ORIGINAL RESEARCH

The Prognostic Value of Body Fat Components in Metastasis Renal Cell Carcinoma Patients Treated with TKIs

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Purpose: To assess the association between body fat components and survival status and tumor response for metastatic renal cell carcinoma (mRCC) patients treated with tyrosine kinase inhibitors (TKIs).

Patients and Methods: Patients with pathologically diagnosed and radiologically indicated mRCC were enrolled into the retrospective study. Three body fat components: total fat accumulation (TFA), visceral fat accumulation (VFA) and subcutaneous fat accumulation (SFA) were measured using standard CT scans. The clinical outcomes included progression-free survival (PFS), overall survival (OS), and tumor response rates. Univariate analysis and multivariate Cox proportion hazard regression models were used to find associated parameters and to calculate the adjusted hazard ratio (HR).

Results: A total of 146 patients were enrolled and the average age of patients was 56.5 years old. According to the univariate analysis, patients with an increased SFA and TFA had a longer PFS and OS. A similar phenomenon was observed among patients with ≥2 increasing body fat components about PFS and OS. As for multivariate analysis, SFA change (p=0.014) or the number of increasing body fat components (p=0.040) were independent indicators to predict PFS. In addition, SFA change (p=0.022) or the number of increasing body fat components (p=0.008) could independently predict OS. Moreover, a better disease control rate (p=0.028) was founded in patients with ≥2 increasing components. In the subgroup of patients with ≥2 metastasis sites, improved OS (p=0.017) and PFS (p=0.027) were found compared to those with <2 increasing components. Further multivariate analysis identified the number of increasing body fat components was an independent factor in predicting PFS (p=0.018) and OS (p=0.029).

Conclusion: Body fat accumulation, such as high SFA or TFA at progression, could improve the survival of patients with mRCC treated with TKIs, especially patients with higher tumor burden. It should be considered as an important parameter to predict the survival status of patients with mRCC.

Keywords: tyrosine kinase inhibitor, body fat component, prognosis

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Introduction

Obesity has become a major public health problem of epidemic proportions and there is much evidence that obesity is a modifiable risk factor for cancer.[1] About 20% of cancers are associated with excess weight.[2] Moreover, obesity is confirmed to be associated with treatment-related adverse effects, quality of life, risk of cancer recurrence and mortality in several cancers.[3–5] Over the last decade, obesity has

been shown to be associated with increased renal cell carcinoma (RCC) risk and the prognosis of patients.[5–7]

Body fat accumulation, as one of the important parameters of obesity, which could be measured from a routine computed tomography (CT) image, has recently shown its contribution to the survival of RCC patients.[8–10] Several studies have suggested that visceral fat accumulation (VFA) be involved in the prognostic risk stratification.[8–10] However, controversial results were reported from studies of different disease stages of RCC.[8,11–13] Ladoire et al firstly reported that visceral obesity had significant prognostic value in patients with advanced RCC treated with targeted therapy.[11] However, some studies reported that overweight patients with diagnosed RCC might have a favorable prognosis compared to those with normal or underweight;[14,15] and another European group also came to an opposite conclusion–more than average adipose tissue was associated with longer survival.[12]

As a traditional measure of obesity, body mass index (BMI) was regarded by some studies to measure excess weight instead of excess fat. However, BMI could not show the differences among body fat, muscle and bone mass. In addition, BMI also fails to display the distribution of fat among individuals. Given these limitations, some studies that used BMI as a direct measurement of body fat might yield a more accurate estimate of the association between obesity and the risk of cancer.[10]

Until now, the roles of body composition, especially body fat components, in the progression and prognosis of RCC patients still are not conclusive. In view of these contradictory data, we conducted this retrospective study to evaluate the associations between body fat components and the survival status and tumor response of patients with metastatic RCC (mRCC) treated with tyrosine kinase inhibitors (TKIs).

Materials and Methods
Patients Assessment and Data Collection
This retrospective study enrolled mRCC patients who had been treated with tyrosine kinase inhibitors from January 2008 to November 2018 at our hospital. All subjects had been pathologically diagnosed with RCC and were radiographically indicated with metastasis lesion by CT, magnetic resonance imaging (MRI), radionuclide bone imaging, single-photon emission computed tomography (SPECT) or positron emission tomography/computed tomography (PET/CT). All patients were given TKIs, including sunitinib, sorafenib, and axitinib. Patients were followed up and given a safety examination everyone months and effect evaluation every 3 months by CT. The Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 was applied to assess the treatment efficacy.[16] This study was approved by the Ethics Committee of West China Hospital, Sichuan University and conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

The Measurement of Body Fat Components
The patients' baseline weight and height were collected when enrolled in our study. Body mass index (BMI) was calculated by the standard formula: $BMI=weight/height^2$. Body surface area (BSA) was calculated by Mosteller formula: $BSA=square$ root (weight*height/3600).[17] Quantitative radiological measures using CT scans have been reported as the gold standard method to assess fat accumulation.[18] Body fat components: total fat accumulation (TFA), VFA and subcutaneous fat accumulation (SFA) were measured at the level of the umbilicus using standard CT scans according to reported study previously.[19] After outlining the border of the abdominal muscular wall at the level of umbilicus manually on the CT image, the cross-sectional surface areas of the visceral fat and total fat were separately calculated by two radiologists using MMWP 4 Workstation CT software package (Siemens, Germany). An image display window width from −150 to −50 Hounsfield units was used to identify the region of fat.[20] Both body fat components at baseline and at progression were measured. The changes in different body fat components and their percentages were also calculated.

Clinical Outcomes
The primary outcomes of this study were overall survival (OS) and progression-free survival (PFS). OS was defined as the time from targeted agent administration to the date of death or last follow-up. PFS was defined as the time from targeted agent administration to the date of tumor progression, death or last contact. The second outcomes were tumor response rates, included complete response (CR) rate, partial response (PR) rate, stable disease (SD) rate, and progression of disease (PD) rate; objective response rate (ORR, =CR+PR) and disease control rate (DCR, =CR+PR+SD) were calculated.

Statistical Analyses
X-tile software was used to find the optimal cutoffs for all patients.[21] Survival curves of PFS and OS for patients in

different groups were plotted using the Kaplan–Meier method, and the Log rank test was used to compare the survival difference by categorized adiposity variables. And the generated prespecified multivariate regression models were performed with all covariates chosen on the basis of previous studies and theoretical considerations. To evaluate the prognostic value of investigated variables, the hazard ratio (HR) and 95% confidence interval (CI) were calculated using univariate and multivariate Cox analyses by SPSS 22.0. Characteristics that showed potential significance (p<0.05) in the univariate analyses were further evaluated using a multivariate Cox regression model. In all tests, p<0.05 were considered to indicate significance.

Results
Clinicopathological Characteristics
A total of 146 mRCC patients treated with TKIs were enrolled in this study. The average age of patients was 56.5 years old, and 70% of patients were older than 50 years old. The clinicopathological characteristics are shown in Table 1. What's more, 64(43.8%) patients had gained increasing TFA as tumor progressed. There were nearly half of the patients had higher VFA than before (Table 1, Figure 1 and Figure 2A). Moreover, 47.9% (70/146) patients had higher SFA at baseline and some of them had more than 10% increase of SFA (Table 1 and Figure 2B). The number of patients with TFA increasing was comparable with TFA decreasing; however, TFA had increased at a higher rate (Table 1 and Figure 2C).

The Association Between Body Fat Components and Treatment Efficacy
The tumor response rates of patients were analyzed and the results showed that only one patient achieved CR (0.7%), 19 patients achieved PR (13.0%), 55 patients kept SD (37.7%), and 71 patients appeared PD (48.6%). As shown in Table 2, we found that the PD rate was significantly different between patients with <2 increasing body fat components and ≥2 increasing components (p=0.010) and the latter had a better DCR (p=0.028). This suggested that patients with more body fat components increased could obtain better disease control.

Subsequently, we further analyzed the tumor efficacy in the subgroup of patients treated with sunitinib. For patients with ≥2 increasing parameters, 11 patients appeared PD (31.4%). Meanwhile, the DCR of this subgroup was 68.6% (24/35). As shown in Supplemental Table 1, a significant difference in PD was found between patients with <2

increasing components and those with ≥2 increasing components (58.1% vs 31.4%, p=0.019) and the latter also got a better DCR (44.4% vs 68.6%, p=0.028).

Survival Outcomes in All Patients
101 patients suffered tumor progression and 64 patients died during a median follow up of 36.0 months (30.893–41.107 months). The median PFS was 14 months (from 1 to 110 months) and the median OS was 50 months (from 2 to 122 months). According to the univariate analyses, some body fat variables were significantly associated with PFS and OS (Table 3). SFA change (HR: 0.569, 95% CI: 0.378–0.857, p=0.005), TFA change (HR: 0.612, 95% CI: 0.540–0.916, p=0.015) and the number of increasing body fat components (HR: 0.593, 95% CI: 0.423–0.833, p=0.003) were all positively correlated with tumor progression (Table 3 and Figure 3A). The correlation between OS and SFA change (HR: 0.534, 95% CI: 0.321–0.887, p=0.015), TFA change (HR: 0.539, 95% CI: 0.311–0.895, p=0.018) and the number of increasing body fat components (HR: 0.503, 95% CI: 0.332–0.761, p=0.001) was also found among all patients (Table 3 and Figure 3B).

Subsequently, due to the linear correlation between the number of increasing body fat components and SFA change or TFA change, two multivariate analysis was performed (one included SFA and TFA; another included number of increasing body fat components). Finally, multivariate analysis showed that patients with increasing SFA (p=0.023) or with BMI more than 25 Kg/m^2 (p=0.026) had longer PFS; and patients with increasing SFA (p=0.003) or with BMI more than 25 Kg/m^2 (p=0.023) also had longer OS (Table 4 and Figure 4). Moreover, the relationship between the number of increasing body fat components and PFS (HR: 0.620, 95% CI: 0.392–0.979, p=0.040) and OS (HR: 0.395, 95% CI: 0.200–0.781, p=0.008) were also found positive in multivariate analysis (Table 4).

Survival Outcomes in the Subgroup of Patients with More Than 2 Metastasis Sites
To investigate the correlation between body fat components and tumor burden, we did a subgroup analysis and further found that the number of increasing body fat components played a crucial role in predicting tumor progression (HR: 0.362, 95% CI: 0.147–0.893, p=0.027) and patient's survival (HR: 0.403, 95% CI: 0.192–0.849,

Table 1 The Baseline Characteristics of All Included Patients with mRCC (n=146)

	All Patients n (%)		All Patients n (%)		All Patients n (%)
Age		Resection of Metastasis		bSFA(cm^2)	
<50	43(29.5)	Yes	39(25.3)	<100	64(43.8)
≥50	103(70.5)	No	107(71.9)	≥100	82(56.2)
Gender		Metastasis		bVFA(cm^2)	
Male	105(71.9)	Lung	81(54.8)	<100	65(44.5)
Female	41(28.1)	Visceral (except lung)	8(5.5)	≥100	81(55.5)
ISUP		Bone	36(24.7)	pTFA(cm^2)	
<3	35(24.0)	Lymph node	17(11.6)	<220	68(46.6)
≥3	111(76.0)	Others	59(39.7)	≥220	78(53.4)
Histological Type		IMDC Grade		pSFA(cm^2)	
ccRCC	119(81.5)	Favorable	36(24.7)	<112	73(50.0)
Non-ccRCC	27(18.5)	Intermediate	76(52.1)	≥112	73(50.0)
ECOG score		High	34(23.3)	pVFA(cm^2)	
<2	105(71.9)	Type of first-line TKIs		<110	76(52.1)
≥2	41(28.1)	Sunitinib	98(67.1)	≥110	70(47.9)
T stage		Axitinib	40(27.4)	VFA change	
<3	81(55.5)	Sorafenib	8(5.5)	Increasing	64(43.8)
≥3	65(44.5)	BMI (kg/m^2)		Decreasing	82(56.2)
Nephrectomy		<23	65(44.5)	SFA change	
Yes	116(79.5)	23–25	32(21.9)	Increasing	70(47.9)
No	30(20.5)	>25	39(26.7)	Decreasing	76(52.1)
Interval from diagnosis to Metastasis		BSA (m^2)		TFA Change	
Metachronous	79(54.1)	<3	89(61.0)	Increasing	64(43.8)
Synchronous	67(45.9)	≥3	47(32.2)	Decreasing	82(56.2)
Number of Metastasis Sites		bTFA(cm^2)			
<2	83(56.8)	<212	69(47.3)		
≥2	63(43.2)	≥212	77(52.7)		

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ISUP, international society of urological pathology; IMDC, international metastatic renal cell carcinoma database consortium; TKI, tyrosine kinase inhibitor; BMI, body mass index; BSA, body surface area; bTFA, baseline total fat accumulation; bSFA, baseline subcutaneous fat accumulation; bVFA, baseline visceral fat accumulation; pTFA, total fat accumulation when tumor progressed; pSFA, subcutaneous fat accumulation when tumor progressed; pVFA, visceral fat accumulation when tumor progressed.

p=0.017) in the subgroup of patients with ≥2 metastasis sites (Supplemental Table 2, Figure 3C and D).

Just as multivariate analysis in all patients, two types of multivariate analysis were performed (one included SFA and TFA; another included a number of increasing body fat components). Multivariate analysis showed that patients with increasing TFA (p=0.043) or with BMI more than 25 Kg/m^2 (p=0.018) had longer PFS, and patients with increasing TFA (p=0.039) or with BMI more than 25 Kg/m^2 (p=0.003) also had longer OS
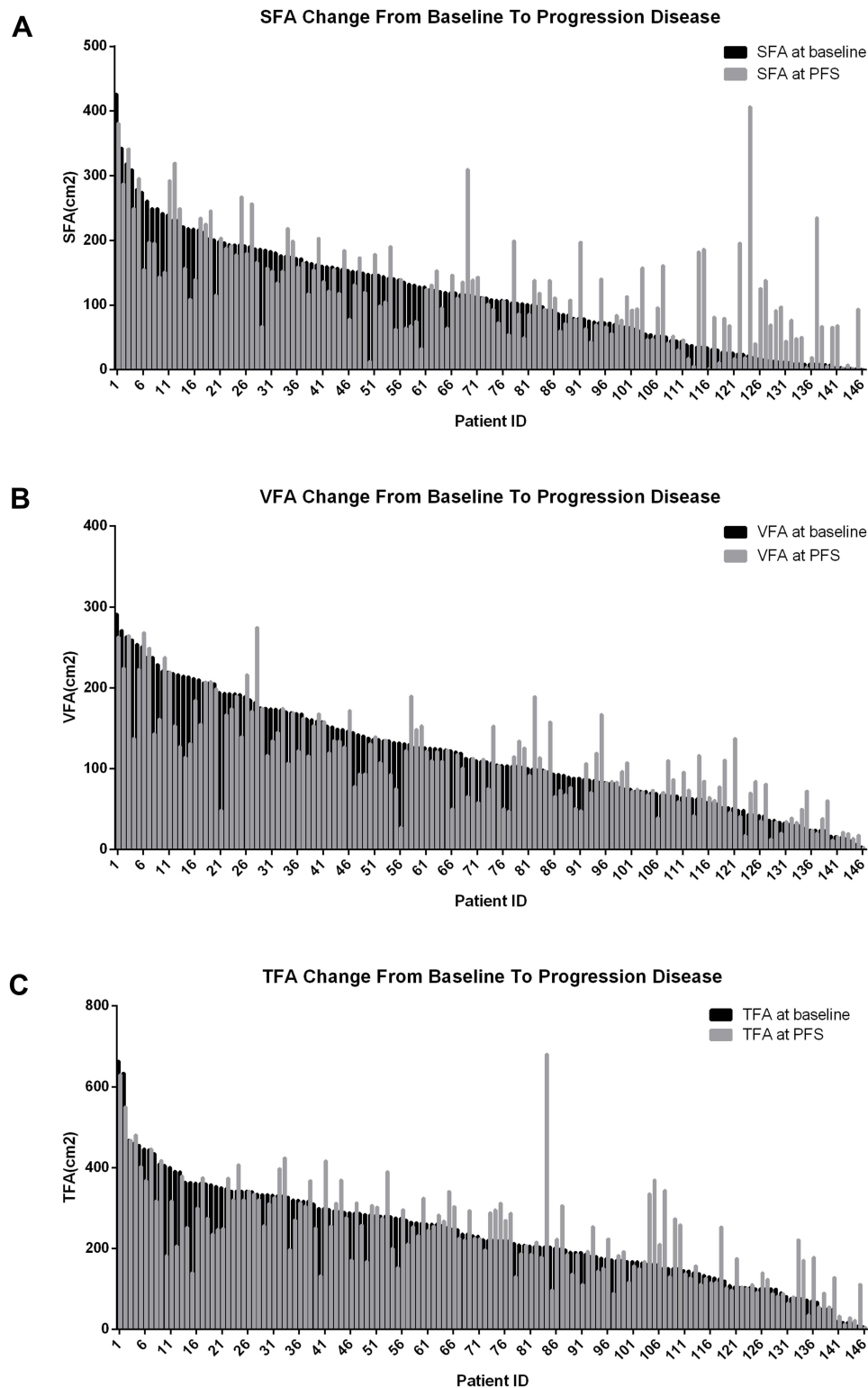
Figure 1 Changes in body fat in all patients. (**A**) The changes in subcutaneous fat accumulation from baseline to tumor progression. (**B**) The changes in visceral fat accumulation from baseline to tumor progression. (**C**) The changes in total fat accumulation from baseline to tumor progression.

(Supplemental Table 3). Moreover, the relationship between the number of increasing body fat components and PFS (HR: 0.620, 95% CI: 0.392–0.979, p=0.040) and OS (HR: 0.395, 95% CI: 0.200–0.781, p=0.008) were also found positive in multivariate analysis (Supplemental Table 3).
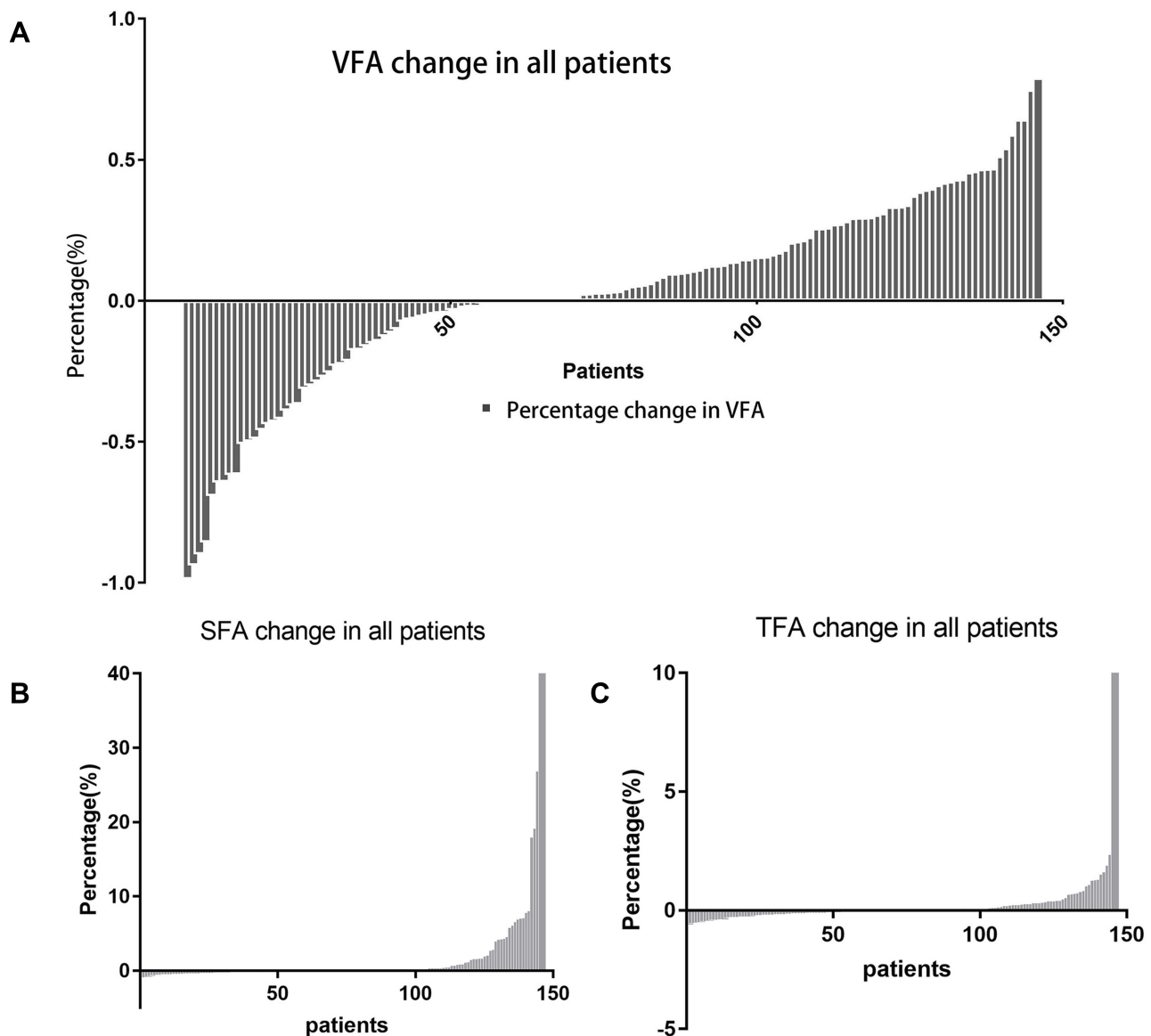
Figure 2 The percentage change of body fat in all patients. (**A**) The percentage change of visceral fat accumulation from baseline to tumor progression. (**B**) The percentage change of subcutaneous fat accumulation from baseline to tumor progression. (**C**) The percentage change of total fat accumulation from baseline to tumor progression.

Discussion

Metastatic renal cell carcinoma is a fetal disease and TKIs are most prevalent the first-line therapy.[22,23] Many pathological and clinical factors could predict and affect the prognosis of patients. Obesity, as one of the well-known etiological factors, increased the risk of developing RCC, was shown a significant association with the progress and prognosis of patients with RCC in some studies.[5,24] Naturally, BMI was considered as one of the crucial factors to calculate patients' obesity and to predict their prognosis with cancer.[15,25–28] However, growing evidence suggested that BMI was only a rough initial measurement and it ignored more information about body fat components on an individual level.[29]

Compared with BMI, body fat composition (such as VFA, SFA, and TFA), as a quantitative method by CT image, has recently been focused on its contributions to the progression of RCC.[6,7] However, the relationship between body fat composition and tumor progression and patients' survival still failed to reach an agreement in different disease stages. Zhu et al reported a positive correlation between the percentage of visceral adipose tissue and the Fuhrman tumor grade in patients with T1a RCC.[30] On the contrary, a study by Steffens et al found that mRCC patients with a higher VFA received targeted therapy, could achieve longer tumor-specific survival and OS.[12] Nevertheless, the clinical study reported by Mano et al

Table 2 The Tumor Responses of All Patients (N=146)

	Tumor Response, n (%)					ORR (%)	P	DCR (%)	P
	CR	PR	SD	PD	P (PD vs PD)				
bTFA(cm^2)					0.342		0.480		0.619
<212	1(1.4)	10(13.0)	24(34.8)	34(49.3)		11(15.9)		35(50.7)	
≥212	0	9(11.7)	32(41.6)	36(46.8)		9(11.7)		41(55.8)	
bSFA(cm^2)					0.866		0.335		0.404
<100	1(1.5)	10(15.6)	26(40.6)	27(42.2)		11(17.2)		37(57.8)	
≥ 100	0	9(11.0)	30(36.6)	43(52.4)		9(11.0)		39(50.0)	
bVFA(cm^2)					0.100		1.000		0.406
<100	1(1.6)	8(12.3)	23(35.4)	33(50.8)		9(13.8)		32(49.2)	
≥100	0	11(13.6)	33(40.7)	37(45.7)		11(13.6)		44(44.9)	
pTFA(cm^2)					0.316		0.232		1.000
<220	1(1.5)	11(16.2)	23(33.8)	32(41.2)		12(17.6)		35(52.6)	
≥220	0	8(10.3)	33(42.3)	38(43.6)		8(10.3)		41(53.8)	
pSFA(cm^2)					0.316		0.090		0.245
<112	1(1.4)	13(17.8)	27(39.7)	30(35.6)		14(19.2)		41(58.9)	
≥112	0	6(8.2)	29(39.7)	40(49.3)		6(8.2)		35(47.9)	
pVFA(cm^2)					0.417		0.814		0.869
<110	1(1.3)	10(13.2)	27(35.5)	30(40.8)		11(14.5)		38(50.0)	
≥110	0	9(12.9)	29(41.4)	40(44.3)		9(12.9)		38(54.3)	
VFA change					1.000		0.630		0.740
Increasing	1(1.6)	9(14.1)	21(35.9)	27(43.8)		10(12.2)		31(51.6)	
Decreasing	0	10(12.2)	35(32.7)	43(41.5)		10(15.6)		45(44.9)	
SFA change					0.210		0.814		0.249
Increasing	0	9(12.9)	30(45.7)	40(53.9)		9(12.9)		39(51.6)	
Decreasing	1(1.3)	10(13.2)	26(34.2)	30(42.3)		11(14.5)		37(48.7)	
TFA change					0.051		1.000		0.133
Increasing	0	9(14.1)	28(46.9)	24(39.1)		9(14.1)		37(47.6)	
Decreasing	1(1.2)	10(12.2)	28(34.1)	46(56.1)		11(13.4)		39(48.9)	
Body fat composition changes					**0.010**		0.625		**0.028**
< 2 increasing parameters	1(1.1)	10(11.2)	28(33.7)	50(58.0)		11(12.4)		39(46.1)	
≥ 2 increasing parameters	0	9(15.8)	28(49.1)	20(35.1)		9(15.8)		37(64.9)	

Abbreviations: bTFA, baseline total fat accumulation; bSFA, baseline subcutaneous fat accumulation; bVFA, baseline visceral fat accumulation; pTFA, total fat accumulation when tumor progressed; pSFA, subcutaneous fat accumulation when tumor progressed; pVFA, visceral fat accumulation when tumor progressed; CR, complete response; PR, partial response; SD, stable disease; PD, progression of disease; ORR, objective response rate; DCR, disease control rate.

showed that neither SFA nor VFA was associated with tumor stage, grade or OS in a non-metastatic clear cell RCC cohort from the United States.[28] Recently, the significant relationship between high VFA and the progression of clear cell RCC among patients from the Chinese south-eastern coast was shown in the study led by Huang et al.[31] These conflicting results clearly indicate that further study about the issue is required. In the current study, we provided more evidence to reveal the prognostic value of body fat composition.

The mechanism by which VFA, SFA or TFA to improve the survival of patients with mRCC is not well understood. VFA and SFA differ by the type of adipocytes (fat cells) involved, endocrine function, lipolytic activity and response to insulin and other hormones. Recently, the perturbed or aberrant metabolisms, such as glucose metabolism and lipid metabolism (especial fatty acid synthesis and β-oxidation), are recognized in cancer cells and could facilitate cell growth and proliferation.[32–34] Coincidently, patients with visceral obesity have been

Table 3 Univariate Analysis of PFS and OS in All mRCC Patients

	PFS			OS		
	HR	95% CI	P value	HR	95% CI	P value
Age (Years) <50 vs ≥50	0.679	0.448–1.027	0.067	0.763	0.452–1.287	0.310
Gender Male vs Female	1.282	0.814–2.018	0.283	1.090	0.826–1.439	0.542
ISUP, n (%) <3 vs ≥3	1.910	1.102–3.312	**0.021**	1.546	0.806–2.965	0.190
Histological Type ccRCC vs non-ccRCC	0.669	0.412–1.086	0.104	0.769	0.416–1.419	0.401
ECOG Score <2 vs ≥2	2.256	1.484–3.428	**<0.001**	3.849	2.320–6.383	**<0.001**

IMDC Grade
  Low
  Intermediate
  High
	Ref
	0.941
	1.587
		Ref
		0.585–1.512
		0.922–2.733
			0.093
			0.801
			0.096
				Ref
				0.749
				2.267
					Ref
					0.406–1.382
					1.202–4.277
						0.001
						0.355
						0.011

T Stage <3 vs ≥3	1.543	1.034–2.302	**0.034**	2.032	1.231–3.354	**0.006**
Nephrectomy Yes vs No	0.682	0.432–1.079	0.102	0.658	0.380–1.139	0.135
Resection of Metastasis Yes vs No	0.764	0.473–1.233	0.270	0.643	0.353–1.173	0.150
Number of Metastasis Sites <2 vs ≥2	1.676	1.123–2.503	**0.012**	1.960	1.195–3.215	**0.008**
Interval from Diagnosis to Metastasis Metachronous vs Synchronous	0.915	0.615–1.362	0.663	0.902	0.550–1.475	0.684

BMI (kg/m^2)
  <23
  23–25
  >25
	Ref
	0.482
	0.671
		Ref
		0.278–0.838
		0.413–1.091
			0.023
			0.010
			0.108
				Ref
				0.378
				0.585
					Ref
					0.179–0.797
					0.325–1.053
						0.019
						0.011
						0.074

BSA (m^2) <3 vs ≥3	1.156	0.739–1.810	0.525	1.207	0.711–2.050	0.486
bTFA(cm^2) <212 vs ≥212	1.045	0.701–1.558	0.828	1.055	0.644–1.728	0.831
bSFA (cm^2) <100 vs ≥ 100	1.376	0.913–2.075	0.127	1.891	1.123–3.184	**0.017**
bVFA(cm^2) <100 vs ≥100	0.694	0.466–1.033	0.072	0.689	0.419–1.131	0.141
pTFA (cm^2) <220 vs ≥220	1.016	0.685–1.508	0.937	0.808	0.494–1.322	0.396
pSFA(cm^2) <112 vs ≥112	0.797	0.450–1.410	0.435	0.768	0.378–1.562	0.467

(Continued)

Table 3 (Continued).

	PFS			OS		
	HR	95% CI	P value	HR	95% CI	P value
pVFA(cm^2) <110 vs ≥110	0.878	0.590–1.307	0.522	0.569	0.344–0.942	**0.028**
VFA Change Increasing vs Decreasing	0.667	0.447–0.995	**0.047**	0.994	0.604–1.638	0.982
SFA Change Increasing vs Decreasing	0.569	0.378–0.857	**0.005**	0.534	0.321–0.887	**0.015**
TFA Change Increasing vs Decreasing	0.612	0.540–0.916	**0.015**	0.539	0.311–0.895	**0.018**
Number of Increasing Body Fat Components <2 vs ≥2	0.593	0.423–0.833	**0.003**	0.503	0.332–0.761	**0.001**

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ISUP, international society of urological pathology; IMDC, international metastatic renal cell carcinoma database consortium; BMI, body mass index; BSA, body surface area; bTFA, baseline total fat accumulation; bSFA, baseline subcutaneous fat accumulation; bVFA, baseline visceral fat accumulation; pTFA, total fat accumulation when tumor progressed; pSFA, subcutaneous fat accumulation when tumor progressed; pVFA, visceral fat accumulation when tumor progressed; PFS, progression-free survival; OS, overall survival.

reported to have a high risk of metabolic complications, eg metabolic syndrome.[35]

SFA and TFA are always considered as factors of patients' nutritional status. The reduction of body fat is a mark of cancer cachexia, and malnutrition is related to poor OS in malignant tumors.[36,37] As far as we know, the adverse effects of targeted therapy are significant, and gastrointestinal symptoms, like nausea, and inappetence are the most notable.[38,39] Furthermore, there were also some studies suggested that body fat be lost more rapidly
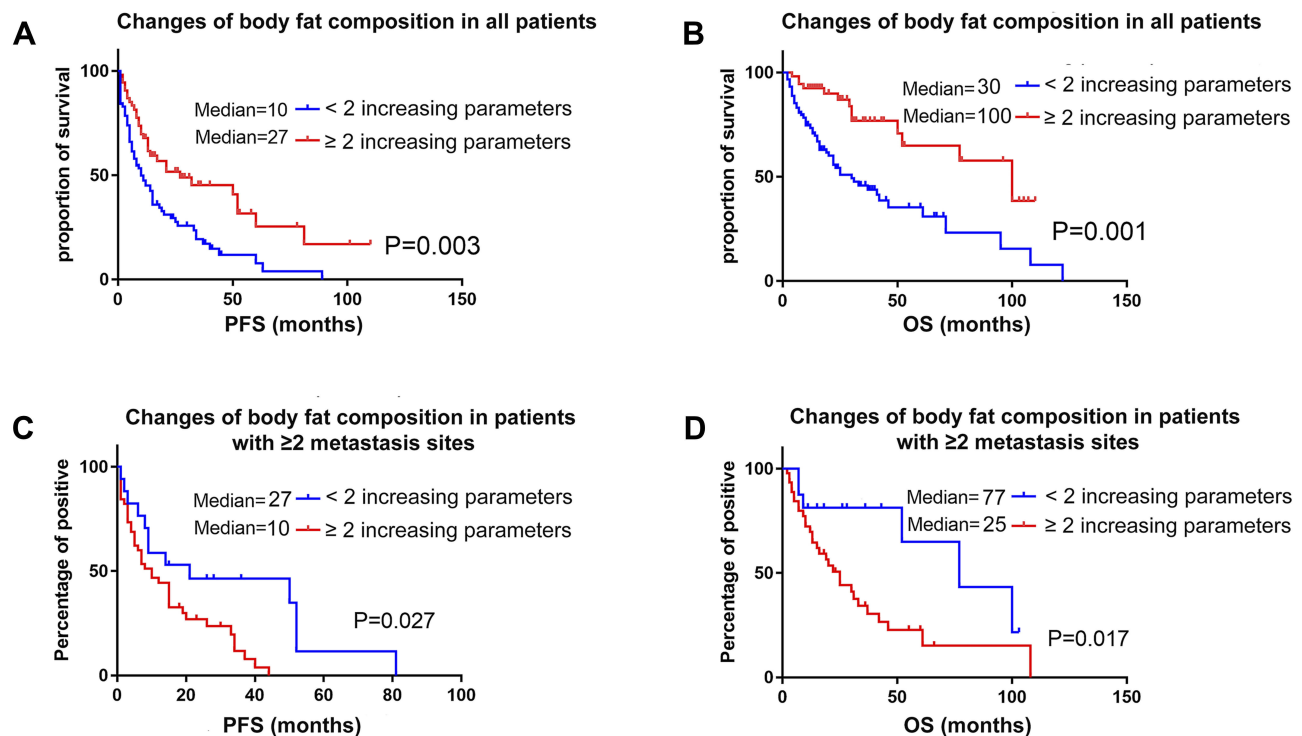

Figure 3 Kaplan-Meier assessment of progression-free survival and overall survival according to the number of increasing body fat components. (**A**) Kaplan-Meier assessment of progression-free survival in all patients. (**B**) Kaplan-Meier assessment of overall survival in all patients. (**C**) Kaplan-Meier assessment of progression-free survival in patients with ≥2 metastasis sites. (**D**) Kaplan-Meier assessment of overall survival in patients with ≥2 metastasis sites.

Table 4 Multivariate Analysis of PFS and OS in All Patients

	PFS						OS					
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
ECOG Score												
<2 vs ≥2	1.724	0.984–3.019	0.057	2.089	1.199–3.639	**0.009**	2.010	1.054–3.834	**0.034**	2.276	1.205–4.297	**0.011**
Type of First-Line TKIs	-	-	0.133	-	-	**0.057**	-	-	0.151	-	-	0.171
Sunitinib vs Axitinib	0.887	0.508–1.551	0.675	1.041	0.600–1.806	0.887	0.410	0.163–1.029	0.058	0.533	0.221–1.287	0.162
Sunitinib vs Sorafenib	0.381	0.146–0.993	**0.048**	0.307	0.117–0.811	**0.017**	0.830	0.286–2.410	0.732	0.501	0.172–1.459	0.205
Histological Type												
ccRCC vs Non-ccRCC	0.543	0.312–0.945	**0.031**	0.663	0.388–1.133	0.133	0.610	0.288–1.294	0.198	0.920	0.449–1.885	0.920
ISUP												
<3 vs ≥3	2.007	1.089–3.701	**0.026**	2.068	1.137–3.760	**0.017**	1.174	0.570–2.417	0.663	1.297	0.640–2.630	0.470
IMDC Grade												
Low	-	-	0.298	-	-	0.823	-	-	**0.010**	-	-	0.106
Intermediate	0.934	0.541–1.613	0.808	1.041	0.612–1.772	0.882	0.600	0.290–1.242	0.169	0.896	0.453–1.769	0.751
High	1.574	0.780–3.178	0.206	1.226	0.631–2.383	0.548	2.172	0.941–5.014	0.069	1.929	0.867–4.292	0.107
BMI (kg/m²)												
<23	-	-	**0.010**	-	-	0.074	-	-	**0.029**	-	-	0.055
<23 vs 23–25	0.438	0.240–0.800	**0.007**	0.521	0.290–0.936	**0.029**	0.440	0.196–0.988	**0.047**	0.472	0.211–1.058	0.068
<23 vs >25	0.528	0.301–0.926	**0.026**	0.709	0.426–1.179	0.185	0.450	0.226–0.897	**0.023**	0.507	0.262–0.983	**0.044**
T Stage												
<3 vs ≥3	1.099	0.678–1.782	0.701	0.952	0.583–1.555	0.844	1.417	0.756–2.657	0.277	1.074	1.043–3.235	0.820
Number of Metastasis Sites												
<2 vs ≥2	1.513	0.973–2.352	0.066	1.373	0.888–2.122	0.154	1.989	1.121–3.527	**0.019**	1.837	1.043–3.235	**0.035**
pVFA(cm²)												
<110 vs ≥110	1.596	0.948–2.685	0.078	-	-	-	1.467	0.741–2.904	0.272	-	-	-
SFA Change												
Increasing vs decreasing	0.525	0.301–0.916	**0.023**	-	-	-	0.374	0.195–0.717	**0.003**	-	-	-
TFA Change												
Increasing vs decreasing	0.863	0.483–1.543	0.620	-	-	-	1.144	0.549–2.383	0.719	-	-	-
Number of Increasing Body Fat Components												
<2 vs ≥2	-	-	-	0.567	0.353–0.910	-	-	-	-	0.463	0.244–0.879	**0.018**

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ISUP, international society of urological pathology; IMDC, international metastatic renal cell carcinoma database consortium; BMI, body mass index; pVFA, visceral fat accumulation; TFA, total fat accumulation; SFA, subcutaneous fat accumulation; PFS, progression-free survival; OS, overall survival.
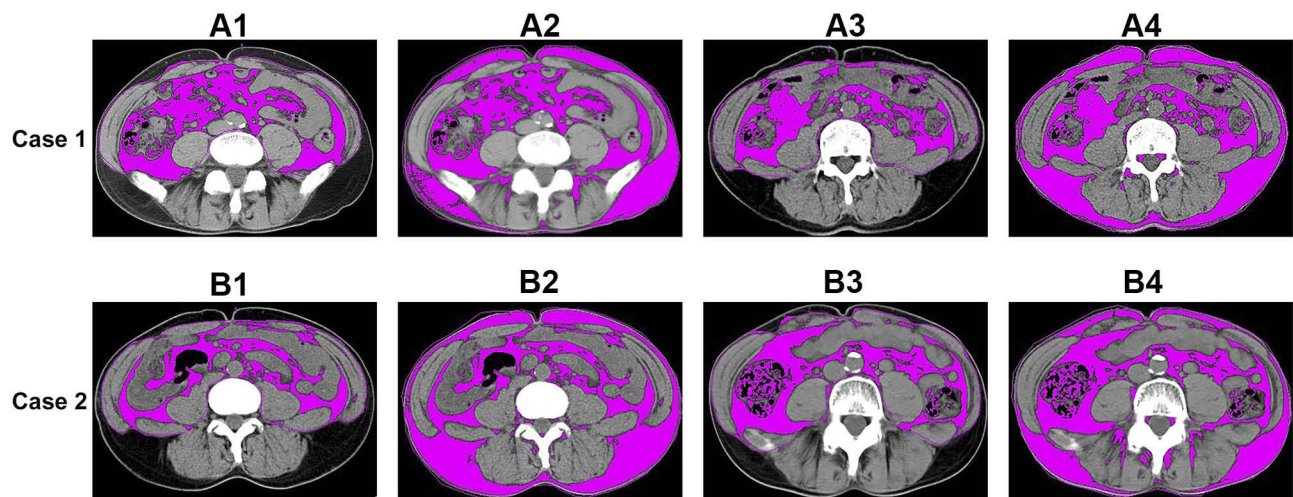
Figure 4 Case 1: Axial CT images of a patient with worse clinical outcomes at the level of the umbilicus. (PFS=4 months; OS=29 months). A1. The region in red represents the VFA at baseline (VFA=194.28 cm^2). A2. The region in red represents the TFA at baseline (TFA=203.40 cm^2). A3. The region in red represents the VFA at progression (VFA=48.65 cm^2). A4. The region in red represents the TFA at progression (TFA=96.82 cm^2). Case 2: Axial CT images of a patient with better clinical outcomes at the level of the umbilicus. (PFS=15months; OS=46months). B1. The region in red represents the VFA at baseline (VFA=26.34 cm^2). B2. The region in red represents the TFA at baseline (TFA=133.00 cm^2). B3. The region in red represents the VFA at progression (VFA=72.16 cm^2). B4. The region in red represents the TFA at progression (TFA=126.30 cm^2).

than lean mass in patients with cancers.[40] Therefore, patients who have been undergoing targeted therapy, are more likely to be cachexia. That might be one of the reasons why measurement of VFA, SFA, and TFA could be a more sensitive estimation of nutritional status than BMI.

In this study, we firstly found that the number of increasing body fat components could predict the prognosis of patients treated with TKIs. Combined with these three crucial body fat parameters (VFA, SFA, TFA), body fat accumulation could comprehensively predict patients' survival status. Taken together, accurate measurement of visceral or subcutaneous obesity might play a vital role in assessing nutritional status (cachexia or not) that could influence survival in patients with mRCC.

The major limitations of our study included retrospective design, small sample and relatively short follow-up. Further study is needed to explore the biological mechanism about the relationship among nutritional factors, therapies, tumor progression, and patient's survival.

Conclusion

Body fat accumulation, such as high SFA and TFA at progression could improve the survival of patients with mRCC treated with TKIs, especially patients with higher tumor burden. Moreover, the number of increasing body fat components also played a critical role in those patients as a prognostic factor. Body fat accumulation should be considered as an important parameter to assess the survival status of patients with mRCC.

Abbreviations

TKIs, tyrosine kinase inhibitor; mRCC, metastatic renal cell carcinoma; BMI, body mass index; VFA, visceral fat accumulation; SFA, subcutaneous fat accumulation; TFA, total fat accumulation; CR, complete response; PR, partial response; SD, stable disease; PD, progression of disease; ORR, objective response rate; DCR, disease control rate.

Ethics

This study was approved by the Ethics Committee of West China Hospital, Sichuan University. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. All the patients voluntarily participated in this study and provided written informed consent. All the participants' personal information is confidential.

Disclosure

The authors report no conflicts of interest in this work.

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