

Article

Association of Body Composition with Tumor Proteomics and Survival in Patients with Clear Cell Renal Cell Carcinoma

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Simple Summary

Patients with kidney cancer who have low muscle mass or excess body fat generally face poorer outcomes. However, the biological mechanisms linking body traits to tumor behavior are not well understood. Most prior research has looked at muscle mass and body fat independently, and their relationship to tumor biology in kidney cancer has not been thoroughly investigated. In our study, we integrated computer tomography-based measurements of muscle and body fat with data on tumor proteins and survival using a public dataset of kidney cancer patients. We identified specific combinations of muscle and body fat that were associated with tumor proteins and biological processes linked to increased mortality. Patients exhibiting both an unfavorable body composition and a certain tumor protein had worse survival compared to those with either factor alone. These results imply that body composition may influence tumor behavior, pointing toward new opportunities for personalized treatment options.

Abstract

Background/Objectives: Prognoses for patients with clear cell renal cell carcinoma (ccRCC) are associated with complex interactions between tumor and patient characteristics. This cross-sectional study investigated associations between body composition and tumor proteomics and their interaction with survival among patients with ccRCC. **Methods:** Data from 178 patients in the TCGA-KIRC project were analyzed to assess adipose and skeletal muscle tissue areas at the third lumbar vertebra of diagnostic computed tomography scan images. Patients were classified into four body composition types: high muscle with low adiposity; high muscle with high adiposity; low muscle with low adiposity; and low muscle with high adiposity. Proteins with differential expression ($p < 0.05$) were screened for interactions with body composition type on survival. Linear regression was used to assess associations, and Cox regression models—adjusted for age, tumor stage, sex, race, and ethnicity—were utilized for survival analysis. **Results:** Patients with low muscle with low adiposity exhibited worse survival than those having high muscle with high adiposity (hazard ratio, 3.74 [95% CI, 1.69–8.27]). Low muscle with low adiposity was also associated with increased expression of P-cadherin and decreased expression of DIRAS3 ($p < 0.05$; false discovery rate—corrected $p < 0.1$), both associated with poor survival in the entire TCGA-KIRC cohort. Among patients having low muscle with high adiposity, high (vs. low) PREX1 expression was associated with 15.8-fold (95% CI, 3.08–80.78) increased mortality. **Conclusions:** Body composition is associated with differential protein expressions and survival in ccRCC. Therefore, body composition and its associated tumor proteomics may serve as prognostic biomarkers and therapeutic targets in ccRCC.



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Keywords: clear cell renal carcinoma; adipose tissue; skeletal muscle; body composition; tumor protein expression

1. Introduction

Clear cell renal cell carcinoma (ccRCC) is the most prevalent type of kidney cancer, accounting for about 80% of all kidney cancer cases in the United States [1]. The incidence of ccRCC has been steadily rising, with an estimated 81,000 new diagnoses and nearly 15,000 deaths in 2023 [1]. The 5-year relative survival rate varies widely by the stage of disease: from 94.4% in localized disease, 82.6% in regional, and 25.7% in distant disease, based on SEER's prediction in 2022 [2]. The prediction of prognosis for patients with ccRCC mainly relies on histological and clinical data [3]. Nonetheless, there is a growing consensus on the need to enhance patient stratification methods by incorporating characteristics that influence both risk and survival outcomes.

Obesity has been well established as a primary risk factor for kidney cancers [4], likely due to chronic inflammation and alterations in the insulin signaling pathway [5]. Despite the increased risk, obesity is associated with less aggressive pathologic features and a more favorable prognosis among patients with ccRCC [6–8]. Most studies assessing this association used body mass index (BMI) as a measure of adiposity. However, BMI does not accurately estimate the quantities of adipose and muscle—important body composition components that may play important yet different roles in patient outcomes. Some studies have investigated the associations between body fat and muscle mass with ccRCC outcomes [9–11]. Specifically, low muscle mass and low subcutaneous adipose tissue have been associated with shorter overall survival [11–13]. However, findings examining visceral adipose tissue have been inconsistent, with some studies associating lower quantities with shorter survival, while others associate higher quantities and radiodensity to poor outcomes [12,13]. These findings underscore the complex relationships between body composition components and ccRCC, highlighting the need for further research. Given that most patients with ccRCC undergo computed tomography (CT) scans for diagnosis, cancer staging, and follow-up, body composition assessment can be readily performed using available images. By analyzing CT scans at the third lumbar (L3) vertebral level, muscle and adipose tissue areas, which strongly correlate with the total quantities of these tissues in the whole body, can be accurately measured [14].

The molecular profile of ccRCC also significantly affects patient prognosis [15]. Historically, ccRCC was mainly linked to mutations in the VHL gene, but recent research shows that additional genetic alterations and molecular signatures correlate with prognosis, metastasis, and response to therapy [16–18]. Thus, there is a pressing need to assess the combined effects of tumor signaling pathways and body composition profiles in patients with ccRCC.

This study aims to investigate the role of body composition components and tumor protein expression in the survival of patients with ccRCC. Findings from this research would advance the understanding of the impact of body composition on ccRCC progression and integrate body composition and tumor protein markers in risk stratification.

2. Materials and Methods

2.1. Study Participants

Data for patients were obtained from The Cancer Genome Atlas—Kidney Renal Clear Cell Carcinoma (TCGA-KIRC) cohort. TCGA is a collaborative initiative spearheaded by the National Cancer Institute and the National Human Genome Research Institute.

This project combines research data from multiple institutions to map and understand the germline and somatic alterations in cancers. The clinical, pathologic, and molecular data are stored at the Genomic Data Commons data portal [19], and the imaging data are stored at the Cancer Imaging Archive [20]. We obtained the CT scans in the archive from routine clinical imaging procedures conducted immediately before the pathologic diagnosis or a follow-up image taken within a 3-month window after the initial diagnosis.

The TCGA-KIRC has 537 patients with clinical data. Among them, 300 patients were excluded from the present study due to a lack of CT scan images. An additional 38 patients were excluded for ineligible CT scans that were truncated, of poor resolution (resulting in low detail and clarity for separating different tissue types using Hounsfield unit or anatomic position criteria), or lacked an L3 slice in the axial (transverse) view. Samples of these images are provided in Supplementary Figure S1. The remaining 199 patients with CT scan images were included in the survival analysis. No significant differences in demographic and clinical variables were observed between the included and excluded participants (Supplementary Table S1). Among these patients, 21 with missing proteomic data were further excluded. Therefore, 178 patients were included in the analysis of the association between body composition and protein expression. In cases of multiple CT scans being available for a patient, the earliest eligible scan was used. Proteins in the TCGA-KIRC data were assayed by reverse-phase protein array. All TCGA samples were evaluated by board-certified pathologists for confirmation of histological diagnosis and included only if tumor purity passed a predefined threshold (70%) [21]. For the analysis, 233 proteins with non-missing values for KIRC patients present in the proteomic dataset were included. Supplementary Figure S2 shows the flowchart of patient selection.

2.2. CT Image Analysis

An image corresponding to the L3 vertebra for each patient was selected using Sante DICOM Viewer Lite Version 3.1.5 (64-bit) (Santesoft Ltd.; Nicosia, Cyprus). Images were analyzed with SliceOmatic, version 5.0 revision 11b (Tomovision; Magog, Quebec, Canada. RRID:SCR_026268) to quantify visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), intramuscular adipose tissue (IMAT), and total skeletal muscle (TSM) areas using a semi-automated method [22]. Tissue identification relied on Hounsfield unit values and anatomical positioning (Supplementary Table S2) [23]. A trained researcher performed all annotations, which a board-certified radiologist subsequently reviewed for confirmation. The method has high interobserver reliability ($r = 0.992$ for VAT area and 0.999 for SAT area) using scans from 49 patients [24]. In a separate study, annotated areas from the semi-automated method were highly correlated ($r = 0.936$ for SAT, 0.945 for VAT, and 0.763 for TSM; 273 patients) with those from the manual segmentation method, but the former tended to provide smaller areas than the latter [22]. Total adipose tissue (TAT) was calculated by summing VAT, SAT, and IMAT values. Optimal cutoff values for TAT and TSM quantities were identified using maximally selected rank statistics, using the *surv_cutpoint* function in the *survminer* package (version 0.4.9) in R (version 4.4.0; R Core Team, 2024. RRID:SCR_001905). This outcome-oriented method evaluates candidate thresholds and selects the cutoff that maximizes the separation in overall survival between patients categorized as having low versus high TAT or TSM quantities. The optimal cutoff values for TAT and TSM area quantities were calculated separately for male and female patients because of significant differences in adipose and muscle mass by sex [25,26]. Patients were then classified into four mutually exclusive body composition groups based on the areas of the TSM and TAT categories: (1) high muscle with high adiposity, (2) high muscle with low adiposity, (3) low muscle with high adiposity, and (4) low muscle with low adiposity.

2.3. Statistical Analysis

Descriptive statistics were computed to summarize demographic and clinical data. Means and standard deviations were used for continuous variables, whereas frequencies and percentages were used for categorical variables. Survival analysis was conducted using Kaplan–Meier curves and adjusted Cox proportional hazards models. The group with the best overall survival, i.e., the high muscle/high adiposity group, was selected as the reference group for estimating hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs). The analysis was adjusted for age, sex, race, ethnicity, and cancer stage. The Cox proportional hazards assumption was examined using the Schoenfeld residuals test; all body composition variables had $p > 0.05$, indicating no violation of the assumption (Supplementary Figure S3).

To assess the association between the body composition types and tumor protein expression (in $\log_2$ normalized values), linear regression analysis adjusted for age, sex, race, ethnicity, and cancer stage was employed, with the high muscle with high adiposity type as the reference group. False discovery rate (FDR) adjustment was performed using the Benjamini–Hochberg method. The FDR cutoff was set at 0.1. Thus, our findings should be interpreted as hypothesis generation. We investigated the association of proteins showing differential expression (nominal $p < 0.05$) with survival overall and by body composition types. Optimal cutoff values for protein expression levels were determined using maximally selected rank statistics to effectively stratify patients into two distinct risk groups (high vs. low) based on overall survival. This analysis was performed using the *surv_cutpoint* function in the *survminer* package in R software. The corresponding survival curves were then generated using the *ggsurvplot* function in the same package. Cox proportional hazards models were constructed, incorporating an interaction term between body composition groups and proteins.

All statistical analyses were performed using SAS 9.4 (SAS Institute Inc; Cary, NC, USA. RRID:SCR_008567) and R (version 4.4.0; R Core Team, 2024. RRID:SCR_001905). The volcano plots were generated using GraphPad Prism version 10.1.2 (GraphPad Software; Boston, MA, USA. RRID:SCR_002798).

3. Results

3.1. Patient Characteristics

Table 1 summarizes the demographic and clinical characteristics of the patients with clinical, proteomic, and CT scan data based on their body composition distribution. Their age at diagnosis ranged from 26 to 88 years, with a mean of 59.6 years. Most patients (94.4%) were White, with non-Hispanic or Latino being the predominant ethnicity (94.3% among those with a non-missing value). Male patients comprised approximately two-thirds (66.9%) of the sample population. Most patients (51.7%) were diagnosed as having stage I ccRCC, with 8.4%, 25.3%, and 14.6% of patients having stages II, III, and IV, respectively. The majority of patients (57.9%) were categorized as being in the high muscle with high adiposity body composition type, with 9.0% in the high muscle with low adiposity type, 20.8% in the low muscle with low adiposity type, and 12.4% in the low muscle with high adiposity type.

Table 1. Summary of descriptive statistics.

Characteristic	Total	Low Muscle with High Adiposity	Low Muscle with Low Adiposity	High Muscle with High Adiposity	High Muscle with Low Adiposity	<i>p</i> -Value
No. (%) in group	178 (100%)	22 (12.4%)	37 (20.8%)	103 (57.9%)	16 (9.0%)	
Age						<0.001 ¹
Mean (SD), y	59.6 (13.2)	68.4 (10.6)	65.7 (13.2)	56.3 (12.5)	55.2 (10.5)	
Sex, n (%)						<0.001 ²
Female	59 (33.1%)	11 (50.0%)	29 (78.4%)	11 (10.7%)	8 (50.0%)	
Male	119 (66.9%)	11 (50.0%)	8 (21.6%)	92 (89.3%)	8 (50.0%)	
Race, n (%)						0.116 ²
Asian	2 (1.1%)	0 (0%)	1 (2.7%)	0 (0.0%)	1 (6.3%)	
Black or African American	8 (4.5%)	0 (0%)	0 (0%)	7 (6.8%)	1 (6.3%)	
White	168 (94.4%)	22 (100%)	36 (97.3%)	96 (93.2%)	14 (87.5%)	
Ethnicity, n (%)						0.718 ²
Hispanic or Latino	7 (3.9%)	1 (4.5%)	1 (2.7%)	4 (3.9%)	1 (6.3%)	
Not Hispanic or Latino	116 (65.2%)	16 (72.7%)	26 (70.3%)	62 (60.2%)	12 (75.0%)	
Not reported	55 (30.9%)	5 (22.7%)	10 (27.0%)	37 (35.9%)	3 (18.8%)	
AJCC pathologic stage, n (%)						<0.001 ²
I	92 (51.7%)	11 (50.0%)	11 (29.7%)	63 (61.2%)	7 (43.8%)	
II	15 (8.4%)	1 (4.5%)	0 (0%)	14 (13.6%)	0 (0%)	
III	45 (25.3%)	5 (22.7%)	15 (40.5%)	18 (17.5%)	7 (43.8%)	
IV	26 (14.6%)	5 (22.7%)	11 (29.7%)	8 (7.8%)	2 (12.5%)	
Vital status, n (%)						<0.001 ²
Alive	122 (68.5%)	15 (68.2%)	13 (35.1%)	84 (81.6%)	10 (62.5%)	
Dead	56 (31.5%)	7 (31.8%)	24 (64.9%)	19 (18.4%)	6 (37.5%)	
Visceral adipose tissue area						<0.001 ¹
Mean (SD), cm ²	191.6 (117.93)	243.6 (133.32)	77.9 (44.38)	240.5 (97.10)	67.4 (40.57)	
Intramuscular adipose tissue area						<0.001 ¹
Mean (SD), cm ²	9.2 (6.42)	12.6 (7.60)	9.3 (6.95)	9.2 (5.81)	4.0 (3.66)	
Subcutaneous adipose tissue area						<0.001 ¹
Mean (SD), cm ²	234.0 (119.30)	297.8 (142.44)	161.3 (56.17)	261.7 (117.61)	136.7 (59.50)	

Table 1. Cont.

Characteristic	Total	Low Muscle with High Adiposity	Low Muscle with Low Adiposity	High Muscle with High Adiposity	High Muscle with Low Adiposity	<i>p</i> -Value
Total adipose tissue area						<0.001 ¹
Mean (SD), cm ²	434.8 (198.76)	554.0 (189.00)	248.5 (84.46)	511.4 (168.22)	208.1 (70.82)	
Muscle area						<0.001 ¹
Mean (SD), cm ²	159.9 (41.74)	125.6 (19.46)	108.4 (18.87)	186.4 (27.94)	155.5 (27.35)	

¹ Kruskal–Wallis *p*-value. ² Chi-Square *p*-value. Abbreviation: AJCC, American Joint Committee on Cancer; SD, Standard Deviation.

3.2. Body Composition and Survival

The identified cutoff values for TSM were 153.00 cm² for male patients and 120.70 cm² for female patients (Supplementary Figure S4). The cutoff values for TAT were 239.11 cm² for male patients and 383.05 cm² for female patients (Supplementary Figure S5). Survival analysis of the TAT groups presented in Table 2 showed that individuals in the low TAT group had more than three times the mortality risk of those in the high TAT group (HR, 3.24 [95% CI, 1.56–6.74; *p* = 0.002) (Figure 1A). Total muscle groups did not demonstrate a significant association with overall survival (low vs. high; HR, 1.15 [95% CI, 0.58–2.30]; *p* = 0.685) (Table 2 and Figure 1B). Compared with the high muscle with high adiposity body composition type, which had the best overall survival, the low muscle with low adiposity type experienced the worst overall survival outcomes (HR, 3.74 [95% CI, 1.69–8.27]; *p* = 0.001), followed by the high muscle with low adiposity type (HR, 3.20; [95% CI, 1.22–8.42]; *p* = 0.018) (Table 2 and Figure 1C). The associations of other covariates with mortality are presented in Supplementary Table S3.

Table 2. Mortality Risk by Body Composition.

	Events/Total	Hazard Ratio (95% CI)	<i>p</i> -Value
Total Adiposity *			
Low	32/58	3.24 (1.56–6.74)	0.002 ¹
High	29/141	Reference	
Skeletal Muscle **			
Low	32/67	1.15 (0.58–2.30)	0.685 ¹
High	29/132	Reference	
Body Composition ***			0.005 ²
High muscle with low adiposity	7/17	3.20 (1.22–8.42)	0.018 ¹
Low muscle with low adiposity	25/41	3.74 (1.69–8.27)	0.001 ¹
Low muscle with high adiposity	7/26	1.14 (0.45–2.91)	0.786 ¹
High muscle with high adiposity	22/115	Reference	

¹ Covariate Wald *p*-value. ² Type 3 Wald *p*-value. * Total adiposity: Adjusted for stage, sex, race, ethnicity, age, and Total Muscle area. ** Skeletal muscle: Adjusted for stage, sex, race, ethnicity, age, and Total Adiposity. *** Body composition: Adjusted for stage, sex, race, ethnicity, and age. Abbreviation: CI, confidence interval.

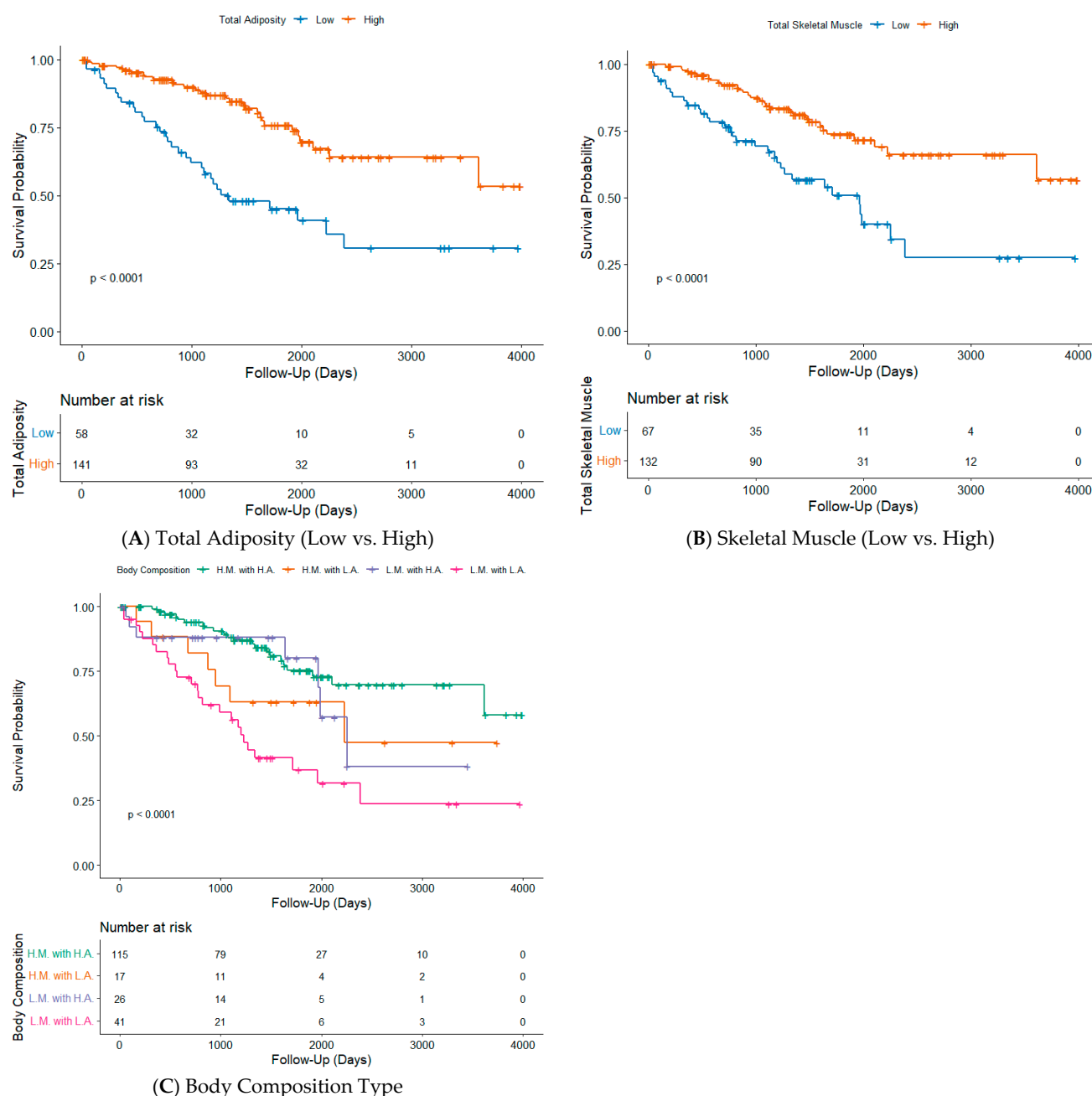


Figure 1. Kaplan–Meier curves exploring the survival trend of participants based on body composition components and categories. Abbreviations: H.M., High Muscle; H.A., High Adiposity; L.M., Low Muscle; L.A., Low Adiposity.

3.3. Body Composition and Tumor Protein Expression

TSM and TAT levels were associated with distinct expression levels in a number of protein markers. Specifically, high (vs. low) TSM levels were associated with higher expression of androgen receptor ($\log_2$ fold change, 0.2; $p = 0.02$), carbonic anhydrase IX (CA9) ($\log_2$ fold change, 0.3; $p = 0.037$), interferon regulatory factor 1 (IRF-1) ($\log_2$ fold change, 0.1; $p = 0.034$), and BCL2-related protein A1 (BCL2A1) ($\log_2$ fold change, 0.2; $p = 0.038$), but lower expression of P-cadherin ($\log_2$ fold change, -0.2 ; $p = 0.025$), caspase-3 ($\log_2$ fold change, -0.1 ; $p = 0.018$), and phosphorylated myosin IIa at serine 1943 (phospho-myosin IIa (S1943)) ($\log_2$ fold change, -0.2 ; $p = 0.024$) (Figure 2A).

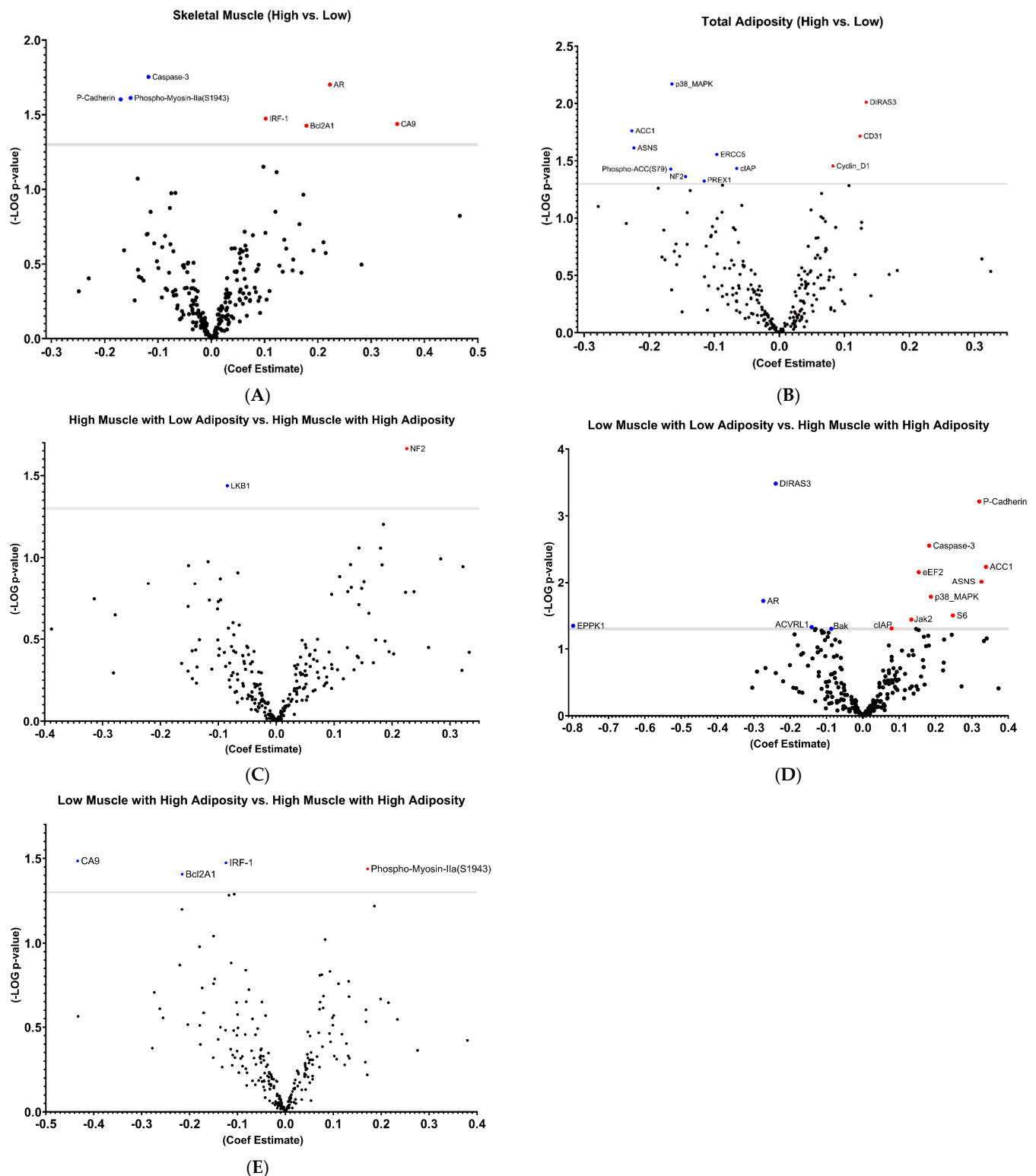


Figure 2. Volcano Plot of Differential Tumor Protein Expression Based on Total Skeletal Muscle, Total Adiposity Categories, and Body Composition Group. ●, Downregulated. ●, Upregulated. Abbreviations: Coef, coefficient. (A) Abbreviations: AR, androgen receptor; Bcl2A1, BCL2-related protein A1; CA9, carbonic anhydrase IX; IRF-1, interferon regulatory factor 1; phospho-myosin-IIa(S1943), phosphorylated myosin IIa at serine 1943. (B) Abbreviations: ACC1, acetyl-CoA carboxylase 1; ASNS, asparagine synthetase; cIAP, cellular inhibitor of apoptosis protein; DIRAS3, DIRAS family GTPase 3; ERCC5, excision repair cross-complementation group 5; NF2, neurofibromin-2; p38 MAPK, p38 mitogen-activated protein kinase; phospho-ACC(S79), phosphorylated acetyl-CoA carboxylase at

serine 79; PREX1, phosphatidylinositol 3,4,5-trisphosphate-dependent Rac exchanger 1. (C) Abbreviations: LKB1, liver kinase B1; NF2, neurofibromin-2. (D) Abbreviations: ACC1, acetyl-CoA carboxylase 1; ACVRL1, activin A receptor type II-like kinase 1; AR androgen receptor; ASNS, asparagine synthetase; Bak, Bcl-2 antagonist killer 1; cIAP, cellular inhibitor of apoptosis protein; DIRAS3, DIRAS family GTPase 3; eEF2, eukaryotic translation elongation factor 2; EPPK1, Epiplakin; Jak2, Janus kinase 2; p38 MAPK, p38 mitogen-activated protein kinase; S6, ribosomal protein S6. (E) Abbreviations: BCL2A1, BCL2-related protein A1; CA9, carbonic anhydrase IX; IRF-1, interferon regulatory factor 1 (IRF-1); phospho-myosin-IIA(S1943), phosphorylated myosin IIa at serine 1943.

High vs. low TAT levels were associated with higher expression of DIRAS family GTPase 3 (DIRAS3) ($\log_2$ fold change, 0.13; $p = 0.010$), CD31 ($\log_2$ fold change, 0.1; $p = 0.020$), and cyclin D1 ($\log_2$ fold change, 0.1; $p = 0.035$), but lower expression of neurofibromin-2 (NF2) ($\log_2$ fold change, -0.1 ; $p = 0.043$), acetyl-CoA carboxylase 1 (ACC1) ($\log_2$ fold change, -0.2 ; $p = 0.017$), asparagine synthetase (ASNS) ($\log_2$ fold change, -0.2 ; $p = 0.024$), p38 mitogen-activated protein kinase (p38 MAPK) ($\log_2$ fold change, -0.2 ; $p = 0.007$), cellular inhibitor of apoptosis protein (cIAP) ($\log_2$ fold change, -0.1 ; $p = 0.037$), excision repair cross-complementation group 5 (ERCC5) ($\log_2$ fold change, -0.1 ; $p = 0.028$), phosphorylated acetyl-CoA carboxylase at serine 79 (phospho-ACC [S79]) ($\log_2$ fold change, -0.2 ; $p = 0.037$) and phosphatidylinositol 3,4,5-trisphosphate-dependent Rac exchanger 1 (PREX1) ($\log_2$ fold change, -0.1 ; $p = 0.048$) (Figure 2B).

Table 3 presents the adjusted regression analysis findings, including proteins that exhibited at least one significant association with the body composition type categories ($p < 0.05$). Supplementary File S1 contains the adjusted regression analysis for all 233 proteins. The high muscle with low adiposity type (vs. the high muscle with high adiposity type) was associated with higher expression of NF2 ($\log_2$ fold change, 0.2; $p = 0.022$) and lower expression of liver kinase B1 (LKB1) ($\log_2$ fold change, -0.1 ; $p = 0.037$) (Figure 2C).

The low muscle with low adiposity type (vs. the high muscle with high adiposity type) was associated with increased expression of P-cadherin ($\log_2$ fold change, 0.3; $p = 0.001$, FDR $p = 0.071$) and with decreased expression of DIRAS3 ($\log_2$ fold change, -0.2 ; $p = 0.0003$, FDR $p = 0.071$). Other differentially expressed proteins (nominal $p < 0.05$) included caspase-3 ($\log_2$ fold change, 0.2; $p = 0.003$), ACC1 ($\log_2$ fold change, 0.3; $p = 0.006$), eukaryotic translation elongation factor 2 (eEF2) ($\log_2$ fold change, 0.2; $p = 0.007$), ASNS ($\log_2$ fold change, 0.3; $p = 0.009$), p38 MAPK ($\log_2$ fold change, 0.2; $p = 0.017$), ribosomal protein S6 (S6) ($\log_2$ fold change, 0.2; $p = 0.032$), Janus kinase 2 (Jak2) ($\log_2$ fold change, 0.1; $p = 0.036$), and cIAP ($\log_2$ fold change, 0.1; $p = 0.049$), androgen receptor ($\log_2$ fold change, -0.3 ; $p = 0.019$), epiplakin (EPPK1) ($\log_2$ fold change, -0.8 ; $p = 0.045$), activin A receptor type II-like kinase 1 (ACVRL1) ($\log_2$ fold change, -0.1 ; $p = 0.047$), and Bcl-2 antagonist killer 1 (Bak) ($\log_2$ fold change, -0.1 ; $p = 0.0499$) (Figure 2D).

The low muscle with high adiposity type (vs. the high muscle with high adiposity type) was associated with higher expression of phospho-myosin IIa (S1943) ($\log_2$ fold change, 0.2; $p = 0.036$) and with lower expression of CA9 ($\log_2$ fold change, -0.4 ; $p = 0.033$), IRF-1 ($\log_2$ fold change, -0.1 ; $p = 0.034$), and BCL2A1 ($\log_2$ fold change, -0.2 ; $p = 0.038$) (Figure 2E). All FDRs exceeded 0.1, except for P-cadherin and DIRAS3 in the low muscle with low adiposity type (vs. the high muscle with high adiposity type).

Table 3. Differential Protein Expression by Body Composition Type.

Protein	High Muscle with Low Adiposity vs. High Muscle with High Adiposity			Low Muscle with Low Adiposity vs. High Muscle with High Adiposity			Low Muscle with High Adiposity vs. High Muscle with High Adiposity		
	Estimate	<i>p</i> -Value	FDR	Estimate	<i>p</i> -Value	FDR	Estimate	<i>p</i> -Value	FDR
Phospho-ACC(S79)	0.143	0.195	0.99	0.174	0.091	0.56	−0.015	0.883	0.98
ACC1	0.16	0.22	0.99	0.339	0.006 *	0.32	0.051	0.672	0.98
AR	−0.042	0.738	0.99	−0.274	0.019 *	0.55	−0.216	0.063	0.98
Bak	−0.014	0.769	0.99	−0.087	0.05 *	0.55	0.025	0.572	0.98
CD31	−0.118	0.106	0.99	−0.132	0.052	0.55	−0.002	0.97	0.98
cIAP	0.032	0.46	0.99	0.079	0.049 *	0.55	−0.017	0.662	0.98
Cyclin_D1	−0.05	0.356	0.99	−0.086	0.088	0.56	0.027	0.586	0.98
eEF2	−0.005	0.932	0.99	0.154	0.007 *	0.32	0.019	0.732	0.98
LKB1	−0.085	0.037 *	0.99	−0.021	0.581	0.93	−0.041	0.27	0.98
NF2	0.225	0.022 *	0.99	0.168	0.066	0.55	0.098	0.278	0.98
P Cadherin	0.047	0.634	0.99	0.32	0.001 *	0.071 **	0.101	0.27	0.98
p38_MAPK	0.143	0.087	0.99	0.187	0.017 *	0.55	0.002	0.981	0.98
S6	−0.078	0.528	0.99	0.247	0.032 *	0.55	−0.015	0.893	0.98
ASNS	0.013	0.925	0.99	0.326	0.01 *	0.37	−0.09	0.47	0.98
Phospho-Myosin-IIa(S1943)	0.004	0.961	0.99	0.126	0.125	0.60	0.172	0.036 *	0.98
EPPK1	−0.281	0.508	0.99	−0.797	0.045 *	0.55	−0.433	0.273	0.98
ACVRL1	−0.053	0.483	0.99	−0.141	0.047 *	0.55	−0.051	0.467	0.98
DIRAS3	−0.073	0.298	0.99	−0.24	<0.001 *	0.071 **	−0.051	0.431	0.98
PREX1	0.128	0.11	0.99	0.147	0.050	0.55	0.043	0.564	0.98
Bcl2A1	−0.042	0.71	0.99	−0.165	0.115	0.60	−0.215	0.039	0.98
Caspase_3	−0.003	0.958	0.99	0.182	0.003 *	0.22	0.073	0.225	0.98
ERCC5	−0.003	0.964	0.99	0.079	0.149	0.63	−0.107	0.051	0.98
IRF-1	0.042	0.506	0.99	−0.027	0.641	0.95	−0.124	0.034	0.98
Jak2	0.058	0.392	0.99	0.133	0.036 *	0.55	0.08	0.207	0.98
CA9	0.168	0.441	0.99	−0.054	0.789	0.97	−0.434	0.033	0.98

* $p < 0.05$. ** $FDR < 0.1$. Note: a protein was included if a nominal p -value was <0.05 in the TAT, TSM, or body composition comparisons.

3.4. Tumor Protein Expression, Interaction with Body Composition Types, and Survival

We examined interactions between differentially expressed protein markers with a nominal p value < 0.05 and body composition type on survival. Only PREX1 significantly interacted with body composition to predict survival (joint interaction p -value = 0.011). The cutoff value categorizing patients into high and low PREX1 groups and the corresponding survival curve are presented in Supplementary Figure S6. Tumor PREX1 high (vs. low) expression was associated with a higher mortality risk (HR, 2.12 [95% CI, 1.17–3.83]) (Table 4). Among the body composition strata, PREX1 high (vs. low) expression was associated with increased mortality risk among the patients having high muscle with high adiposity (HR, 2.99 [95% CI, 1.19–7.51]) as well as a 15-fold higher mortality risk (HR, 15.77 [95% CI, 3.08–80.78]) among patients having the low muscle with high adiposity type.

Table 4. PREX1 Protein Expression and Its Interaction with Body Composition Type on Survival.

Tumor Protein	Event/Total	Hazard Ratio (95% Confidence Interval)
PREX1: Low	28/113	Reference
High	28/65	2.12 (1.17–3.83)
Stratified by Body Composition type		
High Muscle with Low Adiposity	6/16	4.53 (0.73–28.00)
High Muscle with High Adiposity *	19/103	2.99 (1.19–7.51)
Low Muscle with Low Adiposity	23/36	0.79 (0.33–1.90)
Low Muscle with High Adiposity *	8/23	15.77 (3.08–80.78)
Interaction Joint test <i>p</i> value = 0.011		

* Significant interaction, $p < 0.05$. Models were adjusted for age, sex, race, ethnicity, and cancer stage. Abbreviations: PREX1, phosphatidylinositol 3,4,5-trisphosphate-dependent Rac exchanger 1.

4. Discussion

This study extends the findings of previous studies that evaluated the associations between body composition features and survival among patients with ccRCC [9–13] to include how body composition and its components interact with tumor protein expression in survival among patients with ccRCC. After adjusting for confounding factors, we found that the total area of adiposity (high vs. low TAT) as well as the body composition types of high muscle with low adiposity and low muscle with low adiposity (vs. high muscle with high adiposity) were significantly associated with overall survival. We also found that several tumor proteins involved in carcinogenesis, functioning as oncoproteins or tumor suppressors in key cancer signaling pathways, were significantly upregulated or downregulated in high (vs. low) TSM, high (vs. low) TAT, and between the body composition types. The body composition type also modified the association between PREX1 expression levels and overall survival.

Patients with ccRCC displaying low adiposity (TAT low) exhibited overall mortality risk that was increased by more than twice that of patients with high adiposity (TAT high). This finding is consistent with the results of several previous studies and aligns with the “obesity paradox” observed for various obesity-associated malignant tumors, including renal cancers, in which higher adiposity is associated with better survival outcomes despite being a risk factor [6–8,27]. The apparent obesity paradox may be explained by several factors, including that adipose tissue acts as an energy reserve, enabling patients with high adiposity to better withstand the physiological stress of cancer and the pharmacologic stress of cancer treatments. In addition, although we adjusted for cancer stage in our regression models, most patients with early-stage cancer were categorized not only in the high adiposity category but also in the high muscle category.

For the association between the differential expression of protein markers and adipose tissue, low TAT (vs. high TAT) was associated with a distinct molecular profile characterized by decreased expression of DIRAS3, CD31, and cyclin D1 alongside increased expression of several proteins, including NF2, ACC1, ASNS, p38 MAPK, cIAP, ERCC5, phospho-ACC (S79), and PREX1. This finding suggests that adipose tissue modulates tumor-suppressive and oncogenic mechanisms. Notably, DIRAS3, a tumor suppressor downregulated in patients with ccRCC with low TAT, binds to and disrupts RAS activation, thus inhibiting the RAS/MAPK pathway and limiting tumor growth. DIRAS3 also slows tumor progression and induces autophagy, which can support tumor dormancy and reduce tumor proliferative capacity [28]. Thus, lower DIRAS3 expression in patients with low TAT is consistent with their poorer survival.

We observed no significant association between total muscle and overall survival. This finding contrasts with those of previous studies reporting that among patients with ccRCC, those with higher muscle mass exhibit significantly longer overall survival than those with lower muscle mass [11–13]. Additionally, sarcopenia, characterized by a marked reduction in lean mass and weakened muscle strength, has been associated with increased mortality among patients with ccRCC [29,30]. The difference between our findings and those of previous studies may involve the body composition classification methods employed. Our method resulted in twice as many patients categorized in the high TSM group as in the low TSM group, and most of these patients had early-stage cancer. While total muscle mass alone was not associated with overall survival, the combination of low muscle mass with low adiposity was associated with a worse overall survival compared with the high muscle with high adiposity group, after adjusting for patient and tumor characteristics. This low muscle mass with low adiposity body composition profile likely reflects poor nutritional status at baseline, which has been linked to diminished benefits from medical treatments and lower overall survival rates for various types of cancer [31]. Another group associated with high mortality in our study was the high muscle with low adiposity group. This finding underscores the importance of adiposity as a prognostic factor among patients with ccRCC, and it is consistent with our observation that high (vs. low) total adiposity is associated with better overall survival.

Tumor samples from patients with ccRCC having low muscle mass and/or low adiposity showed distinct and overlapping proteomic alterations associated with host body composition phenotypes. In patients with low muscle mass, tumors showed downregulation of androgen receptor, CA9, IRF1, and BCL2A1 proteins, alongside upregulation of P-cadherin, caspase-3, and phospho-myosin-IIA (S1943) proteins, indicating suppression of hormone and immune signaling with concomitant activation of apoptotic and cytoskeletal remodeling pathways. In contrast, tumor samples from patients with low adiposity exhibited increased expression of proteins related to metabolic regulation and cellular stress, including NF2, ACC1, phospho-ACC (S79), ASNS, p38 MAPK, ERCC5, cIAP, and PREX1, together with reduced expression of DIRAS3, CD31, and cyclin D1, suggesting dysregulated lipid metabolism, enhanced stress kinase signaling, impaired angiogenesis, and altered cell cycle control. Interestingly, tumor samples from patients presenting with both low muscle mass and low adiposity uniquely displayed a common proteomic signature characterized by upregulation of JAK2, ribosomal S6, and eEF2, reflecting sustained activation of inflammatory and mammalian target of rapamycin signaling, along with downregulation of EPPK1, ACVRL1, and pro-apoptotic BAK, suggesting disruption of epithelial structure, angiogenic signaling, and apoptotic regulation.

In particular, DIRAS3 and P-cadherin, proteins that were significantly associated with the low muscle with low adiposity type after FDR correction, may be key proteins linking body composition and survival. Notably, DIRAS3, a tumor suppressor, binds and disrupts RAS activation, thus inhibiting the RAS/MAPK pathway and limiting tumor growth. DIRAS3 also slows tumor progression and induces autophagy, which can support tumor dormancy and reduce tumor proliferative capacity. Cadherins (calcium-dependent adhesion proteins) are important in cellular adhesion. In ccRCC, P-cadherin expression is associated with higher nuclear grade, distant metastasis, and higher stage [32]. The mechanisms by which P-cadherin affects tumorigenesis and progression remain unclear; they may involve altered DNA methylation in *CDH3*, the gene encoding P-cadherin [33]. In our study, P-cadherin expression was upregulated in the low muscle with low adiposity type. This upregulation is consistent with the survival data in the TCGA-KIRC cohort, showing that high (vs. low) P-cadherin expression was associated with increased mortality risk (Log-Rank P , 2.468×10^{-7}) [34]. Similarly, DIRAS3 expression was downregulated in

the low muscle with low adiposity type in our study, and in the TCGA-KIRC cohort, low (vs. high) DIRAS3 expression was associated with increased mortality risk, although the association was not significant (Log-Rank P, 0.153) [34].

Our analysis revealed that body composition modified the association between PREX1 and survival. High expression of PREX1 in patients having low muscle with high adiposity was associated with a 15.8-fold increase in mortality risk. This finding is in agreement with previous studies, with high PREX1 expression consistently associated with poor prognosis across various cancers [35–37] and with preclinical models demonstrating that PREX1 knockdown hinders tumor growth and metastasis [35,36]. Located downstream of receptor tyrosine kinases and G protein-coupled receptors [38,39], PREX1 activates Rho GTPases, primarily Rac1, orchestrating cellular functions such as cytoskeletal remodeling and promoting cell migration and proliferation [39,40]. We found that PREX1 was upregulated in tumors of patients with higher adiposity, in concordance with a recent study suggesting that PREX1 may promote glucose intolerance, as PREX1 knockout mice fed a high-fat diet were protected from developing diabetes [41]. Overall, our findings speak to the prooncogenic and metabolic roles of PREX1. In patients with high adiposity, obesity-induced inflammation and metabolic deregulation may have enhanced the oncogenic effects of PREX1, leading to more aggressive tumor behavior, increased metastatic potential, and poorer survival. High PREX1 expression was associated with even poorer survival when high adiposity coexisted with low muscle, typical of sarcopenic obesity [42,43]. A low muscle with high adiposity phenotype along with high PREX1 expression may create a particularly vulnerable state that independently predicts poor cancer prognosis.

A major strength of this study is that our evaluation of the association between CT-assessed muscularity and adiposity in relation to tumor proteomics among patients with ccRCC highlighted distinct interactions of muscle vs. adipose tissue with tumor biology. However, this study has several limitations. The retrospective design may have introduced selection bias. Additionally, the analysis was cross-sectional using a single CT scan image obtained close to diagnosis; hence, establishing causal relationships between body composition and tumor proteomics was not possible. Systematic errors may have arisen from variability in CT scan images obtained from different centers. This variability could not be addressed in the analysis due to a lack of detailed imaging and center information. In addition, the TCGA-KIRC cohort lacked weight and height data, which would have been valuable in model adjustment or comparison with the body composition variables. Caution should be taken when interpreting our results, as the TCGA proteomic data were derived from whole-tissue lysates, which may reflect both tumor epithelium and other components of stromal and adipose tissue, although tumor impurity was controlled at a level of 70% or above. In addition, the generalizability of our findings may be limited by the demographic homogeneity of the study population (e.g., 94.4% white). We cannot rule out confounding. Also, the maximally selected rank statistics method may introduce potential overfitting. Our findings warrant future validation.

Our findings suggest that repurposing clinical CT scans can benefit medical decision-making by providing risk stratification and treatments targeting adipose and skeletal muscle as a supplementary regimen. Artificial intelligence or machine learning-based tools for body composition annotation are available, and a workflow can be established among surgical oncology, radiology, and medical oncology departments. Although our biomarker findings require validation, clinical settings should consider implementing CT-derived body composition given strong, consistent evidence on its association with clinical outcomes.

5. Conclusions

The body composition type of low muscle mass combined with low adiposity was associated with poor survival among patients with ccRCC. The low muscle with low adiposity body composition type was associated with distinct tumor proteomic patterns, including increased expression of proteins related to cell proliferation and migration, and decreased expression of tumor suppressor proteins. The modification of body composition type on tumor PREX1 expression and its association with survival highlights the critical interactions between host body composition and tumor molecular characteristics, supporting the potential utility of integrating both types of factors in prognostic assessment and risk stratification of ccRCC.

Supplementary Materials: The following supporting information can be downloaded at <https://www.mdpi.com/article/10.3390/cancers18193161/s1>. File S1: Regression results for body composition association with all 233 proteins; Table S1: Descriptive statistics comparison between included patients and excluded patients; Table S2: Tissue radiodensity cutoff points in Hounsfield units for computed tomography image annotation; Table S3: Risk of mortality for covariates; Figure S1: Samples of Excluded images; Figure S2: Flowchart of patient selection from the TCGA-KIRC cohort; Figure S3: Evaluation of the Proportional Hazards Assumption Across Body Composition Categories; Figure S4: Total muscle area cutoffs; Figure S5: Total adipose tissue cutoffs; Figure S6: PREX1 distribution and corresponding Kaplan-Meier survival curve.

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Informed Consent Statement: Informed consent from all subjects in this study was waived. All patients consented to TCGA. The data were publicly available, and no identifying or protected health information was present. Researchers accessing the data agreed to the Data Use Certification Agreement, which ensures compliance with privacy protections, secure data access, and publication guidelines.

Data Availability Statement: Data analyzed in this study are publicly available in the following repositories: The CT images analyzed in this study were obtained from the Cancer Imaging Archive at TCIA: TCGA-KIRC [20]; Clinical and protein data are available in the National Cancer Institute’s Genomic Data Commons at GDC: TCGA-KIRC [19] and at MD Anderson Cancer Center’s The Cancer Proteome Atlas, respectively. All computational codes used in this study are available in the following GitHub repository: GitHub—Body Composition, Tumor Proteomics and Survival: ccRCC. Data generated by the authors is available in the Supplementary file.

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References

1. National Cancer Institute. Clear Cell Renal Cell Carcinoma—National Cancer Institute. Available online: <https://www.cancer.gov/pediatric-adult-rare-tumor/rare-tumors/rare-kidney-tumors/clear-cell-renal-cell-carcinoma> (accessed on 8 May 2025).
2. Surveillance Research Program, National Cancer Institute. SEER*Explorer: An Interactive Website for SEER Cancer Statistics. Available online: <https://seer.cancer.gov/statistics-network/explorer/> (accessed on 19 January 2025).
3. Zheng, W.; Zhu, W.; Yu, S.; Li, K.; Ding, Y.; Wu, Q.; Tang, Q.; Zhao, Q.; Lu, C.; Guo, C. Development and validation of a nomogram to predict overall survival for patients with metastatic renal cell carcinoma. *BMC Cancer* **2020**, *20*, 1066. [CrossRef] [PubMed]
4. Adams, K.F.; Leitzmann, M.F.; Albanes, D.; Kipnis, V.; Moore, S.C.; Schatzkin, A.; Chow, W.H. Body size and renal cell cancer incidence in a large US cohort study. *Am. J. Epidemiol.* **2008**, *168*, 268–277. [CrossRef] [PubMed]
5. Callahan, C.L.; Hofmann, J.N.; Corley, D.A.; Zhao, W.K.; Shuch, B.; Chow, W.H.; Purdue, M.P. Obesity and renal cell carcinoma risk by histologic subtype: A nested case-control study and meta-analysis. *Cancer Epidemiol.* **2018**, *56*, 31–37. [CrossRef] [PubMed]
6. Fu, Z.; Bao, Y.; Dong, K.; Gu, D.; Wang, Z.; Ding, J.; He, Z.; Gan, X.; Wu, Z.; Yang, C.; et al. Association of body mass index with clinicopathological features among patients with clear cell renal cell carcinoma treated with surgery: A retrospective study. *Sci. Rep.* **2025**, *15*, 432. [CrossRef] [PubMed]
7. Sanchez, A.; Furberg, H.; Kuo, F.; Vuong, L.; Ged, Y.; Patil, S.; Ostrovnaya, I.; Petruzella, S.; Reising, A.; Patel, P.; et al. Transcriptomic signatures related to the obesity paradox in patients with clear cell renal cell carcinoma: A cohort study. *Lancet Oncol.* **2020**, *21*, 283–293. [CrossRef] [PubMed]
8. Hakimi, A.A.; Furberg, H.; Zabor, E.C.; Jacobsen, A.; Schultz, N.; Ciriello, G.; Mikkilineni, N.; Fiegoli, B.; Kim, P.H.; Voss, M.H.; et al. An epidemiologic and genomic investigation into the obesity paradox in renal cell carcinoma. *J. Natl. Cancer Inst.* **2013**, *105*, 1862–1870. [CrossRef] [PubMed]
9. Ged, Y.; Sanchez, A.; Patil, S.; Knezevic, A.; Stein, E.; Petruzella, S.; Weiss, K.; Duzgol, C.; Chaim, J.; Akin, O.; et al. Associations between Pretreatment Body Composition Features and Clinical Outcomes among Patients with Metastatic Clear Cell Renal Cell Carcinoma Treated with Immune Checkpoint Blockade. *Clin. Cancer Res.* **2022**, *28*, 5180–5189. [CrossRef] [PubMed]
10. Lee, J.H.; Hwang, S.; Jee, B.; Kim, J.H.; Lee, J.; Chung, J.H.; Song, W.; Sung, H.H.; Jeon, H.G.; Jeong, B.C.; et al. Fat Loss in Patients with Metastatic Clear Cell Renal Cell Carcinoma Treated with Immune Checkpoint Inhibitors. *Int. J. Mol. Sci.* **2023**, *24*, 3994. [CrossRef] [PubMed]
11. Maurits, J.S.F.; Sedelaar, J.P.M.; Mulders, P.F.A.; Aben, K.K.H.; Kiemeny, L.; Vrieling, A. Skeletal muscle radiodensity and visceral adipose tissue index are associated with survival in renal cell cancer—A multicenter population-based cohort study. *Clin. Nutr.* **2022**, *41*, 131–143. [CrossRef] [PubMed]
12. Kays, J.K.; Koniaris, L.G.; Cooper, C.A.; Pili, R.; Jiang, G.; Liu, Y.; Zimmers, T.A. The Combination of Low Skeletal Muscle Mass and High Tumor Interleukin-6 Associates with Decreased Survival in Clear Cell Renal Cell Carcinoma. *Cancers* **2020**, *12*, 1605. [CrossRef] [PubMed]
13. Bradshaw, P.T.; Olsson, L.T.; Sanchez, A.; Knezevic, A.; Akin, O.; Scott, J.M.; Hakimi, A.A.; Russo, P.; Caan, B.J.; Mourtzakis, M.; et al. Radiodensities of Skeletal Muscle and Visceral Adipose Tissues Are Prognostic Factors in Clear-Cell Renal Cell Carcinoma. *Cancer Epidemiol. Biomark. Prev.* **2024**, *33*, 1375–1382. [CrossRef] [PubMed]
14. Doyle, S.L.; Bennett, A.M.; Donohoe, C.L.; Mongan, A.M.; Howard, J.M.; Lithander, F.E.; Pidgeon, G.P.; Reynolds, J.V.; Lysaght, J. Establishing computed tomography-defined visceral fat area thresholds for use in obesity-related cancer research. *Nutr. Res.* **2013**, *33*, 171–179. [CrossRef] [PubMed]
15. Li, Q.K.; Pavlovich, C.P.; Zhang, H.; Kinsinger, C.R.; Chan, D.W. Challenges and opportunities in the proteomic characterization of clear cell renal cell carcinoma (ccRCC): A critical step towards the personalized care of renal cancers. *Semin. Cancer Biol.* **2019**, *55*, 8–15. [CrossRef] [PubMed]
16. Pezzicoli, G.; Ciciriello, F.; Musci, V.; Salonne, F.; Ragno, A.; Rizzo, M. Genomic Profiling and Molecular Characterization of Clear Cell Renal Cell Carcinoma. *Curr. Oncol.* **2023**, *30*, 9276–9290. [CrossRef] [PubMed]
17. Liu, J.Y.; Weng, K.Q.; Gao, Q.D.; Xue, X.Y.; Xu, N. Molecular subtyping of renal clear cell carcinoma based on prognostic RASSF family genes and validation of C1QL1 as a key prognostic marker. *Sci. Rep.* **2025**, *15*, 9786. [CrossRef] [PubMed]

18. Deng, J.; Tu, S.; Li, L.; Li, G.; Zhang, Y. Diagnostic, predictive and prognostic molecular biomarkers in clear cell renal cell carcinoma: A retrospective study. *Cancer Rep.* **2024**, *7*, e2116. [[CrossRef](#)] [[PubMed](#)]
19. Heath, A.P.; Ferretti, V.; Agrawal, S.; An, M.; Angelakos, J.C.; Arya, R.; Bajari, R.; Baqar, B.; Barnowski, J.H.B.; Burt, J.; et al. The NCI Genomic Data Commons. *Nat. Genet.* **2021**, *53*, 257–262. [[CrossRef](#)] [[PubMed](#)]
20. Akin, O.; Elnajjar, P.; Heller, M.; Jarosz, R.; Erickson, B.J.; Kirk, S.; Lee, Y.; Linehan, M.W.; Gautam, R.; Vikram, R.; et al. *The Cancer Genome Atlas Kidney Renal Clear Cell Carcinoma Collection (TCGA-KIRC)*; National Cancer Institute: Bethesda, MD, USA, 2016. [[CrossRef](#)]
21. Akbani, R.; Ng, P.K.; Werner, H.M.; Shahmoradgoli, M.; Zhang, F.; Ju, Z.; Liu, W.; Yang, J.Y.; Yoshihara, K.; Li, J.; et al. A pan-cancer proteomic perspective on The Cancer Genome Atlas. *Nat. Commun.* **2014**, *5*, 3887. [[CrossRef](#)] [[PubMed](#)]
22. Aduse-Poku, L.; Gopireddy, D.R.; Hernandez, M.; Lall, C.; Divaker, J.; Falzarano, S.M.; Masood, S.; Datta, S.; Zhang, W.; Jo, A.; et al. Intraindividual Reliability of Opportunistic Computed Tomography-Assessed Adiposity and Skeletal Muscle Among Breast Cancer Patients. *JNCI Cancer Spectr.* **2022**, *6*, pkac068. [[CrossRef](#)] [[PubMed](#)]
23. Shah, U.A.; Ballinger, T.J.; Bhandari, R.; Dieli-Cornwright, C.M.; Guertin, K.A.; Hibler, E.A.; Kalam, F.; Lohmann, A.E.; Ippolito, J.E. Imaging modalities for measuring body composition in patients with cancer: Opportunities and challenges. *J. Natl. Cancer Inst. Monogr.* **2023**, *2023*, 56–67. [[CrossRef](#)] [[PubMed](#)]
24. Qi, J.; Hu, H.; Yaghjian, L.; An, L.; Kalim, H.A.; Cooke, E.O.; Cheng, T.D. Association of Adipose Tissue Distribution With Type 2 Diabetes in Breast Cancer Patients. *Breast Cancer* **2020**, *14*, 1178223420972369. [[CrossRef](#)] [[PubMed](#)]
25. Kim, H.; Kim, S.E.; Sung, M.K. Sex and Gender Differences in Obesity: Biological, Sociocultural, and Clinical Perspectives. *World J. Mens. Health* **2025**, *43*, 758. [[CrossRef](#)] [[PubMed](#)]
26. Landen, S.; Hiam, D.; Voisin, S.; Jacques, M.; Lamon, S.; Eynon, N. Physiological and molecular sex differences in human skeletal muscle in response to exercise training. *J. Physiol.* **2023**, *601*, 419–434. [[CrossRef](#)] [[PubMed](#)]
27. Takemura, K.; Yonekura, S.; Downey, L.E.; Evangelopoulos, D.; Heng, D.Y.C. Impact of Body Mass Index on Survival Outcomes of Patients with Metastatic Renal Cell Carcinoma in the Immuno-oncology Era: A Systematic Review and Meta-analysis. *Eur. Urol. Open Sci.* **2022**, *39*, 62–71. [[CrossRef](#)] [[PubMed](#)]
28. Bildik, G.; Liang, X.; Sutton, M.N.; Bast, R.C., Jr.; Lu, Z. DIRAS3: An Imprinted Tumor Suppressor Gene that Regulates RAS and PI3K-driven Cancer Growth, Motility, Autophagy, and Tumor Dormancy. *Mol. Cancer Ther.* **2022**, *21*, 25–37. [[CrossRef](#)] [[PubMed](#)]
29. Kummerl, L.; Kraulich, M.; Lesyuk, W.; Binnering, A.; Goebell, P.J.; Kahlmeyer, A. Sarcopenia assessments as predictors of overall survival in patients with metastatic renal cell carcinoma. *Urol. Oncol.* **2023**, *41*, 392 e391–392 e399. [[CrossRef](#)] [[PubMed](#)]
30. Hu, X.; Liao, D.W.; Yang, Z.Q.; Yang, W.X.; Xiong, S.C.; Li, X. Sarcopenia predicts prognosis of patients with renal cell carcinoma: A systematic review and meta-analysis. *Int. Braz. J. Urol.* **2020**, *46*, 705–715. [[CrossRef](#)] [[PubMed](#)]
31. Muscaritoli, M.; Modena, A.; Valerio, M.; Marchetti, P.; Magarotto, R.; Quadrini, S.; Narducci, F.; Tonini, G.; Grassani, T.; Cavanna, L.; et al. The Impact of NUTRItional Status at First Medical Oncology Visit on Clinical Outcomes: The NUTRIONCO Study. *Cancers* **2023**, *15*, 3206. [[CrossRef](#)] [[PubMed](#)]
32. Jang, N.R.; Choi, J.H.; Gu, M.J. Aberrant Expression of E-cadherin, N-cadherin, and P-cadherin in Clear Cell Renal Cell Carcinoma: Association With Adverse Clinicopathologic Factors and Poor Prognosis. *Appl. Immunohistochem. Mol. Morphol.* **2021**, *29*, 223–230. [[CrossRef](#)] [[PubMed](#)]
33. Faraj Tabrizi, P.; Peters, I.; Schimansky, I.; Dubrowinskaja, N.; Reese, C.; Tezval, H.; Kuczyk, M.A.; Serth, J. Alteration of Cadherin 3 Expression and DNA Methylation in Association with Aggressive Renal Cell Carcinoma. *Int. J. Mol. Sci.* **2023**, *24*, 16476. [[CrossRef](#)] [[PubMed](#)]
34. Li, J.; Lu, Y.; Akbani, R.; Ju, Z.; Roebuck, P.L.; Liu, W.; Yang, J.Y.; Broom, B.M.; Verhaak, R.G.; Kane, D.W.; et al. TPCA: A resource for cancer functional proteomics data. *Nat. Methods* **2013**, *10*, 1046–1047. [[CrossRef](#)] [[PubMed](#)]
35. Clements, M.E.; Johnson, R.W. PREX1 drives spontaneous bone dissemination of ER+ breast cancer cells. *Oncogene* **2020**, *39*, 1318–1334. [[CrossRef](#)] [[PubMed](#)]
36. Qin, J.; Xie, Y.; Wang, B.; Hoshino, M.; Wolff, D.W.; Zhao, J.; Scofield, M.A.; Dowd, F.J.; Lin, M.F.; Tu, Y. Upregulation of PIP3-dependent Rac exchanger 1 (P-Rex1) promotes prostate cancer metastasis. *Oncogene* **2009**, *28*, 1853–1863. [[CrossRef](#)] [[PubMed](#)]
37. Wan, S.C.; Wu, H.; Li, H.; Deng, W.W.; Xiao, Y.; Wu, C.C.; Yang, L.L.; Zhang, W.F.; Sun, Z.J. Overexpression of PREX1 in oral squamous cell carcinoma indicates poor prognosis. *J. Mol. Histol.* **2020**, *51*, 531–540. [[CrossRef](#)] [[PubMed](#)]
38. Barrows, D.; He, J.Z.; Parsons, R. PREX1 Protein Function Is Negatively Regulated Downstream of Receptor Tyrosine Kinase Activation by p21-activated Kinases (PAKs). *J. Biol. Chem.* **2016**, *291*, 20042–20054. [[CrossRef](#)] [[PubMed](#)]
39. Welch, H.C.; Coadwell, W.J.; Ellson, C.D.; Ferguson, G.J.; Andrews, S.R.; Erdjument-Bromage, H.; Tempst, P.; Hawkins, P.T.; Stephens, L.R. P-Rex1, a PtdIns(3,4,5)P₃- and Gbetagamma-regulated guanine-nucleotide exchange factor for Rac. *Cell* **2002**, *108*, 809–821. [[CrossRef](#)] [[PubMed](#)]
40. Welch, H.C. Regulation and function of P-Rex family Rac-GEFs. *Small GTPases* **2015**, *6*, 49–70. [[CrossRef](#)] [[PubMed](#)]

41. Chu, J.Y.; Tsonou, E.; Machin, P.A.; MacLellan-Gibson, K.; Roberts, A.; Chetwynd, S.A.; McCormack, A.T.; Stephens, J.C.; Benetti, E.; Kinsella, G.K.; et al. Prex1 controls glucose homeostasis by limiting glucose uptake and mitochondrial metabolism in liver through GEF-independent regulation of Gpr21. *bioRxiv* **2025**. [[CrossRef](#)]
42. Anjanappa, M.; Corden, M.; Green, A.; Roberts, D.; Hoskin, P.; McWilliam, A.; Choudhury, A. Sarcopenia in cancer: Risking more than muscle loss. *Tech. Innov. Patient Support. Radiat. Oncol.* **2020**, *16*, 50–57. [[CrossRef](#)] [[PubMed](#)]
43. Koylu, B.; Sulu, C.; Yumuk, V.D.; Yumuk, P.F. The impact of sarcopenic obesity on cancer clinical outcomes. *Semin. Cancer Biol.* **2025**, *114*, 203–214. [[CrossRef](#)] [[PubMed](#)]

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