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Original Article

Sarcopenia is an independent predictor of survival outcomes for patients with upper tract urothelial carcinoma

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Abstract: Purpose: We evaluated the association between sarcopenia (loss of skeletal muscle mass) and overall survival, disease-free survival and cancer-specific survival in patients with upper tract urothelial carcinoma treated with radical nephroureterectomy. Materials and methods: From March 2005 to August 2015, we conducted a retrospective study of patients with upper tract urothelial carcinoma who underwent radical nephroureterectomy. Sarcopenia was assessed by the third lumbar vertebra skeletal muscle index (L3 SMI), and diagnosed by cut-off values obtained using the method of optimum stratification. Univariate and multivariate analyses were performed to evaluate risk factors for long-term survival. Results: A total of 227 patients were included in this study, and 68 (30%) patients were diagnosed with sarcopenia based on the cut-off values (38.95 cm^2/m^2 for men and 34.55 cm^2/m^2 for women). Multivariate analysis identified sarcopenia as an independent risk factor for overall survival (HR=2.955, $P < 0.001$), progression-free survival (HR=2.362, $P=0.001$) and cancer-specific survival (HR=2.279, $P=0.002$). Conclusions: The presence of sarcopenia is independently associated with poor overall survival, progression-free survival and cancer-specific survival after radical nephroureterectomy for upper tract urothelial carcinoma.

Keywords: Upper tract urothelial carcinoma, survival rate, sarcopenia, radical nephroureterectomy

Introduction

UTUC is relatively uncommon compared to bladder tumors, accounting for only 5-10% of urothelial carcinomas [1]. Appropriately 60% of UTUCs are invasive at diagnosis, which portends poor outcomes following surgery, with a 5-year overall mortality of 23% [1, 2]. To date, the gold standard management of UTUC remains RNU with ipsilateral bladder cuff removal, while kidney-sparing surgery or endoscopic ablation are typically reserved for patients with solitary kidney or who cannot tolerate radical surgery [1]. The risk factors previously reported to predict survival outcomes for UTUC following RNU are tumor stage, tumor grade, tumor multifocality, advanced age, and tobacco consumption [1, 3-7]. Other authors have reported tumor necrosis, lymphovascular invasion, systemic symptoms, ASA score, and hydronephrosis as prognostic factors to predict oncologic outcomes for UTUC [1, 8-11]. Sarcopenia is characterized by age-related decline of skeletal muscle plus low muscle strength and/or physical performance [12]. Severe skeletal muscle deficiency or sarcopenia has been reported to be associated with adverse prognosis of various malignancies, including breast, colorectal, and hepatobiliary cancer, urothelial carcinoma of the bladder and renal cell carcinoma [9, 13-15]. Taken together, these findings suggest that sarcopenia may represent a potentially promising risk factor for UTUC. Previously, Ishihara et al identified the sarcopenia as an independent predictor of RFS, CSS, and OS in 137 consecutive Japanese patients with UTUC following RNU [16]. In their study, the HR of sarcopenia were even higher than that of pathologic T and N stage for OS (12.1 vs. 5.21 and 8.58) and CSS (13.3 vs. 3.78 and 9.25) in multivariate analysis. Therefore, the HR of sarcopenia for survival might be overestimated due to

their limited sample size. In addition, they used BMI-adjusted cut-off values for SMI to define sarcopenia, which were established in a Canadian patient cohort rather than Asian patients. Therefore, the objective of the current study was to accurately describe the prevalence of sarcopenia in a cohort of patients with UTUC who underwent RNU, and to evaluate the impact of sarcopenia on OS, PFS, and CSS, using optimum stratification and log-rank Chi-square statistics.

Patients and methods

Patients

315 consecutive patients underwent RNU for UTUC at The First Affiliated Hospital of Wenzhou Medical University, China from March 2005 to August 2015. Exclusion criteria were as follows: no preoperative abdominal CT scans (no more than 30 days before surgery); receipt of palliative surgery instead of RNU; receipt of renal transplantation pre-operation; and evidence of metastatic disease at the time of surgery. Finally, 227 patients with complete follow-up information were included in this study. None of the patients received neoadjuvant chemotherapy.

Data collection

Referring to our prospectively maintained computer database, the following data were collected and analyzed retrospectively: (1) clinicopathological features, including age, sex, smoking history, ASA grade, BMI, hydronephrosis, previous upper tract tumor, TNM stage of tumor, tumor grade, tumor location (renal pelvis, ureter, or simultaneous tumor in both regions), multifocality (multiple tumors in the same anatomical location), lymphovascular invasion, tumor history (pure urothelial vs. mixed type), and sarcomatoid differentiation; (2) surgical and treatment details, including laparoscopic surgery, and distal ureter management (extravesical, extravesical and open intravesical, extravesical and endoscopic resection of the ureter orifice); and (3) postoperative outcomes, including mortality, OS, PFS and CSS. Tumors were staged according to 2002 TNM classification system. Tumor grading was assessed according to the World Health Organization (WHO) 2004 grading system. This study was approved by the ethics committee of The First Affiliated Hospital of Wenzhou Medical University, China.

Definition

OS was defined as the time from the date of surgery to death from any cause (event) or alive at last follow-up (censored). PFS was defined as the time from the date of surgery until local recurrence, evidence of distant metastasis, or death from UTUC or still alive at last follow-up (censored). CSS was defined as death from UTUC, and censored data were those still alive or whose death had been attributed to a cause other than UTUC.

Image analysis of skeletal muscle mass

A cross-sectional CT image at the third lumbar vertebra (L3) in the inferior direction was selected for analysis as described previously [17]. Skeletal muscles at L3 were separated by a threshold range of -29 to +150 Hounsfield units [18], using INFINITT PACS software version 3.0.11.3 BN17 32bit (INFINITT Healthcare Co., Ltd, Seoul, Korea), and tissue boundaries were manually outlined as needed. The muscles in the L3 region include the psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques, and rectus abdominis. To minimize measurement bias, one investigator (X.-M.G.) who was blinded to the patients' outcomes and surgical characteristics was trained to identify and quantify the muscle areas. L3 muscle areas were normalized for height (m^2) and reported as L3 skeletal muscle index (L3 SMI, cm^2/m^2).

Follow-up

Patients were generally scheduled to visit the treating surgeon in the outpatient clinic every 3 months for the first year after RNU, every 6 months from the second through the fifth years, and annually thereafter. The follow-up assessments included blood and urine tests, cystoscopy, and chest and abdominal CT or magnetic resonance imaging. The cause of death was determined by reviewing death certificates or by the treating clinician.

Statistical analysis

Normally distributed continuous variables are presented as mean ± standard deviation, and

Table 1. Patient characteristics

Factors	Total (n=227)	Sarcopenic (n=68)	Non-sarcopenic (n=159)	*P* value
Age, year, mean (SD)	67.41 (10.27)	71.44 (9.55)	65.68 (10.11)	< 0.001*
Sex				0.006*
Female, n (%)	62 (22)	27 (40)	35 (22)	
Male, n (%)	165 (78)	41 (60)	124 (78)	
Smoking history, n (%)				0.001*
Never, n (%)	115 (51)	47 (69)	68 (43)	< 0.001*
Former, n (%)	25 (11)	5 (7)	20 (12)	
Current, n (%)	87 (38)	16 (24)	71 (45)	0.003*
ASA grade				0.048*
≤ II, n (%)	170 (75)	45 (66)	125 (79)	
III, n (%)	57 (25)	23 (34)	34 (21)	
BMI, Kg/m^2, mean (SD)	22.44 (2.95)	20.37 (2.25)	23.32 (2.77)	< 0.001*
Hydronephrosis				0.677
No, n (%)	78 (34)	22 (32)	56 (35)	
Yes, n (%)	149 (66)	46 (68)	103 (65)	
L3 SMI, cm^2/m^2, mean (SD)	41.1 (8.17)	33.35 (4.02)	45.60 (6.28)	*< 0.001**
TNM stage				0.047*
I/0, n (%)	68 (30)	13 (19)	55 (35)	0.011*
II, n (%)	79 (35)	24 (35)	55 (35)	
III, n (%)	52 (23)	18 (24)	34 (21)	
IV, n (%)	28 (12)	13 (19)	15 (9)	0.042*
Pathological T stage				0.043*
≤ pT2, n (%)	149 (66)	38 (56)	111 (70)	
≥ pT3, n (%)	78 (34)	30 (44)	48 (30)	
Pathological N stage				0.048*
N0 or Nx, n (%)	204 (90)	57 (84)	147 (92)	
N1-3, n (%)	23 (10)	11 (16)	12 (8)	
Grade				0.029*
G1, n (%)	55 (24)	10 (15)	45 (28)	
G2/3, n (%)	172 (76)	58 (85)	114 (72)	
Tumor location				0.261
Renal pelvis, n (%)	146 (64)	45 (66)	101 (64)	
Ureter, n (%)	71 (31)	18 (26)	53 (33)	
Pelvis and ureter, n (%)	10 (5)	5 (8)	5 (3)	
Previous upper tract tumor				0.386
No, n (%)	219 (96)	64 (94)	155 (97)	
Yes, n (%)	8 (4)	4 (6)	4 (3)	
Multifocality				0.301
No, n (%)	183 (81)	52 (76)	131 (82)	
Yes, n (%)	44 (19)	16 (24)	28 (18)	
Histology				0.217
Pure urothelial, n (%)	215 (95)	62 (91)	153 (96)	
Mixed type[a], n (%)	12 (5)	6 (9)	6 (4)	
Sarcomatoid differentiation				0.288
No, n (%)	217 (96)	63 (93)	154 (97)	
Yes, n (%)	10 (4)	5 (7)	5 (3)	
Lymphovascular invasion				0.002*

No, n (%)	187 (82)	48 (71)	139 (87)	
Yes, n (%)	40 (18)	20 (29)	20 (13)	
Laparoscopic surgery				0.286
No, n (%)	75 (33)	19 (28)	56 (35)	
Yes, n (%)	152 (67)	49 (72)	103 (65)	
Distal ureter management				0.004*
Extravesical, n (%)	62 (27)	28 (41)	34 (21)	0.002*
Open bladder cuff, n (%)	156 (69)	36 (53)	120 (75)	
TUR of orifice[b], n (%)	9 (4)	4 (6)	5 (4)	

*Indicates statistically significant. [a]Mixed type carcinomas include sarcomatoid differentiated carcinoma and lymphoepithelioma-like carcinoma. [b]TUR of orifice indicates extravesical and endoscopic resection of the ureteral orifice.

non-normally distributed continuous variables are presented as median and interquartile ranges. Categorical variables are presented as counts and percentages. Clinical variables were compared using Student's t test (normally distributed variables), Pearson's chi-square test, or Fisher's exact test (categorical variables), and the Mann-Whitney U test (non-normally distributed continuous variables and ranked data) as appropriate. OS, PFS and CSS rates were estimated by Kaplan-Meier method, and the log-rank test was used to assess the differences. Variables demonstrating a significant trend ($P < 0.10$) in the univariate analysis were included into the subsequent multivariate analysis (Cox proportional hazards regression).

To determine the sex-specific cut-off values of the L3 SMI at which the survival difference was most significant, we used optimum stratification and log-rank Chi-square statistics to find the most significant *p* value. We used this cut-off value to classify patients as sarcopenic or non-sarcopenic. This method has been previously applied to solve the threshold value of the continuous covariable (L3 SMI) at which sarcopenic and non-sarcopenic patients are best separated with respect to time to OS [19].

All tests were two-sided and considered statistically significant at $P < 0.05$. Statistical analyses were performed by using the SPSS software package version 22.0 (IBM, Armonk, NY) and SAS version 9.3 (SAS Institute, Inc., Cary, NC).

Results

Clinicopathologic characteristics

From March 2005 to August 2015, a total of 227 patients met our inclusion criteria and were included in our study. The median follow-up duration was 32.5 (14.5-58.9) months. The patients' clinicopathologic characteristics are summarized in **Table 1**. With respect to overall mortality, the final cut-off values of L3 SMI associated with OS obtained by means of optimum stratification were 38.95 cm^2/m^2 for men and 34.55 cm^2/m^2 for women. Using the same method, Zhuang et al firstly identified the diagnostic cut-off values for sarcopenia (40.8 cm^2/m^2 for men and 34.9 cm^2/m^2 for women) in their study with a total of 937 Chinese patients, which were similar to our cut-off values [20]. Clinicopathological features of patients with and without sarcopenia are listed in **Table 1**. According to these cut-off values, 30% of patients were diagnosed as sarcopenia. Whereby, 41 patients were male and 27 patients were female. Patients with sarcopenia had more advanced age, higher ASA grade, lower BMI, more advanced T stage and N stage, higher tumor grade, lymphovascular invasion, and were more likely to be treated with extravesical distal ureter management than those without sarcopenia. Additionally, male patients with a smoking history and TNM stage IV tumors were more likely to be sarcopenic. Patients with TNM stage I/0 tumors were more likely to be non-sarcopenic. The sarcopenia and non-sarcopenia groups were comparable with regard to hydronephrosis, TNM stage II and III, tumor location, previous upper tract tumor, multifocality, histology, sarcomatoid differentiation, and laparoscopic surgery.

Association of sarcopenia with survival

During follow-up, 85 (37%) patients died and 66 (29%) suffered from cancer-specific death in this study. The 1-, 3-, 5-year survival rate were 87%, 67% and 57% for OS, 81%, 66% and

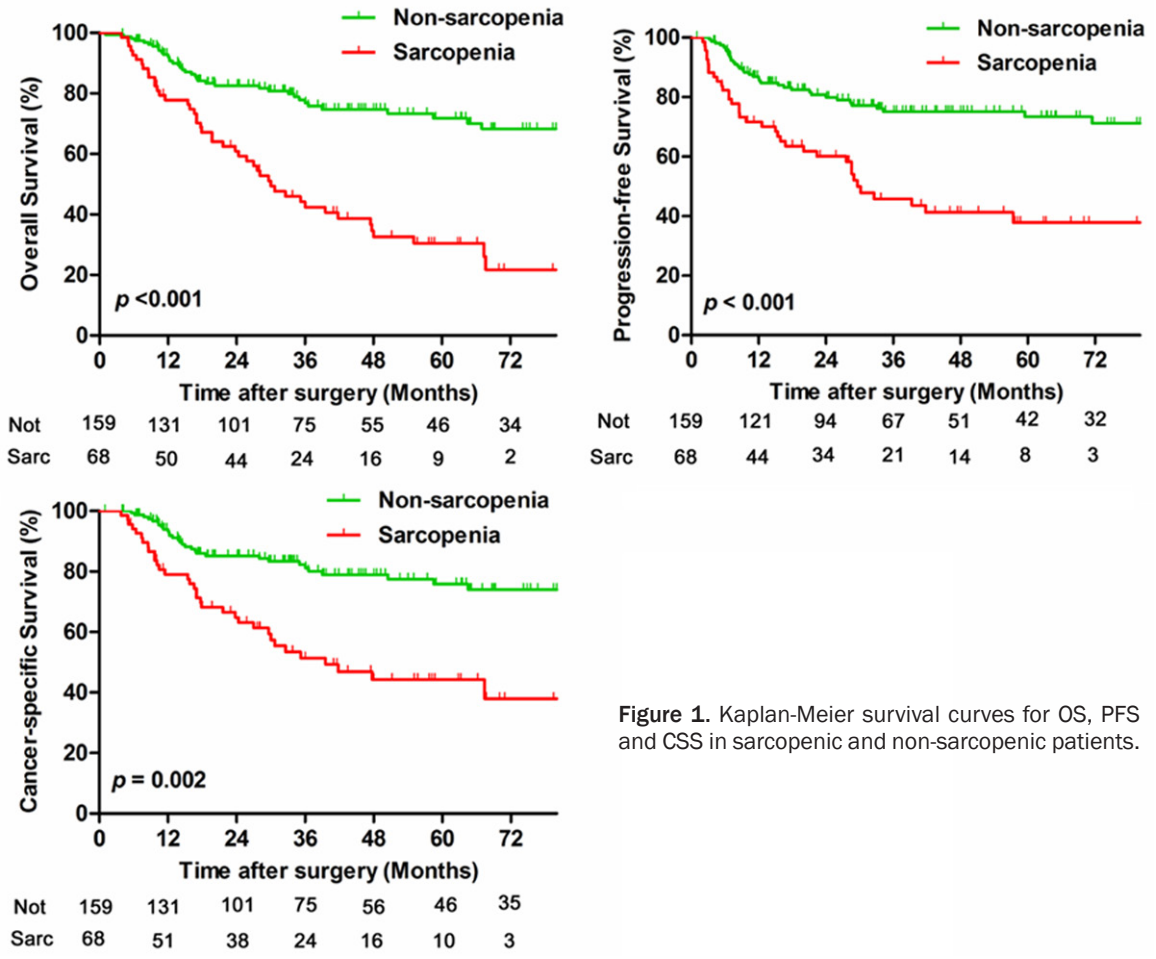

Figure 1. Kaplan-Meier survival curves for OS, PFS and CSS in sarcopenic and non-sarcopenic patients.

51% for PFS, and 89%, 71%, and 66% for CSS, respectively. Patients with sarcopenia had significantly poorer OS, PFS, and CSS ($P < 0.001$) than those without on Kaplan-Meier survival analysis (**Figure 1**). For non-sarcopenic patients, the 1-, 3-, and 5-year survival rates were 92%, 77% and 72% for OS, 94%, 87% and 82% for PFS, and 93%, 81% and 76% for CSS, respectively. For sarcopenic patients, the 1-, 3-, and 5-year survival rate were 78%, 42% and 30% for OS, 84%, 58% and 38% for PFS, and 79%, 51% and 44% for CSS, respectively. Patients with sarcopenia had significantly poorer 3-year OS (42% vs. 77%, $P < 0.001$), PFS (87% vs. 58%, $P < 0.001$), and CSS (51% vs. 81%, $P < 0.001$).

Univariate analysis revealed that sarcopenia was a statistically significant predictor of OS, PFS, and CSS; therefore, multivariate analysis for OS, PFS, and CSS was applied to determine various independent predictors (**Tables 2-4**). The following factors were included in the multivariate Cox proportional hazards model: age, smoking history, ASA grade, BMI, Hydronephrosis, L3 SMI, T and N stage, grade, history, lymphovascular invasion, sarcomatoid differentiation, tumor location and distal ureter management. The results indicated that sarcopenia was an independent risk factor for OS (HR=2.955, $P < 0.001$), PFS (HR=2.362, $P=0.001$) and CSS (HR=2.279, $P=0.002$). Moreover, sarcomatoid differentiation, T stage, and N stage were also independent risk factors for OS, PFS, and CSS, and lymphovascular invasion was a statistically significant risk factor of CSS.

Finally, patients with no independent risk factors were classified as low-risk, patients with one independent risk factor were classified as moderate-risk, and patients with two or more independent risk factors were classified as high-risk. The results of OS, PFS, and CSS with risk stratification by means of Kaplan-Meier survival analysis are shown in **Figure 2**.

Table 2. Univariable and multivariate Cox regression analysis of factors associated with OS

Factors	Univariable	Multivariable
	HR (95% CI), *p* value	HR (95% CI), *p* value
Age, year (≥ 75 vs. < 75)	2.171 (1.371-3.438), 0.001*	
Sex (male vs. female)	0.890 (0.555-1.428), 0.629	
Smoking history		
Never (reference)	1	
Former	1.515 (0.950-2.418), 0.081	
Current	1.177 (0.555-2.497), 0.671	
ASA grade (III vs. ≤ II)	1.643 (1.048-2.575), 0.030*	
BMI, Kg/m^2 (< 25 vs. ≥ 25)	2.072 (1.038-4.138), 0.039*	
Hydronephrosis (yes vs. no)	1.593 (0.980-2.590), 0.060	
L3 SMI, cm^2/m^2 (< 38.95 for male, < 34.55 for female vs. ≥ 38.95 for male, ≥ 34.55 for female)	3.249 (2.110-5.003), < *0.001**	2.955 (1.893-4.613), < *0.001**
Pathological T stage (≥ pT3 vs. ≤ pT2)	4.349 (2.805-6.745), < *0.001**	2.746 (1.624-4.641), < *0.001**
Pathological N stage (N1-3 vs. N0 or Nx)	6.946 (4.123-11.701), < *0.001**	4.557 (2.475-8.388), < *0.001**
Grade (G2/3 vs. G1)	2.638 (1.272-5.474), 0.009*	
Tumor location		
Pelvis (reference)	1	
Ureter	0.780 (0.281-2.164), 0.634	
Ureter and pelvis	1.116 (0.393-3.173), 0.836	
Previous upper tract tumor (yes vs. no)	0.759 (0.240-2.405), 0.639	
Multifocality (yes vs. no)	1.465 (0.887-2.421), 0.136	
Histology (mixed type vs. pure urothelial)	3.590 (1.792-7.192), < *0.001**	
Sarcomatoid differentiation (yes vs. no)	50787 (2.876-11.645), < *0.001**	4.738 (2.154-10.420), < *0.001**
Lymphovascular invasion (yes vs. no)	5.045 (3.220-7.905), < *0.001**	
Laparoscopic surgery (yes vs. no)	0.742 (0.449-1.228), 0.246	
Distal ureter management		
TUR of orifice (reference)	1	
Open bladder cuff	0.818 (0.291-2.304), 0.704	
Extravesical	0.318 (0.204-0.495), < *0.001**	

HR, hazards ratio; CI, confidence interval. *Indicates statistically significant.

Table 3. Univariable and multivariate Cox regression analysis of factors associated with PFS

Factors	Univariable	Multivariable
	HR (95% CI), *p* value	HR (95% CI), *p* value
Age, year (≥ 75 vs. < 75)	1.399 (0.841-2.328), 0.196	
Sex (male vs. female)	0.965 (0.577-1.612), 0.891	
Smoking history		
Never (reference)	1	
Former	1.665 (1.003-2.766), 0.049*	
Current	1.333 (0.595-2.984), 0.484	
ASA grade (III vs. ≤ II)	1.389 (0.843-2.289), 0.193	
BMI, Kg/m^2 (< 25 vs. ≥ 25)	2.087 (1.001-4.350), 0.050*	
Hydronephrosis (yes vs. no)	1.480 (0.886-2.474), 0.134	
L3 SMI, cm^2/m^2 (< 38.95 for male, < 34.55 for female vs. ≥ 38.95 for male, ≥ 34.55 for female)	2.775 (1.752-4.396), < 0.001*	2.362 (1.448-3.855), 0.001*
Pathological T stage (≥ pT3 vs. ≤ pT2)	4.840 (3.007-7.791), < 0.001*	2.420 (1.348-4.343), 0.003*
Pathological N stage (N1-3 vs. N0 or Nx)	8.077 (4.739-13.768), < 0.001*	4.186 (1.806-9.705), 0.001*
Grade (G2/3 vs. G1)	4.418 (1.781-10.961), 0.001*	
Tumor location		
Pelvis (reference)	1	
Ureter	1.608 (0.993-2.605), 0.053	
Ureter and pelvis	1.559 (0.558-4.357), 0.397	
Previous upper tract tumor (yes vs. no)	0.279 (0.039-2.012), 0.206	
Multifocality (yes vs. no)	1.386 (0.806-2.383), 0.238	

Histology (mixed type vs. pure urothelial)	3.911 (1.942-7.877), < 0.001*	
Sarcomatoid differentiation (yes vs. no)	6.132 (3.032-12.400), < 0.001*	4.785 (2.072-11.052), < 0.001*
Lymphovascular invasion (yes vs. no)	6.648 (4.160-10.622), < 0.001*	
Laparoscopic surgery (yes vs. no)	0.770 (0.457-1.300), 0.328	
Distal ureter management		
TUR of orifice (reference)	1	
Open bladder cuff	0.894 (0.315-2.536), 0.833	
Extravesical	0.349 (0.216-0.564), < 0.001*	

*Indicates statistically significant.

Table 4. Univariable and multivariate Cox regression analysis of factors associated with CSS

Factors	Univariable	Multivariable
	HR (95% CI), *p* value	HR (95% CI), *p* value
Age, year (≥ 75 vs. < 75)	1.707 (0.996-2.925), 0.052	
Sex (male vs. female)	0.945 (0.550-1.625), 0.838	
Smoking history		
Never (reference)	1	
Former	1.656 (0.963-2.849), 0.068	
Current	1.485 (0.653-3.378), 0.345	
ASA grade (III vs. ≤ II)	1.463 (0.871-2.458), 0.151	
BMI, Kg/m^2 (< 25 vs. ≥ 25)	2.030 (0.927-4.447), 0.077	
Hydronephrosis (yes vs. no)	1.863 (1.047-3.315), 0.034*	
L3 SMI, cm^2/m^2 (< 38.95 for male, < 34.55 for female vs. ≥ 38.95 for male, ≥ 34.55 for female)	2.962 (1.819-4.821), < 0.001*	2.279 (1.354-3.836), 0.002*
Pathological T stage (≥ pT3 vs. ≤ pT2)	5.490 (3.284-9.177), < 0.001*	2.688 (1.417-5.101), 0.002*
Pathological N stage (N1-3 vs. N0 or Nx)	8.503 (4.885-14.800), < 0.001*	3.080 (1.321-7.180), 0.009*
Grade (G2/3 vs. G1)	4.383 (1.593-12.062), 0.004*	
Tumor location		
Pelvis (reference)	1	
Ureter	1.591 (0.594-2.655), 0.075*	
Ureter and pelvis	1.772 (0.630-4.986), 0.278	
Previous upper tract tumor (yes vs. no)	0.321 (0.045-2.319), 0.260	
Multifocality (yes vs. no)	1.518 (0.864-2.668), 0.146	
Histology (mixed type vs. pure urothelial)	4.720 (2.327-9.574), < 0.001*	
Sarcomatoid differentiation (yes vs. no)	7.455 (3.658-15.195), < 0.001*	6.042 (2.528-14.437), < *0.001**
Lymphovascular invasion (yes vs. no)	7.048 (4.308-11.532), < 0.001*	2.327 (1.087-4.985), 0.030*
Laparoscopic surgery (yes vs. no)	0.756 (0.430-1.329), 0.331	
Distal ureter management		
TUR of orifice (reference)	1	
Open bladder cuff	0.945 (0.332-2.692), 0.916	
Extravesical	0.292 (0.176-0.484), < 0.001*	

*Indicates statistically significant.

Association of sarcopenia with survival under adjusted TNM stage

Among patients with TNM stage I/0 tumors, those with sarcopenia had a significantly poorer OS (*P*=0.015) than non-sarcopenic patients. However, PFS (*P*=0.818) and CSS (*P*=0.962) did not significantly differ between the sarcopenia and non-sarcopenia groups. Among patients with TNM stage II tumors, OS (*P*=0.001), PFS (*P*=0.002), and CSS (*P*=0.009) were significantly shorter in sarcopenic patients than in non-sarcopenic patients. Similarly, among patients with TNM stage III tumors, poorer OS (*P*=0.008) and CSS (*P*=0.029) were observed in the sarcopenia group compared to the non-sarcopenia groups. Not significant difference of PFS (*P*=0.074) were shown in the two groups. Among patients with TNM stage IV tumors, there were no statistically significant differences in OS (*P*=0.689), PFS (*P*=0.304), or CSS (*P*=0.547) between the sarcopenia patients and non-sarcopenic groups (**Figure 3**).

Discussion

Sarcopenia, firstly described by Rosenberg et al, has been accepted as a new geriatric syn-

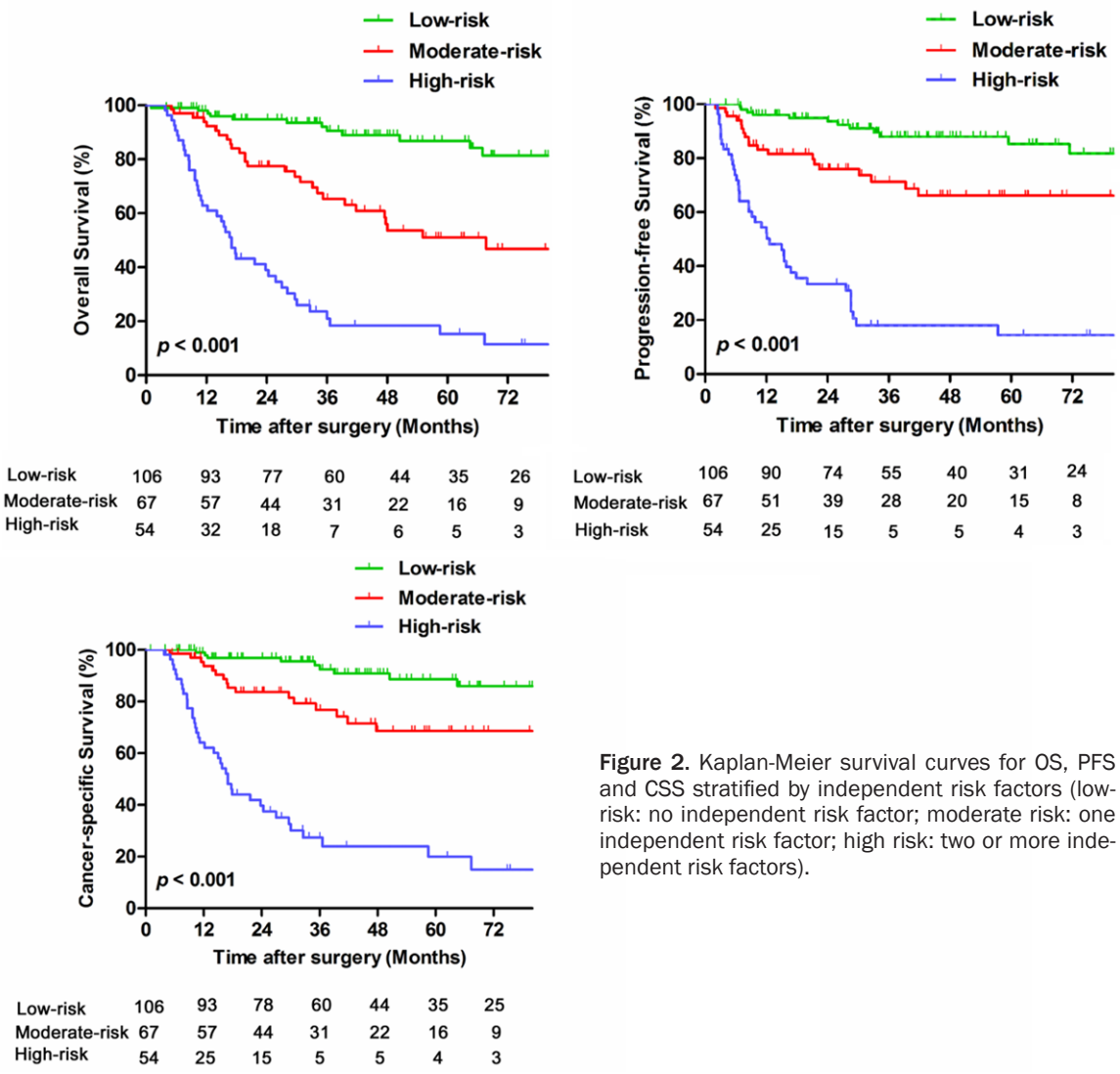

Figure 2. Kaplan-Meier survival curves for OS, PFS and CSS stratified by independent risk factors (low-risk: no independent risk factor; moderate risk: one independent risk factor; high risk: two or more independent risk factors).

drome [12], and knowledge of this condition is growing rapidly worldwide. In the present study, we observed a 30% incidence of sarcopenia in UTUC patients following RNU, using the obtained sex-specific cut-off values. Sarcopenia was an independent risk predictor of OS, PFS, and CSS in UTUC patients.

The EWGSO put forward an operational definition and diagnostic strategy for sarcopenia that has been widely used worldwide [21]. Sarcopenia has been defined as an aged-related decline and progressive loss of skeletal muscle mass and muscle function (defined as strength or physical performance) [22], which can result in poor quality of life and increased incidence of death. Notably, the cut-off values for sarcopenia, determined by Prado et al [19] and van Vledder et al [23], which have been adopted by many previous studies, were determined in Western populations. People from the Asian countries typically have a smaller physique and lower BMI than Western population, and thus the impact of sarcopenia may be greater. In addition, economic development status and population characteristics vary extensively across Asian countries. Therefore, we determined the cut-off values that obtained from our study, which were similar to the cut-off values identified by Zhuang et al [20] for sarcopenia (40.8 cm^2/m^2 for men and 34.9 cm^2/m^2 for women) in their study with a total of 937 Chinese patients.

Previous studies have investigated the impact of sarcopenia on long-term survival in bladder

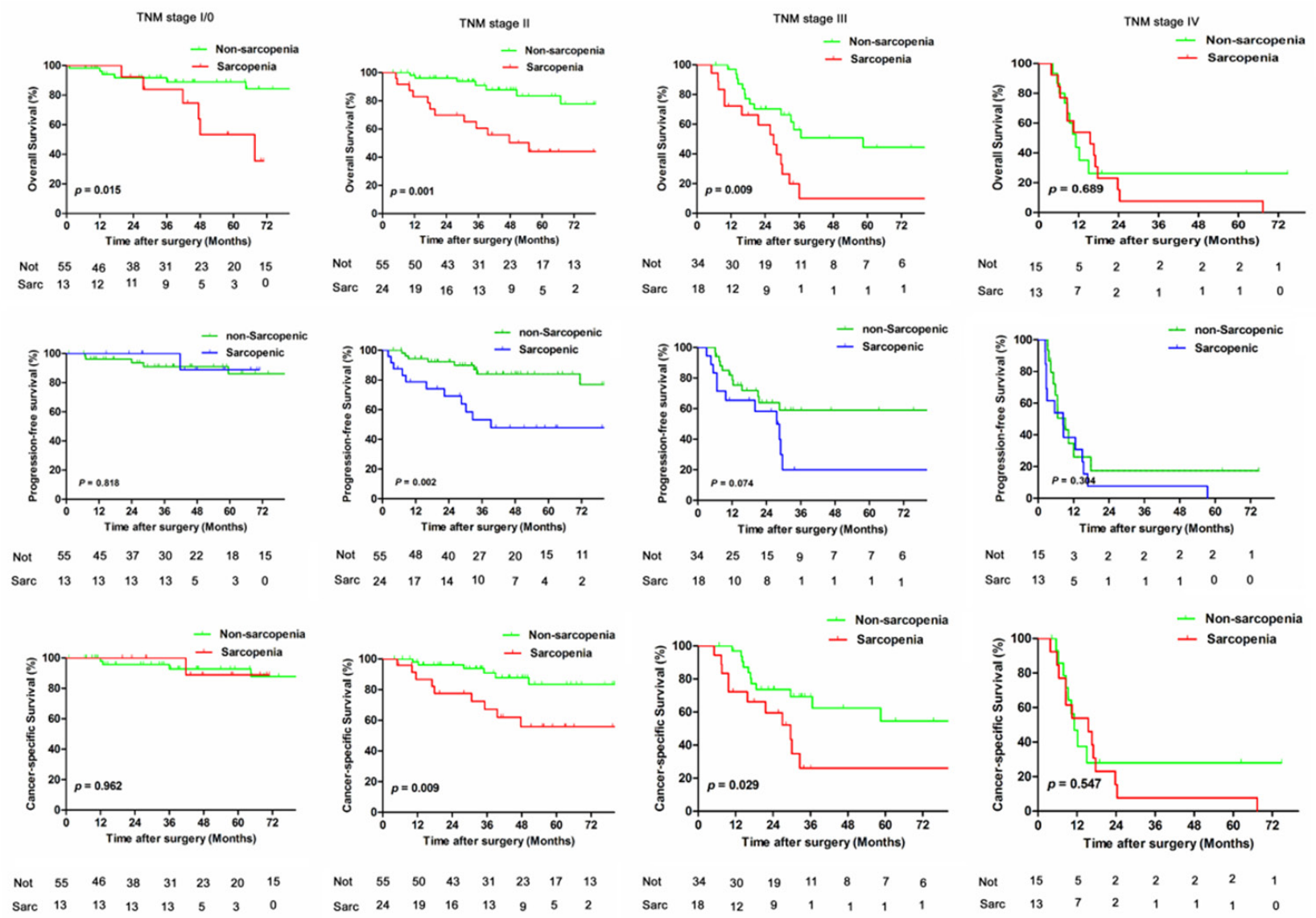

Figure 3. Kaplan-Meier survival curves for OS, PFS and CSS in sarcopenic and non-sarcopenic patients under adjusted TNM stage.

cancer patients undergoing radical cystectomy [14, 24], and patients with advanced urothelial carcinoma [25]. These studies demonstrated that sarcopenia had potential prognostic utility. In addition, a small study with 137 patients suggested the potential prognostic significance of sarcopenia in UTUC patients treated with RNU [16]. The present study is further to identify sarcopenia as an independent risk factor for the long-term survival of UTUC patients after RNU. The 30% prevalence of sarcopenia in this study is lower than had been previously reported among patients with bladder urothelial carcinoma [14] and renal cell carcinoma [15]. Additionally, severe skeletal muscle deficiency was independently associated with declines in OS (HR=2.955, $P < 0.001$), PFS (HR=2.362, $P=0.001$), and CSS (HR=2.279, $P=0.002$), respectively. And patients with sarcopenia had significantly poor 3-year OS (42% vs. 77%, $P < 0.001$), PFS (87% vs. 58%, $P < 0.001$), and CSS (51% vs. 81%, $P < 0.001$) compared with non-sarcopenic patients.

It remains unclear why sarcopenia increases the risk of tumor relapse and mortality, but two possibilities should be addressed. First, sarcopenia may be a clinical manifestation of aggressive tumors with increased metabolic activity, with the underlying metabolic abnormality of the cancer resulting in severe systemic inflammation subsequently leading to muscle wasting [26]. Second, in our study, sarcopenia was accompanied with lower BMI than non-sarcopenic patients. Our results revealed that sarcopenic patients with lower BMI had poor postoperative survival, and this finding is consistent with prior reports on other malignancies [27-29]. In other words, lower BMI may fuel the detrimental outcomes for sarcopenia patients. As such, physical activities, including endurance exercise, resistance exercise training and aerobics have been recommended for people with sarcopenia [30]. There is no consensus about the optimal frequency and intensity of exercise training for sarcopenia, and it is not uncommon for affected patients to experience poor outcomes such as musculoskeletal complaints attributed to inappropriate exercise training [31]. Thus, developing a suitable exercise prescription for sarcopenia should be a focus of future research. Moreover, adequate amino acid supplementation, such as leucine-rich essential amino acid mixture twice per day, has been suggested to be significantly effective for increasing muscle mass and strength in patients with sarcopenia [32].

High TNM stage is well known to correlate with adverse prognosis in patients with malignancies. In our study, we further analyzed the prognosis of sarcopenic patients stratified according to TNM stage, by means of the Kaplan-Meier method, and found that sarcopenic patients with TNM stage II and III disease had poorer OS and CSS, as well as for PFS in patients with TNM stage II. The two groups under TNM stage III were comparable with regard to PFS, while there was a worse PFS trend in the sarcopenic patients. Sarcopenic patients with TNM stage I/0 disease had lower OS but no statistically significant difference in PFS or CSS compared to the non-sarcopenic group. There were no significant differences between sarcopenic and non-sarcopenic patients with TNM stage IV disease, but the sample sizes were small due to the high mortality in this group. Therefore, analysis of more patients with TNM stage IV UTUC are needed to further assess the impact of sarcopenia on long-term survival outcomes after surgery.

The present study also has several limitations. First, it is a retrospective study of a single-institutional database, and we were unable to include muscle function (strength or physical performance). We are planning to conduct a prospective study to further validate these results. Second, 32 patients without preoperative abdominal CT scans were excluded from this study, which may have introduced selection bias into the results. To assess possible bias from the missing CT scans, we compared the characteristics of the 136 excluded patients with those of patients included in this cohort. There were no significant differences between the two groups with regard to clinicopathological features, surgical and treatment details, and postoperative outcomes (data not shown).

Conclusions

We first identified sex-specific cut-off values to diagnose sarcopenia in UTUC patients who underwent RNU. According to those cut-off values, the incidence of sarcopenia was 30% in this cohort. Subsequently, sarcopenia was determined to be an independent risk predictor

for OS and CSS under TNM stage I/0, II and III, as well as for PFS under TNM stage I/0 and II. However, sarcopenia did not significantly influence OS, PFS and CSS under TNM stage IV. These findings indicate that sarcopenia may be a potential therapeutic target to improve the postoperative outcomes of sarcopenic patients. Suitable exercise training combined with adequate nutritional intake is recommended. Further prospective study is essential to validate these results.

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Disclosure of conflict of interest

None.

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