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Risk Factors Influencing the Thickness and Stranding of Perinephric Fat of Mayo Adhesive Probability Score in Minimally Invasive Nephrectomy

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Background: Mayo adhesive probability (MAP) score, an accurate and reliable predictor of adherent perinephric fat (APF), consists of posterior perinephric fat thickness and perinephric fat stranding. The present study aimed to identify the potential clinical characteristics associated with these 2 variables to further our understanding of APF.





Material/Methods: Clinical data of 346 patients subjected to minimally invasive nephrectomy was collected within our prospectively maintained database, between January 2015 and December 2016. Radiological data was assessed by 2 readers in an independent blinded – to each other and APF patient status – fashion. Ordinal logistic regression analyses were performed to evaluate risk factors of posterior perinephric fat thickness and perinephric fat stranding.

Results: On multivariate analysis, posterior perinephric fat thickness was associated with older age ($\beta=1.05$ [range, 1.03–1.07], $P<0.01$); male gender ($\beta=6.06$ [3.18–11.54], $P<0.01$), and higher body mass index (BMI) ($\beta=1.31$ [1.21–1.41], $P<0.01$). Perinephric fat stranding was associated with older age ($\beta=1.05$ [1.02–1.07], $P<0.01$), male gender ($\beta=3.64$ [2.09–6.34], $P<0.01$) and history of diabetes ($\beta=2.09$ [1.24–3.52], $P<0.01$). MAP score was associated with older age ($\beta=1.05$ [1.03–1.07], $P<0.01$), male gender ($\beta=5.07$ [2.96–8.71], $P<0.01$), higher BMI ($\beta=1.14$ [1.07–1.21], $P<0.01$), history of diabetes ($\beta=1.72$ [1.06–2.78], $P=0.03$) and alcoholism ($\beta=1.88$ [1.10–3.20], $P=0.02$).

Conclusions: The current study highlights that different risk factors influence the posterior perinephric fat thickness and perinephric fat stranding. Posterior perinephric fat thickness was correlated with age, gender, and BMI, while perinephric fat stranding was associated with age, gender, and history of diabetes.

MeSH Keywords: **Carcinoma, Renal Cell • Intra-Abdominal Fat • Nephrectomy**

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Background

Partial nephrectomy is recommended by the current guidelines as the standard treatment for patients with localized renal tumors of <4 cm [1,2]. Furthermore, partial nephrectomy is also recommended for T1b tumors when technically feasible, as it has been shown to have better preservation of kidney function, equivalent oncological control and acceptable perioperative outcomes [2]. Adherent perinephric fat (APF), characterized as inflammatory adipose tissue sticking to the kidneys, is challenging to surgeons performing partial nephrectomy because it complicates the identification and exposure of the renal tumors. A growing body of evidence has demonstrated that APF is associated with adverse perioperative outcomes in partial nephrectomy [3–6].

In order to predict the presence of APF, Davidiuk et al. [7] developed a radiological algorithm that quantified the 2 most predictive factors, posterior perinephric fat thickness and perinephric fat stranding, and then summed the individual scores to create a total score, called the Mayo adhesive probability (MAP) score. MAP score has progressively become acceptable in the urologist community owing to its ability to predict the presence of APF and perioperative outcomes. Several studies showed that MAP score was the strongest predictor of APF during partial nephrectomy [3–6,8]. MAP score representing APF was also found to be associated with longer dissection phase during robotic assisted partial nephrectomy [9]. However, scant data exist with regard to the causative clinical characteristics of posterior perinephric fat thickness and perinephric fat stranding of the MAP score. The purpose of this study was to investigate the potential risk factors associated with the 2 aforementioned variables and we sought to elucidate the pathogenesis of APF.

Material and Methods

Study population

This study was approved by the Ethics Committee of PLA General Hospital (approval dated October 15, 2014) and patients' informed consent were obtained. We retrospectively collected the data of patients who underwent minimally invasive nephrectomy for renal tumors at our institution from January 2015 to December 2016. Minimally invasive nephrectomy in our study included laparoscopic partial nephrectomy (LPN) or robotic partial nephrectomy (RPN). LPN was performed transperitoneally or retroperitoneally, and all RPN procedures were performed in a transperitoneal fashion. Briefly, we first opened the Gerota's fascia to dissect the perinephric fat and expose the tumor. Then, we clamped the hilar artery to resect the tumor and close the wound. Patients with history of abdominal

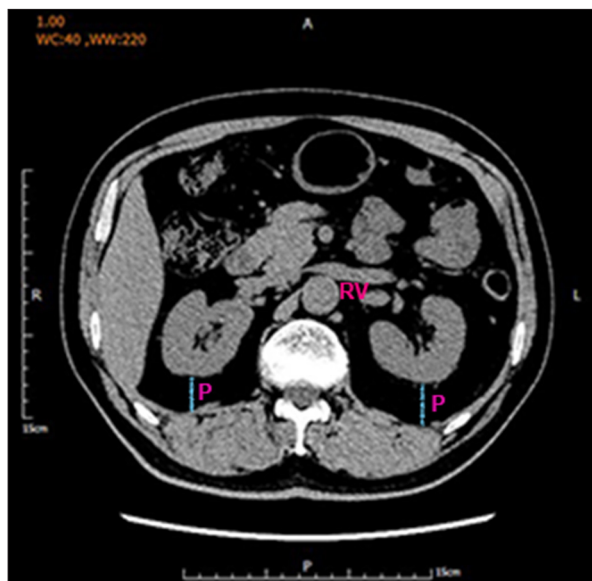


Figure 1. Method of measuring of posterior perinephric fat thickness at the level of the renal vein. P – posterior; RV – renal vein.

surgeries were excluded. A total of 346 patients with complete clinical and radiological data were enrolled. Patients' baseline characteristics were as follows: age, gender, body mass index (BMI), history of diabetes, hypertension, coronary heart disease, dyslipidemia, history of smoking and alcoholism. Tumor characteristics included tumor size, side location, and histology type. We calculated the MAP score as described by Davidiuk et al. [7]. Briefly, the direct length from posterior renal capsule to the posterior abdominal wall at the level of renal vein was scored using computed tomography (CT) or T1-weighted magnetic resonance imaging (MRI) (<1.0 cm=0 points, 1.0–1.9 cm=1 points, ≥2.0 cm=2 points) (Figure 1). The stranding was measured using CT or T2-weighted fat suppress MRI (none=0 points, mild/moderate stranding=2 points, severe stranding=3 points) (Figure 2). The individual scores were summed up to create the MAP score ranging from 0 to 5.

Statistical analysis

For continuous variables, the sample median (first quartile, third quartile) was listed. Categorical variables were reported as proportions with number of patients (percentage). Ordinal logistic regression analysis was used to compare both continuous and categorical variables and the link function was Logit. $P>0.05$ was required in the test of parallel lines in ordinal logistic regression. The independent variables with a score of 0 were taken as reference. P value <0.05 was considered to be statistically significant. All of the analyses were performed with the statistical software packages R (<http://www.R-project.org>, The R Foundation) and EmpowerStats (<http://www.empowerstats.com>, X&Y Solution, Inc., Boston, MA, USA).



Figure 2. Grading of perinephric fat stranding. **(A)** None: 0 points. The fat around the kidney demonstrates no stranding. The tissue surrounding the kidney is completely black on this T1-weighted MRI image. **(B)** Mild: 2 points. The fat around the kidney presents some slight stranding but no thick bars representing inflammation. **(C)** Severe stranding: 3 points. There is severe stranding with thick bars around the kidney.

Results

Patient characteristics

Baseline characteristics of the cohort are summarized in Table 1. A total of 346 patients were included for analysis. The median age was 52 years (interquartile range [IQR]: 45–60 years), the median BMI was 25.9 kg/m² (IQR: 23.4 to –8.0 kg/m²) and most patients were male gender (75.1%). The median size of tumors was 2.5 cm (IQR: 2.0–3.3 cm).

Predictors of posterior perinephric fat thickness and perinephric fat stranding of MAP score

Risk factors of posterior perinephric fat thickness are shown in Table 2. On univariate analysis, posterior perinephric fat thickness was significantly associated with older age ($P<0.01$), male gender ($P<0.01$), higher BMI ($P<0.01$), history of diabetes ($P<0.01$), hypertension ($P<0.01$), dyslipidemia ($P=0.02$), and alcoholism ($P<0.01$). On multivariable analysis, posterior perinephric fat thickness was significantly associated with older age (odds ratio [OR]=1.05 [1.03–1.07], $P<0.01$), male gender (odds ratio=6.06 [3.18–11.54], $P<0.01$), and higher BMI (OR=1.31 [1.21–1.41], $P<0.01$).

As displayed in Table 3, perinephric fat stranding was significantly associated with older age ($P<0.01$), male gender ($P<0.01$), higher BMI ($P=0.03$), history of diabetes ($P<0.01$), hypertension ($P<0.01$), smoking ($P<0.01$), and alcoholism ($P<0.01$). On multivariable analysis, the potential risk factors included older age (OR=1.05 [1.02–1.07], $P<0.01$), male gender (OR=3.64 [2.09–6.34], $P<0.01$), and history of diabetes (OR=2.09 [1.24–3.52], $P<0.01$).

Table 4 summarized the potential risk factors associated with the MAP score. On univariate analysis, it was significantly associated with older age ($P<0.01$), male gender ($P<0.01$), higher BMI ($P<0.01$), history of diabetes ($P<0.01$), hypertension ($P<0.01$), smoking ($P=0.02$), and alcoholism ($P<0.01$). On multivariable analysis, MAP score was associated with older age (OR=1.05 [1.03–1.07], $P<0.01$), male gender (OR=5.07 [2.96–8.71], $P<0.01$), higher BMI (OR=1.14 [1.07–1.21], $P<0.01$), history of diabetes (OR=1.72 [1.06–2.78], $P=0.03$), and alcoholism (OR=1.88 [1.10–3.20], $P=0.02$).

Discussion

Partial nephrectomy is increasingly used in the management of small renal masses when technically feasible. Urologists used to classify the surgical complexity based on tumor-specific factors such as size and location [10–12]. In addition to tumor-specific factors, however, patient-specific factors such as APF should also be considered. In the presence of APF, surgeons feel frustrated when mobilizing the kidney and exposing the tumor during partial nephrectomy even if the tumor is small and exophytic. Bylund et al. [13] noted that operating time of patients with “sticky fat” was much longer than that of controls. Kawamura et al. [4] demonstrated that APF was associated with greater estimated blood loss compared with the non-APF group. In another study, Macleod et al. [14] indicated that in addition to the stickiness of perinephric fat, the thickness was also an independent predictor of increased operative time and estimated blood loss. The aforementioned results suggest that preoperative evaluation of APF could help decision making on patient selection and thereby improve outcomes.

MAP score is a quantitative method to predict the probability of encountering APF [7]. The authors established a model

Table 1. Baseline characteristics (n=346).

Variables	Summary (n=346)	
Age (years), median (IQR)	52	(45–60)
Female	86	(24.9)
Male	260	(75.1)
BMI (kg/m ²), median (IQR)	25.9	(23.4–28.0)
No. diabetes (%)	76	(22.0)
No. hypertension (%)	121	(35.0)
No. coronary heart disease (%)	18	(5.2)
No. dyslipidemia (%)	235	(67.9)
No. smoking (%)	127	(36.7)
No. alcoholism (%)	144	(41.6)
Tumor side (%)		
Right	172	(49.7)
Left	174	(50.3)
Tumor size (cm), median (IQR)	2.5	(2.0–3.3)
Histological subtype		
Clear cell carcinoma	304	(87.9)
Others	42	(12.1)
Posterior perinephric fat thickness score		
0	143	(41.3)
1	145	(41.9)
2	58	(16.8)
Perinephric fat stranding score		
0	108	(31.2)
2	143	(41.3)
3	95	(27.5)
MAP score		
0	64	(18.5)
1	38	(11.0)
2	60	(17.3)
3	98	(28.3)
4	50	(14.5)
5	36	(10.4)

For continuous variables, data is listed as the sample median (first quartile, third quartile). For qualitative variables, data is shown as number (percentage). IQR – inter quartile range; MAP – Mayo adhesive probability.

with the highest AUC of 0.89 including posterior perinephric fat thickness and posterior perinephric stranding. A recently comprehensive review summarized the publications regarding the factors associated with APF, and the results showed that the MAP score is considered acceptable as a reliable indicator of APF [15]. However, the MAP score merely demonstrated thicker and upgraded stranding of perinephric fat, and thus it is necessary to clarify what causes these changes. A number of studies reported that age, gender, BMI, waist circumference, and history of hypertension were risk factors of APF, however, some variables were not comparable among studies due to potential bias of subjective judgements of APF by surgeons [3,6]. Herein, our study directly analyzed the possible risk factors of thickness and stranding of MAP score to provide insight into the understanding of APF.

Obesity is a worldwide health concern and it is a predominant contributor to the development of several health concerns including diabetes, hypertension, coronary heart disease, and certain cancers [16,17]. In the context of chronic caloric excess, subcutaneous adipose tissue initially expands through hyperplasia with little immune cell infiltration and few dead adipocytes. When hyperplastic subcutaneous adipose tissue becomes unable to compensate for the nutrient exposure, visceral adipose tissue will expand in an unhealthy way, which is referred to as hypertrophy [18]. Hypertrophic adipocytes are susceptible to cell death, leading to a systemic, chronic and low-grade inflammation state, referred to as metaflammation (metabolically triggered inflammation) [19]. At the same time, adipocyte hypertrophy will induce local adipose tissue hypoxia, which accelerates adipose tissue fibrosis and induces angiogenesis [20]. Recently, Pan et al. [21] identified that adipocyte-secreted exosomes could transmit the signal of nutrient overload to the resident macrophages and inhibit anti-inflammatory M2 macrophage polarization to promote adipose tissue inflammation.

Several studies showed that both older age and male gender were risk factors of APF using multivariate analysis [5,6]. However, Kawamura et al. demonstrated that older age was not significantly associated with APF [4], and in another study, male gender did not predict APF [8]. Our study confirmed that both variables were contributors to posterior perinephric fat thickness and stranding in a larger cohort, while the β value of male gender was higher than that of older age. Similar to metaflammation, older age has been linked to a progressively proinflammatory status called inflamm-aging [22,23]. Age also contributes to adipose tissue redistribution, from subcutaneous adipose tissue to visceral adipose tissue [24]. This would lead to a significant prevalence of APF in older patients. Published literature also has indicated that males are susceptible to develop APF. According to Kawamura et al. [4] and Davidiuk et al. [7], only 1 of 40 patients and 3 of 30 patients in APF group were

Table 2. Variables association with the posterior perinephric fat thickness.

Variables	Univariate			Multivariate		
	p Value	OR	95% CI	p Value	OR	95% CI
Age	<0.01	1.03	1.01–1.05	<0.01	1.05	1.03–1.07
Gender (female=0)	<0.01	5.45	3.23–9.21	<0.01	6.06	3.18–11.54
BMI	<0.01	1.30	1.22–1.40	<0.01	1.31	1.21–1.41
Diabetes (no=0)	<0.01	1.90	1.17–3.06	0.75	1.09	0.64–1.86
Hypertension (no=0)	<0.01	1.89	1.24–2.86	0.90	0.97	0.61–1.56
Coronary heart disease (no=0)	0.66	1.22	0.50–3.01			
Dyslipidemia (no=0)	0.02	1.65	1.07–2.55	0.25	1.33	0.82–2.14
Smoking (no=0)	0.15	1.35	0.90–2.03			
Alcoholism (no=0)	<0.01	2.30	1.53–3.46	0.45	1.21	0.74–1.98

OR – odds ratio; CI – confidence interval; 0 was taken as reference; BMI – body mass index. Ordinal logistic regression analysis was feasible according to the test of parallel lines and $p < 0.05$ was considered as statistically significant.

Table 3. Variables association with the perinephric fat stranding.

Variables	Univariate			Multivariate		
	p Value	OR	95% CI	p Value	OR	95% CI
Age	<0.01	1.04	1.02–1.06	<0.01	1.05	1.02–1.07
Gender (female=0)	<0.01	3.86	2.40–6.21	<0.01	3.64	2.09–6.34
BMI	0.03	1.07	1.01–1.13	0.40	1.03	0.97–1.09
Diabetes (no=0)	<0.01	2.94	1.79–4.83	<0.01	2.09	1.24–3.52
Hypertension (no=0)	<0.01	1.91	1.25–2.90	0.53	1.16	0.73–1.84
Coronary heart disease (no=0)	0.15	1.85	0.80–4.28			
Dyslipidemia (no=0)	0.64	1.11	0.72–1.69			
Smoking (no=0)	<0.01	1.72	1.14–2.58	0.39	0.78	0.45–1.37
Alcoholism (no=0)	<0.01	2.23	1.49–3.35	0.09	1.65	0.93–2.90

OR – odds ratio; CI – confidence interval; 0 was taken as reference; BMI – body mass index. Ordinal logistic regression analysis was feasible according to the test of parallel lines and $p < 0.05$ was considered as statistically significant.

female, respectively. Hagiwara et al. [25] reported that twice as many males had more visceral adipose tissue ($>100 \text{ cm}^2$) than did females, which was in concordance with Eisner et al. [26]. Thus, it is reasonable that older age and male gender are risk factors of APF by increasing the amount (thickness) and quality (stickiness) of perinephric fat.

Davidiuk et al. [7] showed that obese individuals (BMI $>30 \text{ kg/m}^2$) had a 15-fold risk of getting APF compared with those with normal weight (BMI $<25 \text{ kg/m}^2$). In a larger cohort of patients, higher BMI was also an independent predictive factor of the presence of APF [3]. Nevertheless, other studies also reported there was no significant association between BMI

and APF [4,5,27]. In our study, BMI was significantly associated with the thickness of perinephric fat (OR=1.31, $P < 0.01$) and not associated with the fat stranding, which might partly explain the controversial results among the published literatures.

Diabetes has been reported as a risk factor of MAP score [27]. More specifically, our data showed that it was significantly associated with perinephric fat stranding (OR=2.09, $P < 0.01$) but not posterior perinephric fat thickness. Obesity causes both insulin resistance and adipose tissue inflammation. While insulin resistance and adipose tissue inflammation are also associated, the direction of causality remains controversial [18]. In obesity, adipose tissue homeostasis is perturbed and adipocytes

Table 4. Variables association with MAP score.

Variables	Univariate			Multivariate		
	p Value	OR	95% CI	p Value	OR	95% CI
Age	<0.01	1.04	1.03–1.06	<0.01	1.05	1.03–1.07
Gender (female=0)	<0.01	5.30	3.35–8.38	<0.01	5.07	2.96–8.71
BMI	<0.01	1.18	1.11–1.25	<0.01	1.14	1.07–1.21
Diabetes (no=0)	<0.01	2.62	1.65–4.17	0.03	1.72	1.06–2.78
Hypertension (no=0)	<0.01	1.95	1.31–2.91	0.64	1.11	0.72–1.71
Coronary heart disease (no=0)	0.18	1.73	0.77–3.89			
Dyslipidemia (no=0)	0.09	1.41	0.94–2.12			
Smoking (no=0)	0.02	1.61	1.09–2.37	0.07	0.61	0.36–1.04
Alcoholism (no=0)	<0.01	2.51	1.70–3.70	0.02	1.88	1.10–3.20

OR – odds ratio; CI – confidence interval; 0 was taken as reference; BMI – body mass index. Ordinal logistic regression analysis was feasible according to the test of parallel lines and $p < 0.05$ was considered as statistically significant.

secret potent pro-inflammatory adipokines to recruit macrophages. Chronic inflammation and immune cell infiltration in the adipose tissue causes insulin resistance and subsequent diabetes [28]. Ali et al. [29] speculated that insulin resistance redistributed the adipose tissue and visceral fat increased it further. However, the exact impact of insulin resistance on adipose tissue inflammation remains unclear. The specific mechanism still requires further research.

To our knowledge, our study was the first to report alcohol habits correlated with the MAP score (OR=1.88, $P=0.02$). In a systematic review on the aspects of diet affecting visceral adipose tissue which summarized 3 cross-sectional studies, concluded that there was a positive association between alcohol consumption and visceral adipose tissue [30]. Nevertheless, in our ordinal logistic regression model, the alcohol habit was not associated with posterior perinephric fat thickness or perinephric fat stranding. We hypothesize that alcohol habit usually accompanies an unhealthy diet pattern and eventually leads to metabolic dysfunction. Specific knowledge is limited, and more study is needed in this area.

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Our study had several limitations. First, this was a retrospective study and the patient selection could have generated unanticipated biases. Second, the study focused on the impact of patient-specific factors on the APF and we noticed that stranding was more severe adjacent to the tumor in some cases. We will make conduct further research on the relationship between the tumor and the surrounding fat inflammation in future.

Conclusions

Posterior perinephric fat thickness was associated with male gender, older age, and higher BMI; perinephric fat stranding was associated with older age, male gender, and history of diabetes. The MAP score was associated with older age, male gender, higher BMI, history of diabetes, and alcoholism.

Conflict of interest

We have no potential conflict of interest.

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