Body Mass Index and Metastatic Renal Cell Carcinoma: Clinical and Biological Correlations

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ABSTRACT

Purpose

Obesity is an established risk factor for clear cell renal cell carcinoma (RCC); however, some reports suggest that RCC developing in obese patients may be more indolent. We investigated the clinical and biologic effect of body mass index (BMI) on treatment outcomes in patients with metastatic RCC.

Methods

The impact of BMI (high BMI: ≥ 25 kg/m² v low BMI: < 25 kg/m²) on overall survival (OS) and treatment outcome with targeted therapy was investigated in 1,975 patients from the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) and in an external validation cohort of 4,657 patients. Gene expression profiling focusing on fatty acid metabolism pathway, in The Cancer Genome Atlas data set, and immunohistochemistry staining for fatty acid synthase (FASN) were also investigated. Cox regression was undertaken to estimate the association of BMI with OS, adjusted for the IMDC prognostic factors.

Results

In the IMDC cohort, median OS was 25.6 months (95% CI, 23.2 to 28.6) in patients with high BMI versus 17.1 months (95% CI, 15.5 to 18.5) in patients with low BMI (adjusted hazard ratio, 0.84; 95% CI, 0.73 to 0.95). In the validation cohort, high BMI was associated with improved OS (adjusted hazard ratio, 0.83; 95% CI, 0.74 to 0.93; medians: 23.4 months [95% CI, 21.9 to 25.3 months] v 14.5 months [95% CI, 13.8 to 15.9 months], respectively). In The Cancer Genome Atlas data set (n = 61), *FASN* gene expression inversely correlated with BMI ($P = .034$), and OS was longer in the low *FASN* expression group (medians: 36.8 v 15.0 months; $P = .002$). *FASN* immunohistochemistry positivity was more frequently detected in IMDC poor (48%) and intermediate (34%) risk groups than in the favorable risk group (17%; P -trend = .015).

Conclusion

High BMI is a prognostic factor for improved survival and progression-free survival in patients with metastatic RCC treated with targeted therapy. Underlying biology suggests a role for the *FASN* pathway.

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INTRODUCTION

Obesity is an established risk factor for kidney cancer.¹⁻³ However, large surgical cohorts and one meta-analysis of 20 studies have demonstrated that renal cell carcinomas (RCCs) occurring in obese patients are associated with a lower stage and grade at presentation and thus may be associated with an improved cancer-specific survival in a population with localized RCC.⁴

In metastatic disease, data suggest that, similar to localized disease, obese patients treated with targeted therapies have a better overall survival (OS), even after adjusting for prognostic factors, such as the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk criteria.⁵ From a biologic standpoint, a recent report from The Cancer Genome Atlas (TCGA) data set identified no specific DNA alterations in clear cell RCC (ccRCC) developing in obese patients.⁶ However, gene expression profiling

identified altered fatty acid (FA) pathways in obese patients relative to normal-weight patients, with marked downregulation of *fatty acid synthase* (*FASN*). *FASN* expression has previously been reported to be associated with poor prognosis in several tumor types, including RCC,^{7,8} and is considered a metabolic oncogene in other tumor models, such as prostate cancer.⁹ The current work focuses on investigating the associations of BMI with treatment outcomes in metastatic RCC (mRCC) treated with targeted therapies in two distinct, well-annotated cohorts and elucidating the underlying biologic mechanisms by investigating the role of the *FASN* pathway in patients with mRCC using two unique specimen repositories.

METHODS

Study Populations and Data Collection

IMDC cohort. The IMDC is a consecutive patient series from institutions in North America, Europe, and Asia.^{10,11} This population includes patients with mRCC who received targeted therapy (TT), such as vascular endothelial growth factor (VEGF)/VEGF receptor and mammalian target of rapamycin inhibitors, starting from 2003. Patients may have been treated on or off clinical trials. For this study, we included patients with weight and height data recorded at the initiation of first-line TT. Baseline clinical and laboratory data were retrospectively collected on all patients using a uniform database template to ensure consistent data collection. Laboratory values were standardized against institutional upper limits of normal and lower limits of normal values when appropriate. We collected survival data from patient medical records or publically available records. Institutional review board approval was obtained from each participating center.

Validation cohort. As an independent validation data set, we conducted a pooled analysis of prospective data of patients with mRCC treated in phase II (NCT00054886, NCT00077974, NCT00267748, NCT00338884, NCT00137423) and III trials (NCT00083889, NCT00065468, NCT00678392) sponsored by Pfizer involving sunitinib, temsirolimus, and axitinib. We identified 4,657 patients treated for mRCC between January 2003 and December 2013 with BMI recorded at trial therapy initiation.

TCGA samples. To investigate biologic differences associated with different BMI groups, we used available genomic data of mRNA expression from patients who were part of the Kidney Renal Clear Cell Carcinoma clinical TCGA consortium (cTCGA). The cTCGA consists of 324 patients from five participating institutions with additional clinical and treatment-related data. All genomic data were downloaded through the TCGA data portal¹² and linked with patient characteristics. In the overall ccRCC TCGA data set, 61 patients with metastatic disease, with available information on both *FASN* expression and BMI, were included in this analysis. In addition, survival information and FA pathway score^{13,14} were investigated in 324 cTCGA participants with ccRCC.

IMDC biospecimen repository. Samples from pretreatment primary tumors and/or metastatic lesions of patients treated at Dana-Farber/Harvard Cancer Center for mRCC with TT and part of the IMDC biospecimen repository were used to construct two tissue microarrays containing four tumor tissue cores per case. The objective was to explore the association between *FASN* immunohistochemistry staining with BMI and clinical outcomes. IHC was performed according to protocol detailed in the Appendix (online only).

The *FASN* scoring system was assessed by a senior pathologist (S. Signoretti) blinded to the BMI status and used a combined score (ranging from 0 to 300) defined as the percentage of positive cells (0 to 100) multiplied by the intensity (0 to 3) for each tissue core for each patient. The maximum combined score across the cores was used for each patient. If the maximum score was > 0, then the case was defined as positive. Any case with a null combined score in all cores was defined as negative.

Statistical Analysis

BMI was defined as the ratio of weight (in kilograms) divided by the squared height (in meters). Patients were classified into BMI groups defined by the World Health Organization: underweight (BMI < 18.5 kg/m²), normal weight (BMI, 18.5 to < 25 kg/m²), overweight (BMI, 25 to < 30 kg/m²), and obese (BMI ≥ 30 kg/m²) or condensed to high BMI (≥ 25 kg/m²) versus low BMI (< 25 kg/m²).

The primary clinical outcome was OS. For the IMDC cohort, OS was defined as the time period between TT initiation and the date of death, or it was censored on the day of the last follow-up visit. Time to treatment failure (TTF) was defined as the time period between treatment initiation and progression, drug cessation, or death, or it was censored at the last follow-up. Progression was determined according to clinical criteria or radiographic criteria using the Response Evaluation Criteria in Solid Tumors (RECIST). For the validation data set, OS was calculated from study randomization or trial therapy initiation to death from any cause or censored at time of analysis. Progression-free survival (PFS) was defined similarly but included both progression (per RECIST) and death as events, whichever came first. For the cTCGA samples, OS was calculated from date of TT to death or date of last contact. The distributions of OS, TTF, and PFS were estimated with the Kaplan-Meier method along with 95% CIs. Statistical analysis methods are detailed in the Appendix. For the IMDC cohort, all multivariable Cox regressions were adjusted for the IMDC prognostic risk factors and stratified on study region (Asia, North America, and Europe) and sex, given the different distributions of BMI across region and sexes. For a subset of the IMDC cohort (n = 787 from six centers), we also examined TTF from different causes by a competing risk model. The cumulative incidence functions of time to treatment discontinuation because of disease progression, death, toxicity, and other were estimated and compared among BMI groups using Gray's test with adjustment for the IMDC risk groups. For the validation cohort, the multivariable Cox regression models were adjusted for known prognostic factors in mRCC^{10,15,16} as well as additional potential confounding factors associated with lipid metabolism, such as baseline dyslipidemia and statin use.¹⁷

FASN gene expression was used as a continuous variable; comparison between BMI groups was conducted by Kruskal-Wallis test. *FASN* expression was also dichotomized at the median value for correlation with OS. In addition, to further explore the role of FA metabolism in ccRCC, we investigated a predefined gene set of 168 genes of the FA metabolism from the reactome pathway database^{13,14} in the entire TCGA ccRCC using single-sample gene set enrichment analysis.¹⁸ Subsequently, the population was dichotomized at the FA pathway score means, and we examined the association of the score with OS using the log-rank test.

RESULTS

IMDC Population

A total of 1,975 patients from 19 centers were included; patients were followed until January 2013. Overall, 1,190 (60%) patients were overweight or obese (BMI ≥ 25 kg/m²) and 785 (40%) patients had normal weight or were underweight (BMI < 25 kg/m²). Patient characteristics are presented in Table 1. At the time of data analysis, 1,671 (85%) patients had stopped first-line TT. Median time on first-line TT was 7.2 months (range, 0+ to 82+ months). Median OS after initiation of TT was 21.5 months (95% CI, 20.1 to 23.3 months). Median follow-up (n = 754; 38%) was 21.1 months (range, 0 to 102.7 months). The majority of patients (94.5%) received first-line VEGF axis TT. Furthermore, 921 patients also received second-line therapy; 735 (80%) patients had weight recorded at the start of second-line therapy. Among these, 438 (60%) patients had an overweight/obese BMI and 297 (40%)

Table 1. Characteristics of IMDC Cohort and Validation Cohort

Characteristic	IMDC Cohort			Validation Cohort		
	BMI < 25 (n = 785; 40%)	BMI ≥ 25 (n = 1,190; 60%)	Total (n = 1,975; 100%)	BMI < 25 (n = 1,829; 39%)	BMI ≥ 25 (n = 2,828; 61%)	Total (n = 4,657; 100%)
Age at initiation of therapy						
< 65 years	511 (65.1)	748 (62.9)	1,259 (63.7)	1,249 (68.3)	1,957 (69.2)	3,206 (68.8)
Sex						
Male	557 (71.0)	908 (76.3)	1,465 (74.2)	1,260 (68.9)	2,049 (72.5)	3,309 (71.1)
Ethnicity						
White	268 (34.1)	717 (60.3)	985 (49.9)	1,218 (66.6)	2,377 (84.1)	3,595 (77.2)
Asian	376 (47.9)	165 (13.9)	541 (27.4)	505 (27.6)	247 (8.7)	752 (16.1)
Other	19 (2.4)	48 (4.0)	67 (3.4)	92 (5.0)	178 (6.3)	270 (5.8)
Unknown	122 (15.5)	260 (21.8)	382 (19.3)	14 (0.8)	26 (0.9)	40 (0.9)
ECOG performance status						
0	118 (15.0)	302 (25.4)	420 (21.3)	834 (45.6)	1,621 (57.3)	2,455 (52.7)
1	458 (58.3)	639 (53.7)	1,097 (55.6)	961 (52.5)	1,162 (41.1)	2,123 (45.6)
2	196 (24.9)	228 (19.2)	424 (21.5)	27 (1.5)	31 (1.1)	58 (1.2)
Unknown	13 (1.7)	21 (1.8)	34 (1.7)	7 (0.4)	14 (0.5)	21 (0.5)
Pathology						
Clear cell	636 (81.0)	1,002 (84.2)	1,638 (82.9)	1,636 (89.4)	2,530 (89.5)	4,166 (89.5)
Non-clear cell	118 (15.0)	118 (9.9)	236 (11.9)	124 (6.8)	209 (7.4)	333 (7.2)
Unknown	31 (3.9)	70 (5.9)	101 (5.1)	69 (3.8)	89 (3.1)	158 (3.4)
Baseline metastatic site*						
Lung	481 (71.1)	680 (69.6)	1,161 (70.2)	1,418 (77.5)	2,154 (76.2)	3,572 (76.7)
Bone	259 (36.5)	359 (33.0)	618 (34.4)	543 (29.7)	736 (26.0)	1,279 (27.5)
Liver	122 (17.8)	169 (16.9)	291 (17.3)	537 (29.4)	679 (24.0)	1,216 (26.1)
Previous nephrectomy	582 (74.1)	977 (82.1)	1,559 (78.9)	1,238 (67.7)	2,026 (71.6)	3,264 (70.1)
Prior therapy						
Cytokine therapy	171 (21.8)	238 (20.0)	409 (20.7)	281 (15.4)	378 (13.4)	659 (14.2)
Targeted therapy	—	—	—	256 (14.0)	314 (11.1)	570 (12.2)
IMDC risk group						
Favorable	85 (10.8)	242 (20.3)	327 (16.6)	153 (8.4)	479 (16.9)	632 (13.6)
Intermediate	412 (52.5)	630 (52.9)	1,042 (52.8)	703 (38.4)	1,267 (44.8)	1,970 (42.3)
Poor	247 (31.5)	235 (19.7)	482 (24.4)	586 (32.0)	540 (19.1)	1,126 (24.2)
Unknown	41 (5.2)	83 (7.0)	124 (6.3)	387 (21.2)	542 (19.2)	929 (19.9)
Baseline high blood pressure	—	—	—	637 (34.8)	1,590 (56.2)	2,227 (47.8)
ASI use at baseline or within 30 days of study entry	—	—	—	383 (20.9)	1,082 (38.3)	1,465 (31.5)
Baseline dyslipidemia	—	—	—	216 (11.8)	616 (21.8)	832 (17.9)
Baseline statin use	—	—	—	117 (6.4)	386 (13.6)	503 (10.8)
Baseline body surface area, m ²						
Median	1.70	2.05	1.91	1.73	2.02	1.90
Minimum, maximum	1.21, 2.23	1.50, 3.18	1.21, 3.18	1.18, 2.20	1.32, 3.36	1.18, 3.36
Lean body mass, † kg						
Median	49.34	61.23	55.76	50.52	60.05	55.77
Minimum, maximum	25.87, 71.41	33.70, 99.81	25.87, 99.81	25.02, 69.99	27.94, 103.9	25.02, 103.9

NOTE. Data are No. (%) unless otherwise noted.

Abbreviations: ASI, angiotensin system inhibitor; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; FFM, fat-free mass; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; LBM, lean body mass.

*For IMDC, evaluable n = 1,654, 1,799, and 1,686 for lung, bone, and liver metastasis, respectively.

†Green updated FFM formula: LBM (male) = (9.27 × 1,000 × weight)/[(6.68 × 1,000) + (216 × BMI)]. LBM (female) = (9.27 × 1,000 × weight)/[(8.78 × 1,000) + (244 × BMI)].

patients had a normal/underweight BMI. The type of TT was balanced between high and low BMI groups in both first- and second-line settings (Appendix Table A1, online only).

Patients with high BMI had prolonged OS compared with patients with low BMI (25.6 months [95% CI, 23.2 to 28.6 months] v 17.1 months [95% CI, 15.5 to 18.5] months; Fig 1A) and the adjusted hazard ratio was 0.84 (95% CI, 0.73 to 0.95) in Cox regression adjusted for the IMDC prognostic factors (Table 2). In addition, the association of BMI with OS was present in the intermediate and poor risk groups (hazard ratio [HR], 0.73 [95% CI, 0.62 to 0.87] and 0.80 [95% CI, 0.65 to 0.97], respectively) but not in the favorable group (HR, 1.05 [95% CI, 0.73 to 1.51]; *P*-interaction = .22).

Patients with high BMI had improved TTF compared with the low BMI group in both first- and second-line therapy after adjustment for the IMDC prognostic factors (Table 3; Fig 1C).

Reason for discontinuation of first-line therapy was available from six centers (n = 787). Six hundred sixty-seven patients had discontinued treatment: 353 (53%) due to disease progression or death, 129 (19%) due to toxicity, and 185 (28%) due to other or unknown reason. The estimated cumulative incidence of TTF at 1 year due to toxicity was similar between the low BMI (15% [95% CI, 12% to 19%]) versus high BMI group (13% [95% CI, 10% to 17%]). Cumulative incidence of treatment failure due to progression or death favored the high BMI group (40% [95% CI,

Fig 1. Kaplan-Meier estimates of overall survival (A) in the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) cohort, and (B) in validation cohort, and Kaplan-Meier estimates of (C) time to treatment failure in the IMDC cohort and (D) progression-free survival in validation cohort, stratified by body mass index (BMI) group (total number of events = 1,221 and 1,671 for A and C; total number of events = 2,109 and 2,885 for B and D).

35% to 45%] v 28% [95% CI, 23% to 32%] at 1 year; adjusted $P = .0015$), after adjustment for the IMDC risk groups (Appendix Fig A1, online only).

When BMI was analyzed as four groups, the underweight patients had poorer OS when compared with the normal BMI group ($n = 719$; 36%), but only 66 patients (3%) were underweight. Outcomes were similar for the overweight ($n = 663$; 34%) and obese ($n = 527$; 27%) groups; both groups tended to have prolonged TTF and OS (Appendix Table A2, online only).

Validation Cohort

This independent data set included 4,657 patients with mRCC treated in clinical trials in the era of TT. Overall, 2,828 patients (61%) had a high BMI and 1,829 (39%) patients had low BMI.

Population characteristics are presented in Table 1. The majority of patients ($n = 2,990$; 64.2%) received first-line therapy and 1,667 ($n = 1,667$; 35.8%) received second-line therapy. Patients were treated with VEGF receptor-tyrosine kinase inhibitor ($n = 3,071$) or mammalian target of rapamycin-containing regimen ($n = 1,044$) or interferon alfa-2a alone ($n = 542$).

Overall, the results were similar to those seen in the IMDC cohort (adjusted HR, 0.83 [95% CI, 0.74 to 0.93] for OS; adjusted HR, 0.82 [95% CI, 0.75 to 0.90] for PFS) in favor of the high BMI group (Tables 2 and 3; Figs 1B and 1D). Overall response rate was higher in patients with high BMI than in patients with low BMI: 25.3% versus 17.6% (adjusted odds ratio, 1.53 [95% CI, 1.26 to 1.86]). Results were also similar when stratified by line of therapy. Treatment discontinuation due to adverse events was similar in the high BMI (14.1%) and low BMI groups (14.2%). When BMI was analyzed as four groups, the underweight patients had poorer

Table 2. OS Stratified by BMI Category in the IMDC Cohort and Validation Cohort

Outcome: OS	IMDC Cohort, OS		Validation Cohort, OS	
	BMI < 25	BMI ≥ 25	BMI < 25	BMI ≥ 25
First line: total n, No. of events	785, 507	1,190, 714	1,110, 667	1,880, 838
Median (95% CI), months	17.1 (15.5 to 18.5)	25.6 (23.2 to 28.6)	14.5 (13.4 to 15.9)	25.4 (23.1 to 27.5)
Adjusted HR (95% CI)	1.00 (reference)	0.84 (0.73 to 0.95)	1.00 (reference)	0.81 (0.71 to 0.93)
Second line: total n, No. of events	297, 209	438, 255	719, 363	948, 424
Median (95% CI), months	8.7 (7.5 to 10.2)	16.4 (14.3 to 20.2)	14.9 (13.5 to 17.3)	19.8 (17.6 to 22.9)
Adjusted HR (95% CI)	1.00 (reference)	0.58 (0.45 to 0.74)	1.00 (reference)	0.90 (0.75 to 1.08)
Overall: total n, No. of events			1,829, 1,030	2,828, 1,262
Median (95% CI), months			14.5 (13.8 to 15.9)	23.4 (21.9 to 25.3)
Adjusted HR (95% CI)			1.00 (reference)	0.83 (0.74 to 0.93)

NOTE. IMDC cohort: adjusted for the IMDC prognostic risk factors and stratified on region (Asia, United States, Canada, and Europe) and sex; validation cohort: adjusted for age, sex, ethnicity, histology, prior nephrectomy, sites of metastasis, Eastern Cooperative Oncology Group, IMDC risk factors, baseline high blood pressure, baseline angiotensin system inhibitor use, baseline dyslipidemia, and statin use. IMDC: second-line cohort is a subset of patients who received first-line target therapy; validation cohort: first- and second-line cohorts consist of different subjects. Given the large number in both cohorts, *P* values were not provided, and we focused on reporting the magnitude and precision (ie, confidence interval) of the associations.

Abbreviations: BMI, body mass index; HR, hazard ratio; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; OS, overall survival.

OS when compared with the normal BMI group, but only 63 patients (2%) and 72 patients (4%) were underweight in first and second line, respectively. Outcomes were similar for the overweight and obese groups; both groups tended to have prolonged PFS and OS both in first and second line (Appendix Table A3, online only).

TCGA Analysis

We identified 61 patients with mRCC in the ccRCC TCGA cohort (Appendix Table A4, online only). Overall, 39 patients (63.9%) had a high BMI and 22 patients (36.1%) had a low BMI. Median BMI was 27 kg/m² (range, 17 to 43 kg/m²). Overall, 50 deaths had occurred at the time of analysis. Median survival was 19.2 months (95% CI, 15.6 to 31.2 months). There was a trend toward an association between OS and BMI category (median, 25.2 v 14.5 months for high BMI and low BMI, respectively; log-rank *P* = .07). Patients with high BMI had lower *FASN* expression compared with the low BMI group (*P* = .03; Fig 2A). High *FASN* was associated with worse OS (median, 15.0 v 36.8 months for high

FASN and low *FASN*, respectively; log-rank *P* = .002; Fig 2B). In the overall ccRCC TCGA cohort (patients with metastatic and non-metastatic disease), data were available on both survival and FA pathway score for 324 TCGA participants. Five-year OS was 53% (95% CI, 45% to 61%) in patients with an FA pathway score below the mean versus 72% (95% CI, 65% to 81%) in patients with FA pathway score above the mean (*P* < .001).

FASN Immunohistochemistry Staining

Finally, we investigated the relationship between *FASN* IHC expression and BMI using samples from the IMDC biospecimen cohort. We used tissue microarrays from a total of 146 patients with mRCC treated with TT (Appendix Table A5, online only). At the time of analysis, 122 deaths had occurred (84%). Median OS from start of systemic therapy was 21.5 months (95% CI, 17.6 to 28.1 months).

FASN staining positivity was recorded in 45 cases (31%) overall (Appendix Fig A2, online only). *FASN* positivity was more frequently detected in poor (11 of 23, 48%) and intermediate (20 of 59, 34%) risk groups compared with the favorable risk group (5 of

Table 3. TTF and PFS Stratified by BMI Category in the IMDC Cohort and Validation Cohort

Outcome: TTF or PFS	IMDC Cohort, TTF		Validation Cohort, PFS	
	BMI < 25	BMI ≥ 25	BMI < 25	BMI ≥ 25
First line: total n, No. of events	779, 671	1,177, 1,000	1,110, 791	1,880, 1,218
Median (95% CI), months	5.7 (5.3 to 6.6)	8.1 (7.6 to 8.7)	5.4 (5.1 to 5.8)	9.0 (8.3 to 9.4)
Adjusted HR (95% CI)	1.00 (reference)	0.86 (0.76 to 0.96)	1.00 (reference)	0.85 (0.75 to 0.96)
Second line: total n, No. of events	297, 256	436, 370	719, 478	948, 604
Median (95% CI), months	3.0 (2.8 to 3.7)	4.2 (3.7 to 5.0)	5.6 (4.8 to 6.4)	6.6 (6.4 to 7.4)
Adjusted HR (95% CI)	1.00 (reference)	0.70 (0.57 to 0.87)	1.00 (reference)	0.80 (0.69 to 0.94)
Overall: total n, No. of events			1,829, 1,269	2,828, 1,822
Median (95% CI), months			5.5 (5.2 to 5.8)	8.2 (7.8 to 8.4)
Adjusted HR (95% CI)			1.00 (reference)	0.82 (0.75 to 0.90)

NOTE. IMDC cohort: adjusted for the IMDC prognostic risk factors and stratified on region (Asia, United States, Canada, and Europe) and sex; validation cohort: adjusted for age, sex, ethnicity, histology, prior nephrectomy, sites of metastasis, Eastern Cooperative Oncology Group, IMDC risk factors, baseline high blood pressure, baseline angiotensin system inhibitor use, baseline dyslipidemia, and statin use. IMDC: second-line cohort is a subset of patients who received first-line target therapy; validation cohort: first- and second-line cohorts consist of different subjects. Given the large number in both cohorts, *P* values were not provided, and we focused on reporting the magnitude and precision (ie, confidence interval) of the associations.

Abbreviations: BMI, body mass index; HR, hazard ratio; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; PFS, progression-free survival; TTF, time to treatment failure.

Fig 2. Fatty acid synthase (FASN) expression level in The Cancer Genome Atlas patients with metastatic clear cell renal cell carcinoma. (A) FASN expression level association with body mass index category. (B) FASN expression level association with overall survival (total N = 60; number of deaths = 50).

30, 17%; P -trend = .02). When stratified by FASN IHC expression, OS was 27.5 months (95% CI, 19.3 to 36.7 months) in FASN-negative patients versus 14.5 months (95% CI, 10.4 to 20.5 months) in FASN-positive patients (HR, 1.71 [95% CI, 1.17 to 2.51]; P = .005; Fig 3). However, the adjusted HR of FASN was reduced to 1.28 (95% CI, 0.84 to 1.95) in the multivariable model, with adjustment of IMDC risk group and BMI (Table 4). By contrast, BMI remained associated with OS when adjusted for IMDC risk groups and FASN (adjusted HR, 0.44 [95% CI, 0.29 to 0.66]), and this association was seen in both FASN-negative (HR, 0.39 [95% CI, 0.24 to 0.64]) and

FASN-positive groups (HR, 0.55 [95% CI, 0.27 to 1.13]; P -interaction = .434).

DISCUSSION

We investigated the prognostic significance of BMI in two large distinct cohorts of patients with mRCC treated in the modern therapy era. We demonstrated that patients with high BMI had a more favorable survival outcome than patients with low BMI. This finding is consistent in the first- and second-line settings

Fig 3. Association of fatty acid synthase (FASN) immunohistochemistry staining with overall survival (OS; total N = 146; number of deaths = 122).

Table 4. Associations of Overall Survival With BMI, IMDC Risk Group, and FASN Staining in IMDC Biospecimen Cohort

Variable	No.	No. of Deaths	Cox Regression When a Single Explanatory Variable Is Included in the Model		Multivariable Cox Model Including All Three Explanatory Variables in the Model	
			HR (95% CI)	P	Adjusted HR (95% CI)	P
BMI, ≥ 25 v < 25	92 v 41	69 v 40	0.40 (0.27 to 0.60)	< .001	0.44 (0.29 to 0.66)	< .001
IMDC risk group						
Favorable	30	22	1.00 (reference)	< .001	1.00 (reference)	.021
Intermediate	59	50	1.87 (1.13 to 3.09)		1.39 (0.82 to 2.35)	
Poor	23	21	4.25 (2.31 to 7.80)		2.86 (1.45 to 5.64)	
Unknown	34	29	1.74 (0.99 to 3.03)		1.64 (0.92 to 2.93)	
FASN, positive v negative	45 v 101	41 v 81	1.71 (1.17 to 2.51)	.006	1.28 (0.84 to 1.95)	.250

Abbreviations: BMI, body mass index; FASN, fatty acid synthase; HR, hazard ratio; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium.

for all end points examined including OS, even after adjustment for IMDC prognostic criteria and other baseline characteristics.

In 2010, we first reported the potential correlation between high BMI and favorable outcome in 475 patients with mRCC included in the IMDC.⁵ Subsequently, two cohorts of patients with mRCC investigated the role of visceral and subcutaneous fat areas with inconsistent results for the prognostic value of these computed tomography measures.^{19,20}

Several hypotheses have been proposed to explain the apparent “obesity paradox” and include the opposite effects hypothesis, detection bias, reverse causation, and collider stratification bias.^{21–23} Most recently, Nishihara et al²⁴ suggested that the inverse association between BMI and mortality among certain disease subgroups can be reconciled by disease heterogeneity; that is, the longer survival among obese compared with normal-weight patients is due to a less aggressive disease subtype.²⁵ Our findings support this hypothesis, because *FASN* gene expression was downregulated in obese patients compared with patients with normal BMI, and higher *FASN* expression was associated with worse survival. To explore the underlying biology, we focused on the lipogenesis pathway. The process by which tumors undergo de novo biogenesis of FA irrespective of the levels of circulating lipids is called neoplastic lipogenesis.^{26,27} An upregulation of *FASN* represents a nearly universal phenotypic alteration in most human malignancies, potentially conferring a survival growth advantage to tumor cells. However, the relation between obesity, *FASN*, and outcome seems tumor specific.^{7,28} A large TCGA investigation confirmed that *FASN* upregulation is associated with worse cancer-specific survival for ccRCC.⁶ In fact, *FASN* is downregulated in obese patients in contrast with normal-weight patients.⁶ Regulation of *FASN* is controlled by several upstream proteins of lipid homeostasis.^{29–31} Preclinical models have established that regulation of lipid composition by sterol regulatory element binding transcription factor 1 is essential to support cell survival and tumor growth.³² In the current report, we identified an association between *FASN* gene expression and BMI and subsequently between *FASN* gene expression and outcome in patients with mRCC from the TCGA cohort. We further conducted a pathway analysis within the entire TCGA cohort, which suggested a prognostic role of the FA pathway in ccRCC. In line with these results, we found that *FASN* protein levels determined by IHC were associated with

survival and with the IMDC risk groups in patients with mRCC treated with TT.

We believe this work provides insight to further explore both the biology and ultimately the therapeutic approaches in patients with advanced RCC. In glioblastoma preclinical models, inhibiting *FASN* with orlistat, a lipase inhibitor, induced autophagy and apoptosis and raised the question of potential therapeutic development.³³ Orlistat also inhibits the thioesterase domain of *FASN*.³⁴ Interestingly, preclinical models of pharmacological inhibition of *FASN* can reduce RCC tumor growth in vitro.³⁵

Our study is not without limitations, which include the use of BMI as a single morphometric parameter. BMI is a convenient measurement for a large study but may not provide information on fat repartition that would be obtained through computed tomography assessment. BMI was dichotomized to translate in clinically routinely used assessment; specific outcomes analysis in morbidly obese patients was not performed, nor was the investigation of BMI changes during the course of therapy. Second is the lack of metabolic biomarkers such as leptin or adiponectin to investigate the role of adipokines in the relation between BMI and prognosis. However, we believe that the size of the two clinical data sets as well as the ability to adjust for the known prognostic factors provide consistent results with different clinical outcomes measures. In addition, the hypothesis raised by the TCGA data set on the prognosis role of FA metabolism in patients with mRCC was further investigated in a unique data set of patients treated with TT with available tissue from the IMDC cohort.

In conclusion, in two large and distinct clinical data sets, we demonstrate that BMI affects mRCC clinical outcomes even after adjustment for known prognostic factors. Biologically, we used tumors from patients with mRCC from the ccRCC TCGA and from the IMDC data sets and showed that *FASN* pathway activation (*FASN* gene expression and IHC staining) is associated with BMI and survival. This suggests an integral role for FA metabolism in the prognosis of patients with mRCC and lays the groundwork for future therapeutic interventions that target the *FASN* pathway.

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Disclosures provided by the authors are available with this article at www.jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Body Mass Index and Metastatic Renal Cell Carcinoma: Clinical and Biological Correlations

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Appendix

Immunohistochemistry

Immunohistochemistry was performed on 4- μ m-thick tissue microarray sections, which were initially deparaffinized, rehydrated, and heated with a pressure cooker to 125°C for 30 seconds in citrate buffer for antigen retrieval and then incubated with peroxidase (S2003; Dako, Carpinteria, CA) and protein blocking reagents (X0909; Dako) each for 5 minutes. Sections were then incubated with anti-fatty acid synthase antibody (1:50; 3189; Cell Signaling, Danvers, MA) for 1 hour at room temperature followed by incubation with SignalStain Boost detection reagent (8114; Cell Signaling) for 30 minutes. All sections were developed using the DAB chromogen kit (3468; Dako) for 2 minutes and then lightly counterstained with hematoxylin.

Statistical Analyses

The statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC). For the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) cohort, the association between the body mass index (BMI) groups and other patient and disease characteristics was evaluated using the χ^2 test for categorical variables or Cochran-Armitage trend test for ordered BMI groups if appropriate. Differences between the BMI groups were examined with the log-rank test or the Wald χ^2 test from the Cox regression. To report the associations of BMI with overall survival and progression-free survival from the large IMDC and validation cohorts, we focused on the magnitude and precision of associations, rather than *P* values from test statistics to claim significance. For The Cancer Genome Atlas and IMDC specimen cohorts, two-sided *P* values were provided.

Fig A1. Reason for treatment failure stratified by body mass index (BMI) group in the International Metastatic Renal Cell Carcinoma Database Consortium cohort. Estimates of the cumulative incidence of treatment failure because of toxicity did not differ between the underweight/normal and overweight/obese groups. Cumulative incidence of treatment failure because of progression/death favored the overweight/obese group after adjustment for the International Metastatic Renal Cell Carcinoma Database Consortium risk groups.

BMI Investigation in mRCC

Fig A2. Fatty acid synthase immunohistochemistry staining: renal cell carcinoma tissues (A) positive, (B) negative.

Table A1. Type of Therapy in IMDC Cohort and Validation Cohort

Therapy	IMDC Cohort			Validation Cohort		
	BMI < 25	BMI ≥ 25	Total	BMI < 25	BMI ≥ 25	Total
First line, No.	785	1,190	1,975	1,110	1,880	2,990
Sunitinib	569 (73)	818 (69)	1,387 (70)	237 (21)	521 (28)	758 (25)
Sorafenib	130 (17)	205 (17)	335 (17)	44 (4)	52 (3)	96 (3)
Bevacizumab	16 (2)	64 (5)	80 (4)	291 (26)	491 (26)	782 (26)
Pazopanib	16 (2)	31 (3)	47 (2)	—	—	—
Tivozanib	1 (0.1)	6 (0.5)	7 (0.4)	—	—	—
Axitinib	—	2 (0.2)	2 (0.1)	155 (14)	247 (13)	402 (13)
Temsirolimus	34 (4)	48 (4)	82 (4)	192 (17)	218 (12)	410 (14)
Everolimus	13 (2)	12 (1)	25 (1)	—	—	—
Interferon alfa	—	—	—	191 (17)	351 (19)	542 (18)
Unknown	6 (1)	4 (0.3)	10 (0.5)	—	—	—
Second line, No.	297	438	735	719	948	1,667
Sunitinib	70 (24)	92 (21)	162 (22)	82 (11)	186 (20)	268 (16)
Sorafenib	78 (26)	118 (27)	196 (27)	292 (41)	372 (39)	664 (40)
Bevacizumab	12 (4)	18 (4)	30 (4)	—	—	—
Pazopanib	12 (4)	18 (4)	30 (4)	—	—	—
Axitinib	4 (1)	4 (1)	8 (1)	246 (34)	247 (26)	493 (30)
Cabozantinib	—	3 (1)	3 (0.4)	—	—	—
Temsirolimus	34 (11)	62 (14)	96 (13)	99 (14)	143 (15)	242 (15)
Everolimus	72 (24)	97 (22)	169 (23)	—	—	—
Other*	15 (5)	26 (6)	41 (6)	—	—	—

NOTE. Data are No. (%) unless otherwise noted.

Abbreviations: BMI, body mass index; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium.

*Interferon or investigational drugs.

Table A2. Treatment Outcomes According to Four BMI Categories in IMDC Cohort

Outcome	BMI, kg/m ²				P*
	Underweight (< 18.5)	Normal (18.5 to < 25)	Overweight (25 to < 30)	Obese (> 30)	
First line (n = 1,975)					
Total, No. (%)	66 (3)	719 (36)	663 (34)	527 (27%)	
OS					
No. of deaths	46	461	405	309	
Median (95% CI), months	11.9 (8.9 to 20.2)	17.5 (15.9 to 19.1)	23.5 (20.6 to 26.9)	29.4 (24.5 to 32.7)	< .001
Adjusted HR† (95% CI)	1.23 (0.90 to 1.69)	1.00 (reference)	0.90 (0.77 to 1.04)	0.78 (0.66 to 0.93)	.010
TTF					
No. of failures	58	613	552	448	
Median (95% CI), months	4.1 (3.3 to 7.3)	5.8 (5.5 to 6.6)	7.9 (7.1 to 8.7)	8.3 (7.6 to 9.5)	< .001
Adjusted HR† (95% CI)	1.07 (0.81 to 1.41)	1.00 (reference)	0.87 (0.76 to 0.98)	0.85 (0.73 to 0.98)	.053
Second line (n = 735)					
Total, No. (%)	29 (4)	268 (36)	252 (34)	186 (25)	
OS					
No. of deaths	23	186	152	103	
Median (95% CI), months	7.1 (4.7 to 8.4)	9.2 (7.6 to 10.7)	16.0 (13.2 to 21.7)	17.9 (13.0 to 23.2)	< .001
Adjusted HR† (95% CI)	1.63 (0.90 to 2.96)	1.00 (reference)	0.60 (0.45 to 0.79)	0.61 (0.44 to 0.84)	< .001
TTF					
No. of failures	25	231	214	156	
Median (95% CI), months	3.8 (2.3 to 6.0)	3.0 (2.8 to 3.5)	4.4 (3.4 to 5.5)	4.2 (3.4 to 5.0)	.006
Adjusted HR† (95% CI)	0.95 (0.54 to 1.67)	1.00 (reference)	0.67 (0.53 to 0.86)	0.74 (0.57 to 0.97)	.014

Abbreviations: BMI, body mass index; HR, hazard ratio; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; OS, overall survival; TTF, time to treatment failure.

*Log-rank test or Wald χ^2 test with 3 degrees of freedom.

†Adjusted for the International Metastatic Renal Cell Carcinoma Database Consortium prognostic risk factors and stratified on region (Asia, United States, Canada, and Europe) and sex.

Table A3. Treatment Outcomes According to Four BMI Categories in Validation Cohort

Outcome	BMI, kg/m ²				P*
	Underweight (< 18.5)	Normal (18.5 to < 25)	Overweight (25 to < 30)	Obese (> 30)	
First line (n = 2,990)					
Total, No. (%)	63 (2)	1,047 (35)	1,115 (37)	765 (26)	
OS					
No. of deaths	44	623	522	316	
Median (95% CI), months	9.7 (5.03 to 14.01)	14.5 (13.57 to 16.32)	23.0 (20.80 to 26.68)	28.7 (24.90 to 31.67)	
Adjusted HR† (95% CI)	1.19 (0.83 to 1.72)	1.00 (reference)	0.85 (0.73 to 0.98)	0.75 (0.63 to 0.89)	.007
PFS					
No. of failures	45	746	729	489	
Median (95% CI), months	3.6 (1.88 to 6.18)	5.5 (5.19 to 6.28)	8.6 (8.06 to 9.23)	9.1 (8.18 to 10.78)	
Adjusted HR† (95% CI)	0.96 (0.67 to 1.37)	1.00 (reference)	0.84 (0.74 to 0.96)	0.86 (0.74 to 1.00)	.065
Second line (n = 1,667)					
Total, No. (%)	72 (4)	647(39)	593(36)	355 (21)	
OS					
No. of deaths	45	318	262	162	
Median (95% CI), months	8.7 (6.47 to 13.54)	16.3 (13.83 to 17.67)	19.7 (17.04 to 22.90)	21.0 (16.58 to 26.88)	
Adjusted HR† (95% CI)	1.88 (0.1.36 to 2.61)	1.00 (reference)	0.91 (0.75 to 1.10)	0.97 (0.77 to 1.24)	< .001
PFS					
No. of failures	47	431	364	240	
Median (95% CI), months	5.1 (4.17 to 6.44)	5.7 (4.76 to 6.47)	7.0 (6.47 to 8.18)	6.5 (5.39 to 7.33)	
Adjusted HR† (95% CI)	1.22 (0.89 to 1.66)	1.00 (reference)	0.78 (0.663 to 0.92)	0.90 (0.73 to 1.10)	.0094

Abbreviations: BMI, body mass index; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

*Log-rank test or Wald χ^2 test with 3 degrees of freedom.

†Adjusted for age, sex, ethnicity, Eastern Cooperative Oncology Group, International Metastatic Renal Cell Carcinoma Database Consortium prognostic group, histology, prior nephrectomy, bone or liver metastasis, baseline hypertension, baseline dyslipidemia, baseline angiotensinogen system inhibitor use, statin use.

Table A4. Population Characteristics of the 61 Patients With Metastatic Clear Cell Renal Cell Carcinoma in The Cancer Genome Atlas Data Set

Characteristic	No. (%)
No.	61
Median age at diagnosis (minimum, maximum), years	62 (33, 84)
Sex: male	41 (67.2)
Ethnicity: white	59 (96.7)
Median BMI (minimum, maximum), kg/m ²	27 (17, 43.27)
BMI category	
BMI < 25	22 (36.1)
BMI ≥ 25	39 (63.9)
Median <i>FASN</i> gene expression value (minimum, maximum)	1,027 (525.7, 6,513)

Abbreviations: BMI, body mass index; *FASN*, fatty acid synthase.

Table A5. Population Characteristics of the 146 Patients With Metastatic ccRCC in IMDC Biospecimen Repository

Characteristic	No. (%)
No.	146
Sex: male	100 (68)
Prior nephrectomy: yes	142 (98)
Histology: ccRCC	131 (90)
Systemic therapy: VEGFR TKI	143 (98)
IMDC risk groups (n = 112)	
Favorable	30 (27)
Intermediate	59 (53)
Poor	23 (21)
BMI at first-line TT initiation	
BMI < 25	41 (31)
BMI ≥ 25	92 (69)

Abbreviations: BMI, body mass index; ccRCC, clear cell renal cell carcinoma; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; TKI, tyrosine kinase inhibitor; TT, targeted therapy; VEGFR, vascular endothelial growth factor receptor.