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Pathology associated with adherent perirenal fat and its clinical effect

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Abstract

Introduction: The dissection of perirenal fat is of critical importance to kidney surgery and ease of dissection is more important when using minimally invasive approaches. This study aimed to determine the clinical, radiological, and pathological significance of adherent perirenal fat (APF).

Materials and Methods: This prospective study included 22 patients scheduled for partial nephrectomy and 40 patients for donor nephrectomy. Intraoperative fat dissection time was recorded, and the complexity of perirenal fat dissection was surgeon-classified as easy, moderate, and difficult. Perirenal fat and subcutaneous fat thickness were measured. Measurement of perirenal fat depth and the Hounsfield unit (HU) for both perirenal and subcutaneous fields were performed using computed tomography (CT) images. All specimens were submitted for histopatological analysis. Researchers in each arm were blinded to other researchers' data.

Results: Mean age of the patients was 51.3 ± 12.7 years. Mean perirenal fat dissection time was 15.0 ± 13.5 minutes. Patient demographics, BMI, nor occupational status differed between the 3 complexity of perirenal fat dissection groups. Radiological findings showed that there was a significant correlation between perirenal fat depth and complexity of perirenal fat dissection ($P < .05$), but not with HU measurements or subcutaneous fat thickness. Surgeon classification of the complexity of perirenal fat dissection was in accordance with the duration of dissection ($P < .05$). Perinephric fat contained more fibrous tissue in the patients with histologically proven APF than in those without ($P < .05$).

Conclusions: APF is a challenge during kidney surgery. Difficult dissection prolongs the duration of perirenal fat dissection and surgery. Perirenal fat thickness measured via preoperative CT might be used to predict APF.

1 | INTRODUCTION

The dissection of perirenal fat is of critical importance to kidney surgery, especially in cases of partial and donor nephrectomy.[1,2] Good dissection of perirenal fat provides good exposure, easy manipulation, and shorter surgical duration.[3,4] In 10.6%-55.2% of cases, perirenal fat tissue is adhered to the kidney, which makes it difficult to dissect; this phenomenon is referred to as adherent perirenal fat (APF) or sticky perirenal fat.[4]

Patient-related factors, including gender, and visceral and perinephric fat thickness are clinically associated with the complexity of surgery and surgical outcome.[3,5] For predicting the complexity of perirenal fat dissection, many researchers suggest using such tools as renal scoring systems and preoperative computed tomography

(CT) measurement.[6,7] Prediction of APF can help in choosing the optimal surgical approach.[1] Severe APF can complicate and hinder minimally invasive surgery.[1,4]

All relevant studies in the literature have emphasized the prediction of APF preoperatively, with very little attention to the underlying pathophysiology.[4] Recently, Dariane et al[8] published a study on the histological changes linked to APF. The present study aimed to determine the clinical, radiological, and pathological significance of APF.

What's known

- The ways of prediction of adherent perirenal fat before surgery have been studied previously with complex scoring systems, but there is only one study which adresses the histopathology under this phenomenon.

What's new

- Results of this study revealed that there is no need for complex scoring systems in order to predict adherent perirenal fat. Perirenal fat thickness measured via preoperative CT can predict adherent perirenal fat single handedly. Also, detailed histopathological investigation under adherent perirenal fat has been reported by this study. Contrary to expectations, parameters like gender, weight, BMI, diabetes, and occupational status have no effect on adherent perirenal fat. This study demonstrated that the adherent perirenal fat is mainly caused by fibrotic processes and only radiological findings can predict the complexity of dissection preoperatively.

2 | MATERIALS AND METHODS

2.1 | Patient selection

This prospective study included patients that were scheduled for partial nephrectomy or donor nephrectomy between October 2016 and June 2017. Patients with a history of renal interventions and recurrent urinary tract infection, and those without CT images were excluded from the study. After exclusion of 6 patients, the remaining 62 adults were included, of which 22 underwent partial nephrectomy and 40 underwent donor nephrectomy. Type of surgical approach was chosen according to surgeons preference and experience. The study was carried out with 3 arms: clinical phase, radiological measurement, and histopathological examination. The researchers in each arm were blinded to each other's data. After patient recruitment, patients' codes are presented to the radiologist and the pathologist. In clinical phase; patients' demographic and occupational data were recorded. Then, patients underwent surgery that perioperative data were recorded. In radiological arm, CT measurements are obtained and recorded. In histopathological arm, pathology specimens were examined. The study protocol was approved by our institutional ethics committee (IRB No: GO16/669-26). All the patients provided written informed consent before undergoing surgical intervention.

2.2 | Data collection

Clinical data collection and intraoperative measurements were performed by the same researcher (EC). Patient demographics, weight, height, body mass index (BMI), and occupational status were recorded. Occupational status was categorized as light workers and heavy workers. Patients that worked in jobs requiring physical strength, such as construction, farming, delivery, were categorized as heavy workers, whereas office employees, housewives, and the unemployed were categorized as light workers.

Surgery was performed by experienced surgeons (FTA, CYB or MSY). All nephrectomies were performed via the transperitoneal approach. In order to record surgical data the researcher in charge (EC) and an observer (FI) were present during all surgical procedures. Perirenal fat dissection time was recorded by a time observer (FI). If the removal of fatty tissue from the kidney is not easy and cause unintentional injuries, then this phenomenon is defined as APF. The complexity of perirenal fat dissection was classified by EC and divided into 3 categories: easy, moderate, and difficult. This classification was based on the difficulty of dissection, capsular trauma during dissection, bleeding, and unintentional injuries during removal of perirenal fat from the kidney. The fatty tissue which is separated by a gentle traction is categorized as easy. If renal capsula or perirenal tissue is injured and bleeding from the dissection site occurs, then the fatty tissue is categorized as difficult. The rest were categorized as moderate. In addition, maximum perirenal fat thickness (mm) and maximum subcutaneous fat thickness (mm) were measured intraoperatively by EC. In partial nephrectomies, perirenal fat except the tumor cap was dissected. In donor nephrectomies perirenal fat except the golden triangle was dissected. The removed perirenal fat tissue was sent for histopathological examination after measurement.

2.3 | Radiology

All radiological measurements were performed by the same radiologist (MK). Perirenal fat thickness was measured at the level of the renal vein, from the posterior renal capsule to the posterior abdominal wall using CT images. These measurements from CT images are referred to as perirenal fat depth to eliminate confusion. The perirenal field Hounsfield unit (HU) and subcutaneous fat HU (at the level of the hilus) were recorded according to a circular region of interest measuring 1 cm in diameter, using a PACS workstation and preoperative CT images.

2.4 | Pathology

Following overnight fixation in 4% formaldehyde at room temperature, resected fat tissue was subjected to a routine paraffin embedding procedure. Sections 5 μm thick were obtained from paraffin blocks and initially stained with hematoxylin-eosin using a Shandon Varistain Gemini® (Shandon, Frankfurt) automated slide stainer. Additional histochemical staining with periodic acid methenamine silver and Masson's trichrome was performed to assess morphology and the degree of fibrosis in greater detail. All light microscopic evaluations were conducted using an Olympus BX53® optical microscope. Measurements were performed using digital photos captured using an Olympus SC50 CMOS® camera and the drawing line tools in CellSens Entry Imaging v.1.13® (Olympus Europa SE & Co. KG, Hamburg). Adipocyte diameter was manually drawn and individually measured. In total, 350 adjacent adipocytes were measured in each patient. Cells <35 μm were excluded from analysis to avoid immature multilocular adipocytes. Maximum adipocyte diameter and the presence of brown fat were noted separately.

During microscopic examination the presence of fibrosis was observed in some cases, primarily in the septae between fat lobules (ie, perilobular fibrosis), around blood vessels (ie, perivascular fibrosis), and/or in the outermost Gerota's fascia (Figure 1). Collagen fibers were organized in bundles of variable thickness and some exhibited spiculated infiltration to the periphery of the fat lobules, isolating a few adipocytes from the remainder of the tissue. Moreover, some cases exhibited pericellular fibrosis consisting of thinner collagen fibrils surrounding adipocytes, localized in areas far from fibrotic bundles (Figure 2). The presence or absence of these features was recorded in each case. Additionally, maximum thickness of the collagen at Gerota's fascia and wall thickness of the thickest vessel (from the endothelia to adventitia) in the resected fat were measured, as described above. The number of vessels with a thick wall (>100 μm) in a 1-cm^2 area varied according to patient and was scored as follows: 1: <3 vessels; 2:3-5 vessels; 3: ≥6 vessels. Minimal inflammatory infiltrates that contained a small number of lymphocytes and/or histiocytes existed in a few cases and was also recorded.

Immunohistochemical staining with primary anti-CD31 antibody (Leica Biosystems®; dilution, 1:100; product code: NCL-L-CK7-560), an endothelial marker, was performed to evaluate microvessel density in perinephric fat. The Leica BOND-Max® automated staining platform (Leica Microsystems, Wetzlar, Germany) and Bond Polymer Refine Detection Kit® (Leica Biosystems, Newcastle Ltd., Newcastle Upon Tyne, UK; cat. no: DS9800) were used for this purpose. In each case, 3 fields with the highest number of microvessels were identified at low power. In these areas mean capillary density (ACD) at 400× magnification was determined and expressed as the number of CD31-positive capillaries per high power field.

Specimens were qualified for histopathological examination in 55 (88.7%) of the 62 cases; 7 samples were excluded from the study due to poor sampling or technical problems.

2.5 | Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows v.23® (IBM Corp., Armonk, NY, USA). Continuous variables are shown as mean ± SD and median (range). One-way ANOVA was used to analyse parametric variables, vs the Kruskal-Wallis test for nonparametric quantitative variables. Comparison of categorical variables was performed using the Chi-square test. Correlation between nonparametric data was analysed by Spearman's correlation analysis. The level of statistical significance was set at $P < .05$.

3 | RESULTS

Mean age of the patients was 51.3 ± 12.7 years and the male to female ratio was 34:28. Mean BMI was 28.6 ± 5.2; among the 62 patients, 23 were overweight and 26 were obese. In total, 3/62 patients had diabetes mellitus, 15/62 had hypertension, and 2/62 were smokers. Among the patients, 90.3% (n = 56/62) were light workers. Among the 22 partial nephrectomies, 17 (77.3%) were performed via an open approach and 5 (22.7%) were performed laparoscopically. All 40 donor nephrectomies were performed laparoscopically, of which 36/40 (90%) were hand assisted. Most of the nephrectomies were performed on the left side (52/62). Mean tumor diameter was 35.8 ± 16.7 mm (n = 22).

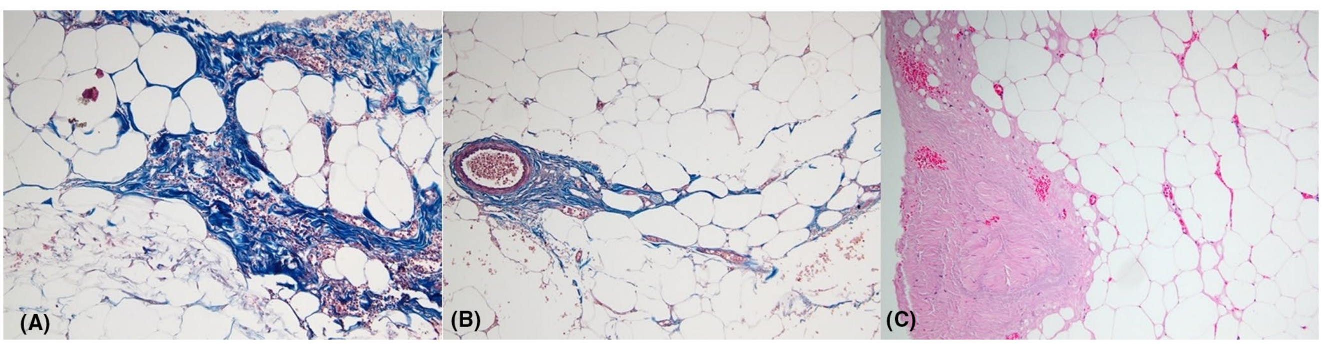

FIGURE 1 Cases showing increased fibrous tissue in the septae surrounding fat lobules (A), around the blood vessels (B) and in the Gerota fascia (C). Spicular infiltration of collagen into the fat lobules can be noted ((A) Masson's trichrome stain × 200; (B) Masson's trichrome stain × 100; (C) H-E stain × 100)

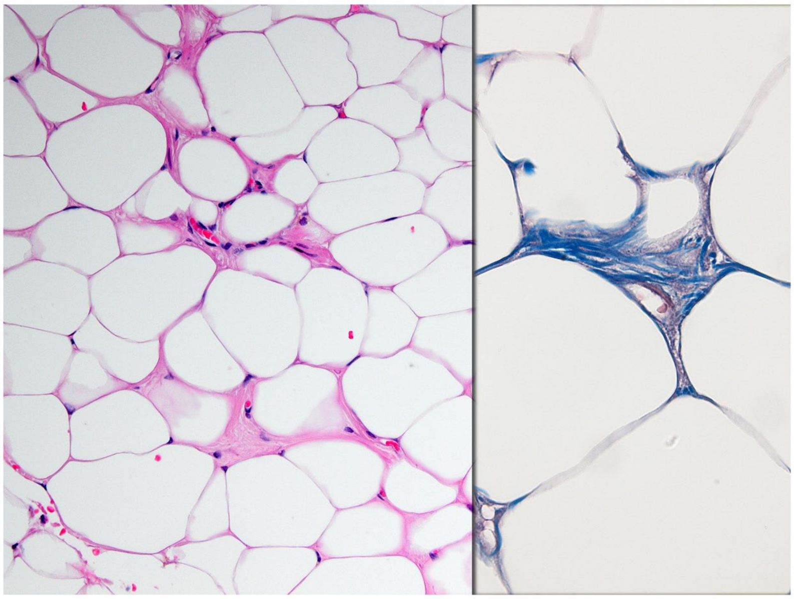

FIGURE 2 Intercellular collagen deposition was noted in some cases expanding the distance between individual adipocytes (Left: H-E stain × 100; Right: Masson's trichrome stain × 400)

The distribution of cases according to dissection complexity was as follows: easy: n = 27 (43.5%); moderate: n = 20 (32.3%); difficult: n = 15 (24.2%). Mean perirenal fat dissection time was 15.0 ± 13.5 minutes. Mean dissection time in the cases with easy, moderate, and difficult dissection complexity was 5.6 ± 2.9, 12.7 ± 2.1, and 35.1 ± 13.0 minutes, respectively. Dissection complexity classification (as easy, moderate and hard) was in correlation with the time required for the dissection ($P < .05$).

There was not a significant difference in perirenal fat dissection complexity between the male and female patients ($P = .074$). Similarly, correlations between weight, height, and BMI were not significant. Moreover, there was not a correlation between perirenal fat dissection complexity, and surgical side, the presence of diabetes mellitus, the presence of hypertension, smoking status, or occupational status ($P > .05$).

The was a significant difference in perirenal fat dissection complexity between open and laparoscopic nephrectomies ($P < .05$); most of the difficult dissection complexity cases underwent open surgery. Subcutaneous fat thickness measured intraoperatively did not differ according to dissection complexity ($P = .87$); however, intraoperative measurement of perirenal fat thickness and dissection complexity were significantly correlated, such that median perirenal fat thickness was lowest in the cases with easy dissection complexity (median: 10, 4-20) group and highest in those with difficult dissection complexity (median: 17, 10-28, $P < .05$).

Radiological findings showed that there was a significant relation between perirenal fat depth and perirenal fat dissection complexity, with a higher difference was greatest in the difficult dissection complexity patients ($P < .05$); however, HU for the perirenal field and subcutaneous fat measured via CT showed that there was not a significant difference according to dissection complexity ($P = .88$ and $P = .52$, respectively). The radiologically measured perirenal fat depth and intraoperative measurement of perirenal fat thickness were significantly correlated ($r = 0.363$, $P = .005$).

Perinephric fat exhibited evidence of histological fibrosis more commonly in the patients with severe APF (Table 1). All 4 parameters that we explored for fibrosis were higher in the patients with difficult dissection complexity. The median thickness of Gerota's fascia at its thickest part was 251 μm (range: 80-716 μm) in the patients with easy dissection complexity, vs 196 μm (range: 67.6-652 μm) and 384.5 μm (range: 151-910.4 μm) in those with moderate and difficult dissection complexity, respectively ($P = .006$). In all, 8 (34.8%) of the 23 patients with easy dissection complexity, 5 (29.4%) of the 17 with moderate dissection complexity, and 12 (80%) of the 15 with difficult dissection complexity had perivascular fibrosis ($P = .007$). Intercellular collagen accumulation was observed in 8.7% (2/23) of the patients with easy dissection complexity, 11.8% (2/17) of those with moderate dissection complexity, and 80% (12/15) of those with difficult dissection complexity ($P = .000$).

Spicules or bands of collagen radiating from the outer fascia, interlobular septae, and perivascular fibrous tissue were more common in the patients with APF (22%, 47%, 87% in the easy, moderate, and difficult dissection complexity patients, respectively, $P = .000$). There were not any significant differences in inflammation, or mean and maximum adipocyte diameter according to perirenal fat dissection complexity. Fat tissue in the severe APF patients contained a higher number of blood vessels with wall thickness > 100 μm ($P = .039$). There was not a significant difference in small capillary density according to perirenal fat dissection complexity ($P > .05$).

4 | DISCUSSION

APF is a clinical phenomenon without a direct effect on patients, yet for surgeons it complicates dissection and release of the kidney.[1,9] Dissection of perirenal fat is an important component of partial nephrectomy and donor nephrectomy. APF can cause excessive hemorrhaging during surgery, trauma to the renal capsule,

TABLE 1 Analysis of histological findings

Variables	Easy dissection complexity group (n = 23)	Moderate dissection complexity group (n = 17)	Difficult dissection complexity group (n = 15)	*P* value
Presence of inflammation, n (%)	2 (8.7%)	3 (17.6%)	4 (26.7%)	.344
Presence of perivascular fibrosis, n (%)	8 (34.8%)	5 (29.4%)	12 (80%)	.007
Capillary density (per unit area)	20 (10-40)	17 (12-33)	15 (10-50)	.641
Presence of brown fat, n (%)	6 (26.1%)	6 (35.3%)	1 (6.7%)	.158
The average adipocyte diameter, μm (range)	101 (56.5-150)	84.8 (62-153)	109 (72-203)	.130
Maximum adipocyte diameter, μm (mean ± SD)	146.4 ± 31.5	139.1 ± 30.2	154.7 ± 17.0	.299
Number of vessels with thick walls[a] (<3, 4-5, ≥6)	<3:7/23 (30.4%) 4-5:15/23 (65.2%) ≥6:1/23 (4.3%)	<3:0/17 (0%) 4-5:16/17 (94.1%) ≥6:1/17 (5.9%)	<3:1/15 (6.7%) 4-5:12/15 (80%) ≥6:2/15 (13.3%)	.039
Wall of the thickest vessel, μm (range)	60 (22-862)	51 (21.4-128)	53 (24.3-149.2)	.913
Exterior fascia thickness[b] μm (range)	251 (80-716)	196 (67.6-652)	384.5 (151-910.4)	.006
Presence of intercellular collagen, n (%)	2 (8.7%)	2 (11.8%)	12 (80%)	.000
Presence of spiculer fibrosis and/or bands of collagen, n (%)	5 (22%)	8 (47%)	13 (87%)	.000

[a]Thickness >100 μm.
[b]Measurements at the thickest point.

iatrogenic vascular injury, and prolongation of operative time.[1,8,10] Hemorrhaging from fatty tissue and vascular injury can complicate endourological manipulations. During laparoscopic and robot-assisted partial nephrectomy APF impedes kidney dissection. Furthermore, prolonged surgery time and renal capsular trauma can interfere with the renal transplantation process. Thusly, APF is a challenging phenomenon, both for open and endoscopic procedures. In addition to the radiological features, the present study focused on the pathological aspects of APF.

In the most recent studies APF was qualified as present or absent; only Narita et al[11-13] classified cases as non-APF, APF, and severe APF, as in the present study. We acknowledge that APF differs in severity from patient to patient. Dissection in some patients is sometimes so difficult that decapsulation occurs multiple times and occasionally complete removal of perirenal fat cannot be achieved; however, in some cases with APF dissection is managed with only minimal trauma and hemorrhaging. For the aforementioned reasons we find that it is appropriate to characterize APF as easy, moderate, and difficult.

The correlation between perirenal fat dissection complexity and dissection time in the present study confirms the pertinence of the dissection classification used. Zheng et al[14] classified APF according to dissection duration, as <10 minutes, 10-20 minutes, and >20 minutes. Their dissection time groupings were comparable to those in the present study, in which mean dissection time in the easy, moderate, difficult dissection complexity patients was 5.6 ± 2.9 minutes, 12.7 ± 2.1 minutes, and 35.1 ± 13.0 minutes, respectively.

Retroperitoneal fat thickness is reported to affect duration of surgery, as it did in the present study. In addition to male gender, Ito et al[5] showed that retroperitoneal fat thickness is positively correlated with surgical duration. In a prospective study of 100 robotic partial nephrectomies, it was reported that surgery time in patients with APF was longer than in those without APF.[13] A study that included 92 donor nephrectomies observed that APF and severe APF significantly prolonged surgery.[11] In the present study dissection time was significantly affected by APF; dissection time was longest in the patients with difficult dissection complexity. Total duration of surgery was not a focus of the present study because it can be deceptive. Total surgery time in donors during the transplantation process is affected by many factors; as such, we think that dissection time is a more reliable measurement for assessment of APF.

For the prediction of APF the image-based Mayo Adhesive Probability (MAP) score has been introduced.[6] This 5-point scoring system uses posterior perinephric fat thickness and perinephric fat stranding. The utility of the MAP score has been verified by several researchers.[9,15] Furthermore, many studies show that there is a clear association between APF and perirenal fat thickness.[8,11,12] Perirenal stranding observed in radiological images is not always an indicator of APF and stranding is a subjective parameter. To assess the clinical relevance of the perirenal field's radiological features, the perirenal field's HU was measured in the present study, and there was not a significant correlation between the perirenal field's HU and APF, yet perirenal fat depth differed significantly according to the complexity of perirenal fat dissection. Based on the present findings, we think use of perirenal fat depth measured via preoperative CT is sufficient for presurgical prediction of APF.

Obesity is thought to play a role in APF, yet there was not a significant correlation between APF and BMI in the present study. Correspondingly, 2 other studies did not note an association between BMI and APF; however, others have observed a marked association.[1,8,12,15,16] Some studies considered waist circumference a predictor of APF.[8] The present study analysed subcutaneous fat thickness as an indicator of internal fat burden, which is assumed to be a more objective parameter than waist circumference, but there was not a significant association between subcutaneous fat thickness and APF.

In addition to a high BMI, many other factors are associated with APF. Khene et al[1] assessed APF in 202 patients that underwent robot-assisted partial nephrectomy and reported that male gender, old age, a high BMI, smoking, and hypertension are risk factors for APF. Similarly, Kawamura et al[15] reported the same risk factors for APF. Kocher et al[12] noted a significant association between APF and increased age and male gender. In the present study, there was not a correlation between APF and any of the aforementioned factors. The donor population in the present study might account for these differences, as the renal donors were for the most part fit and healthy nonsmokers.

Radiologically measured posterior fat thickness is a predictor of APF.[11,12] Additionally, a prospective study that included 125 patients reported that lateral fat thickness was greater in patients with APF.[8] Moreover, increased posterior fat thickness, visceral fat area, and perinephric fat area are reported to be risk factors for APF.[11,16] In the present study, perirenal fat thickness and perirenal fat depth measured via CT differed significantly according to perirenal fat dissection complexity. In the present study measurement of actual perirenal fat thickness was performed in order to detect the thickest part of the fatty tissue and perirenal fat depth was measured in order to use a more standardized measure. HU measurements of the perirenal field and subcutaneous fat via CT in the present study showed no significant difference according to dissection complexity. Histopathological findings supported this finding, no difference was observed in small capillary density according to dissection complexity. Bylund et al[8,16] reported a similar finding; however, Dariane et al indicated the density of fat was an independent predictor of APF.

Histopathlogical analysis in the present study show increased fibrous tissue in the perirenal fat of APF patients, in contrast to the findings reported by Dariane et al.[8] This seems to be the major underlying factor that can lead to surgical difficulty. Thicker Gerota's fascia and more collagen around blood vessels and in between fat cells focally were observed in the present study's severe APF patients, but what caused this variance is not clear. Metabolic disorders, such as obesity and diabetes, and collagen vascular diseases or other systemic problems might have led to an increase in collagen deposition in the tissues; however, the present study's APF and non-APF patients did not differ in these respects. Additionally, there was not a significant difference in mean fat cell diameter, indicating that obese or overweight patients have not accumulated on one arm of the study set. Furthermore, we could not attribute to an inflammatory process for the explanation of fibrosis as both groups of patients have only a very few mononuclear cells over and there. In fact, we think that the amount of fibrous tissue might have been innate and related to the individual's features. The present finding that the APF patients had a higher number of blood vessels with wall thickness >100 μm might be considered supportive of this hypothesis.

The primary limitation of the present prospective study is the small number of patients. As living donor nephrectomy is performed less frequently, the study also included partial nephrectomies. Pathological examination might have been more objective if it had been conducted in donors only.

5 | CONCLUSIONS

APF is a challenge for kidney surgeons. Difficult perirenal fat dissection prolongs surgical duration and can lead to complications. Predicting APF preoperatively helps in choosing which patients qualify for minimally invasive surgery. Perirenal fat thickness measured via pre-operative CT can predict APF. There is a positive correlation between perirenal fat thickness and perirenal fat dissection complexity. It is commonly believed that male gender, high weight, high BMI, presence of diabetes, and heavy workers may have APF. However, this study demostrated that all of the aforementioned factors have no effect on the development of adherent perirenal fat. This study showed that the APF is mainly caused by fibrotic processes and only radiological findings can predict the complexity of dissection preoperatively. Thus, patients' demographics may be misleading for the prediction of APF preoperatively. Surgeons performing minimally invasive renal surgery should rely on radiological findings for the prediction of APF and selection of the surgical approach. In complex surgeries with high possibility of APF, open surgery may offer an easier surgery.

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DISCLOSURES

Authors have nothing to declare.

AUTHOR CONTRIBUTIONS

Research conception and design: EC, FI, MK, DEB. Data acquisition: EC, FI, FTA, MSY, MK, DEB. Statistical analysis: EC, FI, DEB. Data analysis and interpretation: EC, DEB. Drafting of the manuscript: EC, DEB, CYB. Critical revision of the manuscript: EC, FTA, MSY, DEB, CYB. Obtaining funding: N/A. Administrative, technical, or material support: EC. Supervision: DEB, CYB. Approval of the final manuscript: EC, FI, FTA, MSY, DEB, CYB.

DATA AVAILABILITY STATEMENT

Author elects to not share data.

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