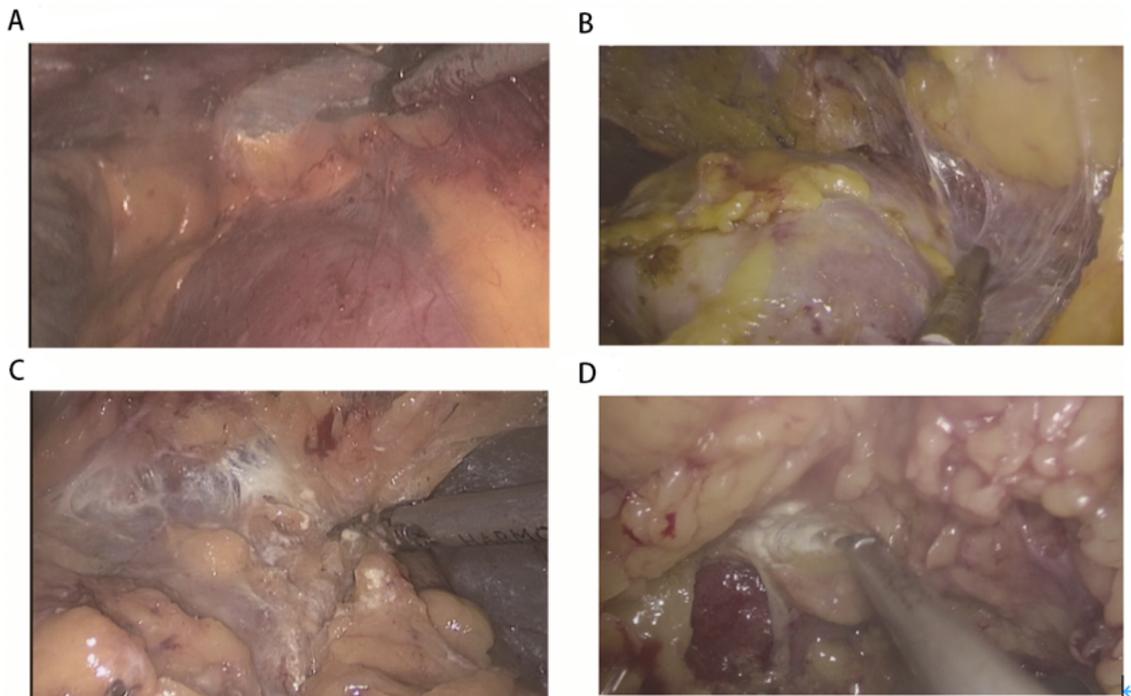


Figure 1
Surgical criterion of APF. (A) normal perinephric fat (NPF). (B) mild adherent perinephric fat (MiPF). (C) moderate adherent perinephric fat (MoPF). (D) severe adherent perinephric fat (SPF)

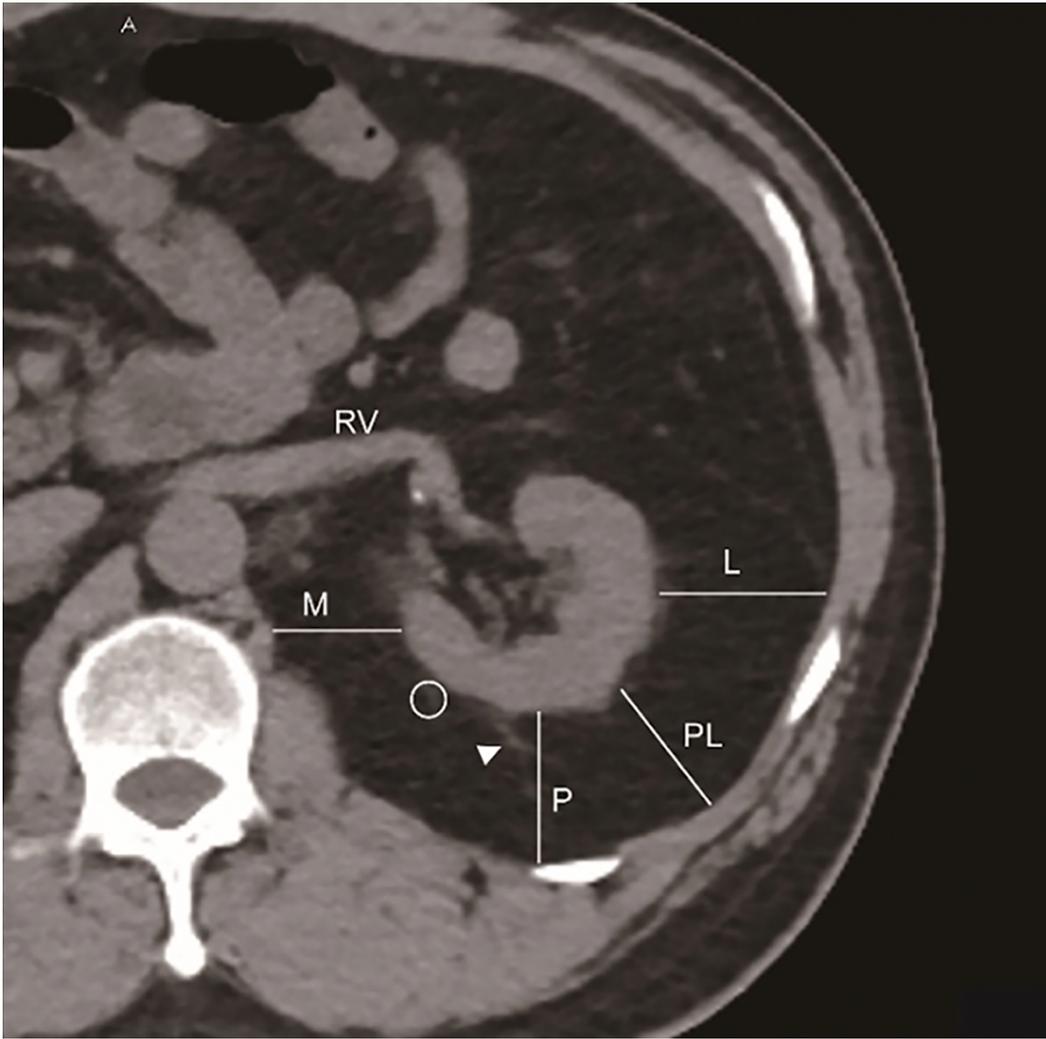


Figure 2
Measurement of perinephric fat at the level of the vein. M - medial perinephric fat thickness; L - lateral perinephric fat thickness; P - posterior perinephric fat thickness; PL - posterolateral perinephric fat thickness; Circle - HU of perinephric fat; Triangle - stranding; RV - renal vein.

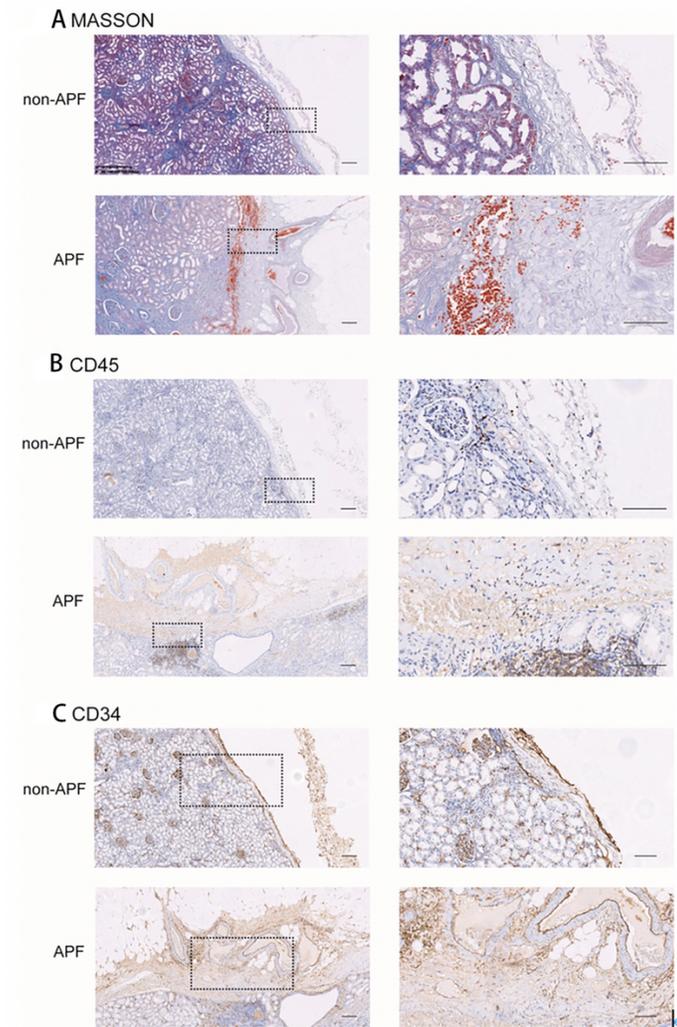


Figure 3

Representative examples of MASSON, CD45 and CD34 staining. (A) Non-APF group has a thin extracapsular fascia, APF group renal capsule and extracapsular fascia fusion thickening. (B) APF CD45 immune cells in the group were highly expressed in the renal capsule and adjacent renal cortex. (C) APF group CD34 for vascular staining. Scale bar = 100 mm.