

Clinical-Bladder cancer  
**Metabolic syndrome and upper tract urothelial carcinoma: A retrospective analysis from a large Chinese cohort**

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**Abstract**

**Background:** Metabolic syndrome (MetS) has been reported to be associated with adverse outcomes in cancer patients. However, the relationship between MetS and upper tract urothelial carcinoma (UTUC) has yet to be explored.

**Objectives:** To investigate the prognostic value of MetS in UTUC after radical nephroureterectomy.

**Patients and methods:** A total of 644 patients with UTUC after radical nephroureterectomy were identified at West China Hospital from May 2003 to December 2016. MetS was defined as the co-existence of 3 or more of 5 components (obesity, hypertension, elevated fasting glucose, decreased high-density lipoprotein-cholesterol, and hypertriglyceridemia). Logistic and Cox regression analyses were performed to evaluate the associations of MetS with pathological features and survival outcomes. Decision curve analysis and Harrell concordance index were used to determine the clinical utility of the prediction models.

**Results:** Of 644 patients, 157 (24.4%) had MetS. Over a median follow-up of 39 months, 269 (41.8%) experienced disease recurrence, 233 (36.2%) died, and 185 (28.7%) died of UTUC. MetS was independently associated with high-grade disease, advanced pT stage ( $\geq pT3$ ), and lymphovascular invasion (each  $P < 0.05$ ). Multivariate Cox regression analysis showed that MetS was an independent factor for decreased cancer-specific survival (hazard ratio [HR]: 1.38, 95% confidence intervals [CI]: 1.01–1.89,  $P = 0.042$ ) but not for recurrence-free survival (HR: 1.27, 95% CI: 0.97–1.67,  $P = 0.078$ ), and overall survival (HR: 1.24, 95% CI: 0.95–1.62,  $P = 0.121$ ). The estimated c-index of the multivariate models for cancer-specific survival was 0.763 compared with 0.769 when MetS added.

**Conclusions:** MetS is a negative prognostic factor in UTUC. Further studies of MetS in UTUC are demanded. © 2018 Elsevier Inc. All rights reserved.

**Keywords:** Upper tract urothelial carcinoma; Radical nephroureterectomy; Metabolic syndrome; Prognosis

**1. Introduction**

Upper tract urothelial carcinoma (UTUC) is a type of rare tumor, which occurs in the renal pelvis and ureter. Currently, radical nephroureterectomy (RNU) is the standard treatment for localized UTUC but the postoperative survival outcomes among this population are still far from satisfactory [1]. Growing preoperative factors have been

investigated to assist the risk stratification of UTUC, but the real effective preoperative factors are still subjected to further investigation.

Metabolic syndrome (MetS) is characterized by a cluster of metabolic risk factors including obesity, elevated blood pressure, elevated fasting glucose, and dyslipidemia. These factors are commonly associated with cardiovascular disease and diabetes [2], which suggest a sedentary lifestyle and unbalanced diets may lead to MetS occurrence. Recent attentions have been placed on the links between MetS and cancer development especially in prostate cancer [3], colorectal cancer [4,5], and breast cancer [6]. Emerging

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evidence suggests MetS can increase cancer mortality in various cancer types [7–9]. To date, several studies have examined the prognostic value of MetS components (e.g., obesity and diabetes) in UTUC [10–12]. Nevertheless, no prior studies have investigated the prognosis of UTUC patients with MetS, and researches with respect to the role of MetS in UTUC are lacking.

In response to the current state in this field of study, we sought to examine whether MetS was associated with adverse pathological outcomes and survival outcomes in UTUC patients treated with RNU. Furthermore, we also intended to evaluate whether each individual component of MetS would have an impact on the prognosis of UTUC.

## 2. Patients and methods

### 2.1. Study population

This study received the approval from the institutional review board of West China Hospital. Patients diagnosed with UTUC treated with RNU from May 2003 to December 2016 were initially retrieved from our database. Clinical and pathological data were obtained through each patient's medical record. We excluded 14 patients with nonurothelial carcinomas, 66 patients who had lost at first follow-up, 58 patients without complete pre- and postoperative information. We thus finally included 644 patients for further study.

### 2.2. MetS definition

The presence of MetS was evaluated before the date of surgery. MetS was determined according to the American Heart Association/National Heart, Lung, and Blood Institute, and International Diabetes Federation interim consensus statement [2], and requiring 3 or more of the following 5 contents: obesity (defined as body mass index [BMI]  $\geq 28$  kg/m<sup>2</sup>); high blood pressure (defined as physician diagnosis of hypertension or antihypertensive drug treatment); elevated fasting glucose ( $\geq 5.6$  mmol/l, or type 2 diabetes mellitus, or drug treatment for hyperglycemia); low high-density lipoprotein-cholesterol (HDL-cholesterol, defined as  $<1.03$  mmol/l in males and  $<1.3$  mmol/l in females or drug treatment for this abnormality); hypertriglyceridemia (defined as  $\geq 1.7$  mmol/l or treatment for this abnormality). Of note, waist circumferences were not routinely measured in our center; instead, we selected BMI (calculated by weight/height<sup>2</sup>) as the substitution. Obesity was defined as BMI  $\geq 28$  kg/m<sup>2</sup> in the Chinese population [13]. Additionally, we defined high blood pressure as physician diagnosis of hypertension or antihypertensive drug treatment because blood pressure measurements before surgery were not always consistent.

### 2.3. Surgical procedure

Open or laparoscopic RNU was conducted (kidney with the whole length of the ureter was removed, and open

bladder cuff excision was conducted) according to the surgeons' decision. Lymph node dissection was conducted to the patients with suspected enlarged lymph nodes, which were confirmed through the preoperative radiology or intraoperative discovery.

Hydronephrosis and multifocality were confirmed through preoperative imaging reports. Multifocality was defined as the occurrence of multiple tumors in the ureter or renal pelvis. Pathological features were extracted from the corresponding reports. Tumor grade was determined based on the World Health Organization/International Society of Urologic Pathology classification of 2004. Tumor stage was assessed according to the 2002 Union for International Cancer Control Tumor Node Metastasis (TNM) classification system. In addition, tumor architecture (sessile or papillary), lymphovascular invasion (LVI), positive surgical margins, and concomitant variant histology (CVH, urothelial carcinomas with abnormal histological differentiation) were recorded as well.

### 2.4. Follow-up

In the first year after surgery, patients were followed every 3 months; the next 2 years postoperatively they were followed every 6 months and then once a year thereafter. Follow-up contents included physical examination, laboratory tests, and cystoscopy. Computed tomography or magnetic resonance imaging were done each year or when disease recurrence suspected. Adjuvant therapy was done according to the urologists' judgment and patient's wish. Disease recurrence was determined radiologically (operating site, lymph nodes, or visceral metastasis). Cancer-specific survival (CSS) was defined as the time from RNU to cancer-related death. Disease recurrence-free survival (RFS) was defined as the time from RNU to disease recurrence. Overall survival (OS) was defined as the time from RNU to patients' death of all cause.

### 2.5. Statistical analysis

Continuous variables were calculated by Wilcoxon–Mann–Whitney test and categorical variables were evaluated using chi-square, Pearson's, or Fisher's test. Binary logistic regression models were used to analyze the associations of MetS with adverse pathological outcomes. Kaplan–Meier methods with Log-rank tests were used to analyze the difference between groups for CSS, RFS, and OS. Univariate and multivariate Cox regression analyses were performed to investigate the associations of MetS with survival outcomes. Variables with a *P* value  $<0.2$  in the univariate analysis were included in the multivariate Cox analysis. Models were adjusted for age, hydronephrosis, surgical approach, tumor size, grade, lymphovascular invasion, tumor architecture, LVI, positive surgical margins, and CVH. Decision curve analysis and Harrell concordance index were used to assess the benefit and predictive

Table 1  
Patients' characteristics in present study

Variables	Total (n = 644)	Non-MetS (n = 487, 75.6%)	MetS (n = 157, 24.4%)	P
Age, y, mean ± SD	66.2 ± 11.1	65.8 ± 11.2	67.4 ± 11.0	0.139
Gender				<b>0.013</b>
Male	367 (57.0)	291 (59.8)	76 (48.4)	
Female	277 (43.0)	196 (40.2)	81 (51.6)	
Smoking status				0.274
Never	462 (71.7)	344 (70.6)	118 (75.2)	
Former/current	182 (28.3)	143 (29.4)	39 (24.8)	
Hydronephrosis				0.052
No	245 (38.0)	175 (35.9)	70 (44.6)	
Yes	399 (62.0)	312 (64.1)	87 (55.4)	
Tumor location				0.156
Pelvicalyceal	338 (52.5)	251 (51.5)	87 (55.4)	
Ureteric	191 (29.7)	141 (29.0)	50 (31.8)	
Both	115 (17.9)	95 (19.5)	20 (12.7)	
Multifocality				0.069
No	535 (83.1)	412 (84.6)	123 (78.3)	
Yes	109 (16.9)	75 (15.4)	34 (21.7)	
Surgical approach				0.370
Open RNU	413 (64.1)	317 (65.1)	96 (61.1)	
Laparoscopic RNU	231 (35.9)	170 (34.9)	61 (38.9)	
Tumor size				0.916
<3 cm	207 (32.1)	156 (32.0)	51 (32.5)	
≥3 cm	437 (67.9)	331 (68.0)	106 (67.5)	
Tumor grade				<b>0.002</b>
Low	163 (25.3)	138 (28.3)	25 (15.9)	
High	481 (74.7)	349 (71.7)	132 (84.1)	
Pathological T stage				0.117
pTaTisT1	196 (30.4)	148 (30.4)	48 (30.6)	
pT2	131 (20.3)	109 (22.4)	22 (14.0)	
pT3	224 (34.8)	164 (33.7)	60 (38.2)	
pT4	93 (14.4)	66 (13.6)	27 (17.2)	
Lymph node status				0.129
pN0/x	582 (90.4)	445 (91.4)	137 (87.3)	
pN+	62 (9.6)	42 (8.6)	20 (12.7)	
Lymphovascular invasion				0.059
No	547(84.9)	421(86.4)	126 (80.3)	
Yes	97 (15.1)	66 (13.6)	31 (19.7)	
Positive surgical margins				0.080
No	595 (92.4)	455 (93.4)	140 (89.2)	
Yes	49 (7.6)	32 (6.6)	17 (10.8)	
Tumor architecture				0.584
Papillary	200 (31.1)	154 (31.6)	46 (29.3)	
Sessile	444 (68.9)	333 (68.4)	111 (70.7)	
Concomitant variant histology				0.462
No	499 (77.5)	374 (76.8)	125 (79.6)	
Yes	145 (22.5)	113 (23.2)	32 (20.4)	
Adjuvant Chemotherapy				0.146
No	374 (58.1)	275 (56.5)	99 (63.1)	
Yes	270 (41.9)	212 (43.5)	58 (36.9)	
Obesity (BMI ≥ 28 kg/m <sup>2</sup> )	92 (14.3)	20 (4.1)	72 (45.9)	<b>&lt;0.001</b>
Hypertension	272 (42.2)	143 (29.4)	129 (82.2)	<b>&lt;0.001</b>
IFG or Diabetes	223 (34.6)	110 (22.6)	113 (72.0)	<b>&lt;0.001</b>
Total cholesterol, mmol/l, mean±SD	4.39 ± 0.97	4.39 ± 0.92	4.38 ± 1.13	0.874
LDL-cholesterol, mmol/l, mean ± SD	2.54 ± 0.75	2.54 ± 0.72	2.54 ± 0.82	0.986
Low HDL-cholesterol	195 (30.3)	101 (20.7)	94 (60.3)	<b>&lt;0.001</b>
Hypertriglyceridemia (≥1.7 mmol/l)	128 (19.9)	55 (11.3)	73 (46.5)	<b>&lt;0.001</b>

BMI = body mass index; HDL = high-density lipoprotein; HR = hazard ratio; IFG = impaired fasting glucose; LDL = low-density lipoprotein; MetS = metabolic syndrome; RNU = radical nephroureterectomy. Bold values indicated statistical significance.

Table 2

Odds ratios for metabolic syndrome for pathological outcomes when adjusting for preoperative factors

Adverse pathological outcomes	Adjusted OR <sup>a</sup> (95% CI)	P value
High-grade carcinoma	2.01 (1.24–3.25)	<b>0.005</b>
High pathological T stage (≥T3)	1.54 (1.05–2.25)	<b>0.027</b>
Lymph node involvement	1.55 (0.86–2.78)	0.144
Lymphovascular invasion	1.71 (1.05–2.78)	<b>0.030</b>
Sessile carcinoma	1.20 (0.80–1.80)	0.377
Concomitant variant histology	0.84 (0.53–1.31)	0.435
Positive surgical margins	1.69 (0.88–3.23)	0.114

CI = confidence interval; OR = odds ratios. Bold values indicated statistical significance.

<sup>a</sup> Adjusting for age, gender, smoking status, hydronephrosis, tumor location, and multifocality.

accuracy of the multivariate models. A 2-sided *P* value <0.05 was considered statistically significant. Especially, as MetS components were also tested in our multivariate analyses, a Bonferroni corrected *P* value of 0.05/5=0.01 was adopted as the threshold for statistical significance when the analyses included these 5 components. statistical analyses were conducted using the IBM Statistical Package for Social Sciences Statistics version 22.0 (IBM Corp., Armonk, NY) and R software (version 22.0).

### 3. Results

#### 3.1. Study population

Table 1 demonstrated the baseline characteristics of patients with or without MetS in the entire cohort. Median patients' age at surgery was 67.5 year (interquartile range: 60–74). Low-grade and high-grade UTUC were seen in 163 patients (25.3%) and 481 patients (74.7%), respectively. 196 (30.4%) patients were nonmuscle-invasive UTUC (pTaTisT1), 131(20.3%) were pT2, 224 (34.8%) were pT3, and 93 (14.4%) were pT4. A total of 92 patients

(14.3%) were diagnosed with obesity. There were 157 (24.4%) patients in the MetS group and 487 (75.6%) in the non-MetS group. Patients with MetS were more females (51.6% vs. 40.2%, *P*=0.013), more high-grade disease (84.1% vs. 71.7%, *P*=0.002) and each component of MetS was also significant higher in MetS group, compared with those without MetS.

#### 3.2. MetS and pathological outcomes

Results from binary logistic regression analyses were shown in Table 2 and Table A.1 in the Supplementary Material. After adjusting preoperative factors including age, gender, smoking status, hydronephrosis, tumor location, and multifocality, MetS was independently associated with high-grade disease (odds ratio [OR]: 2.01, 95% confidence intervals [CI]: 1.24–3.25, *P*=0.005), high tumor stage (≥T3; OR: 1.54, 95% CI: 1.05–2.25, *P*=0.027), and LVI (OR: 1.71, 95% CI: 1.05–2.78, *P*=0.03; Table 2). Subsequently, we examined the effect of each component of MetS on adverse pathological outcomes. Bonferroni correction was adopted and Bonferroni corrected *P* value was 0.01(0.05/5 variables). Our results showed that only low HDL-cholesterol was independently associated with high-grade carcinoma (OR: 1.90, 95% CI: 1.20–3.01, *P*=0.006), high pT stage (OR: 2.10, 95% CI: 1.43–3.08, *P*<0.001), sessile carcinoma (OR: 1.97, 95% CI: 1.30–3.01, *P*=0.002), and CVH (OR: 2.26, 95% CI: 1.48–3.47, *P*<0.001). Obesity, hypertension, impaired fasting glucose or diabetes, and hypertriglyceridemia were not independent factors for all adverse pathological outcomes (all *P*>0.01).

#### 3.3. MetS and survival outcomes

With a median follow-up of 39 months (interquartile range: 17–64), 269 (41.8%) experienced disease recurrence, 233 (36.2%) died, and 185 (28.7%) died of UTUC. The 5-year CSS, RFS, and OS were 65.8%, 51.7%, and

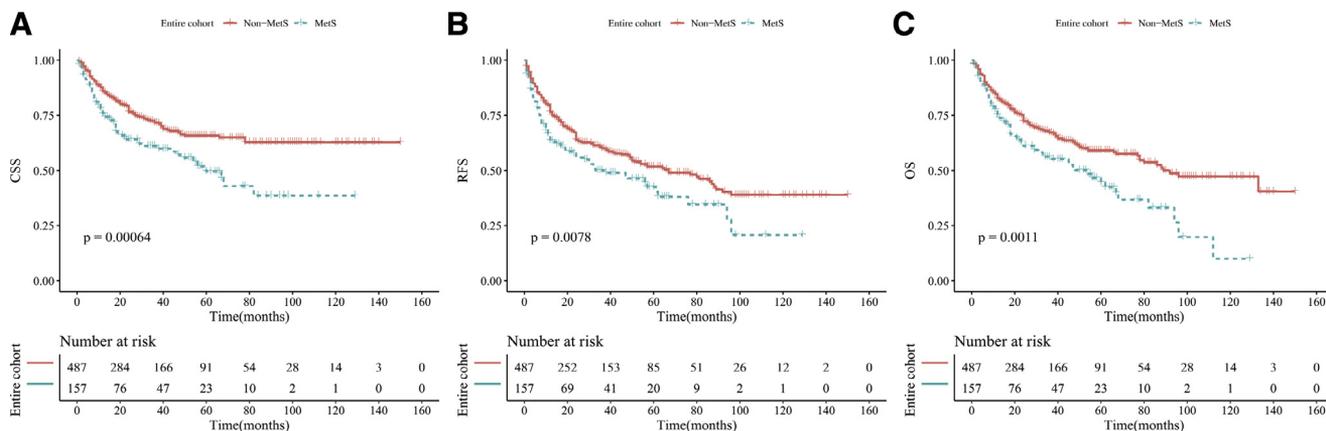


Fig. 1. Kaplan–Meier curves for survival outcomes in all UTUC patients according to the presence of MetS. (A) Cancer-specific survival, (B) disease recurrence-free survival, and (C) overall survival. CSS = cancer-specific survival; RFS = disease recurrence-free survival; OS = overall survival.

Table 3  
Univariable Cox regression analyses

Variables	Cancer-specific survival		Recurrence-free survival		Overall survival	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age (≥65 years vs. <65 years)	0.81 (0.60–1.09)	0.158	0.83 (0.65–1.07)	0.145	0.95 (0.73–1.24)	0.949
Gender (male vs. female)	0.85 (0.64–1.14)	0.276	0.90 (0.71–1.14)	0.381	0.93 (0.72–1.20)	0.562
Smoking (Former/current vs. never)	0.83 (0.59–1.16)	0.268	0.90 (0.69–1.19)	0.466	0.90 (0.67–1.21)	0.497
Hydronephrosis (yes vs. no)	1.21 (0.89–1.64)	0.227	1.37 (1.06–1.77)	<b>0.017</b>	1.28 (0.97–1.68)	0.080
Tumor location		0.660		0.523		0.702
Pelvic/lyceal	Ref.		Ref.		Ref.	
Ureteric	0.99 (0.71–1.38)	0.949	0.92 (0.69–1.22)	0.550	0.92 (0.68–1.24)	0.576
Both	1.18 (0.80–1.74)	0.398	1.13 (0.82–1.57)	0.453	1.08 (0.76–1.54)	0.656
Multifocality (yes vs. no)	1.09 (0.75–1.59)	0.656	1.00 (0.72–1.38)	0.981	0.99 (0.70–1.41)	0.972
Surgical approach (Laparoscopic vs. Open)	1.52 (1.09–2.12)	<b>0.014</b>	1.17 (0.89–1.52)	0.258	1.41 (1.05–1.91)	<b>0.024</b>
Tumor size (≥3 cm vs. <3 cm)	2.05 (1.46–2.89)	<b>&lt;0.001</b>	1.87 (1.42–2.46)	<b>&lt;0.001</b>	1.97 (1.46–2.66)	<b>&lt;0.001</b>
Tumor grade (high vs. low)	3.77 (2.32–6.13)	<b>&lt;0.001</b>	2.25 (1.62–3.13)	<b>&lt;0.001</b>	2.86 (1.94–4.22)	<b>&lt;0.001</b>
Pathological T stage		<b>&lt;0.001</b>		<b>&lt;0.001</b>		<b>&lt;0.001</b>
TaTisT1	Ref.		Ref.		Ref.	
T2	1.71 (0.96–3.02)	0.068	1.60 (1.05–2.45)	<b>0.030</b>	1.67 (1.03–2.71)	<b>0.038</b>
T3	4.12 (2.57–6.60)	<b>&lt;0.001</b>	3.19 (2.24–4.56)	<b>&lt;0.001</b>	3.63 (2.43–5.43)	<b>&lt;0.001</b>
T4	9.98 (6.08–16.39)	<b>&lt;0.001</b>	7.41 (5.01–10.95)	<b>&lt;0.001</b>	8.28 (5.39–12.73)	<b>&lt;0.001</b>
Lymph node status (pN+ vs. pN0/x)	4.07 (2.88–5.76)	<b>&lt;0.001</b>	3.75 (2.75–5.11)	<b>&lt;0.001</b>	3.61 (2.60–5.00)	<b>&lt;0.001</b>
lymphovascular invasion (yes vs. no)	2.69 (1.94–3.74)	<b>&lt;0.001</b>	2.18 (1.64–2.91)	<b>&lt;0.001</b>	2.48 (1.84–3.34)	<b>&lt;0.001</b>
Positive surgical margins (yes vs. no)	2.30 (1.48–3.56)	<b>&lt;0.001</b>	1.92 (1.30–2.84)	<b>&lt;0.001</b>	2.21 (1.47–3.30)	<b>&lt;0.001</b>
Tumor architecture (Sessile vs. Papillary)	3.75 (2.46–5.71)	<b>&lt;0.001</b>	2.52 (1.86–3.42)	<b>&lt;0.001</b>	2.87 (2.04–4.04)	<b>&lt;0.001</b>
Concomitant variant histology (yes vs. no)	2.32 (1.71–3.15)	<b>&lt;0.001</b>	1.89 (1.45–2.45)	<b>&lt;0.001</b>	2.11 (1.60–2.78)	<b>&lt;0.001</b>
Adjuvant Chemotherapy (yes vs. no)	0.94 (0.71–1.26)	0.691	1.10 (0.87–1.40)	0.433	0.88(0.68–1.14)	0.329
MetS (yes vs. no)	1.69 (1.24–2.29)	<b>0.001</b>	1.42 (1.09–1.85)	<b>0.009</b>	1.58 (1.20–2.08)	<b>0.001</b>
Obesity (yes vs. no)	1.13 (0.77–1.65)	0.539	1.06 (0.78–1.46)	0.728	1.11 (0.78–1.56)	0.570
Hypertension (yes vs. no)	1.15 (0.86–1.54)	0.332	1.03 (0.81–1.31)	0.826	1.14 (0.88–1.47)	0.321
IFG or Diabetes (yes vs. no)	0.91 (0.67–1.23)	0.540	1.00 (0.78–1.28)	0.996	0.92 (0.70–1.21)	0.532
Low HDL-cholesterol (yes vs. no)	1.84 (1.37–2.47)	<b>&lt;0.001</b>	1.63 (1.27–2.09)	<b>&lt;0.001</b>	1.56 (1.19–2.03)	<b>0.001</b>
Hypertriglyceridemia (yes vs. no)	0.64 (0.43–0.95)	<b>0.029</b>	0.78 (0.57–1.06)	0.110	0.63 (0.44–0.90)	<b>0.011</b>

HDL = high-density lipoprotein; HR = hazard ratio; IFG = impaired fasting glucose; MetS = metabolic syndrome. Bold values indicated statistical significance.

Table 4  
Multivariate Cox regression analyses of factors for survival outcomes in patients with upper tract urothelial carcinoma

Variables	Cancer-specific survival		Recurrence-free survival		Overall survival	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age (≥65 years vs. <5 years)	0.75 (0.55–1.02)	0.063	0.78 (0.60–1.01)	0.058	-	-
Hydronephrosis (yes vs. no)	-	-	1.09 (0.84–1.42)	0.524	1.09 (0.83–1.42)	0.534
Surgical approach (Laparoscopic vs. Open)	0.93 (0.66–1.32)	0.694	-	-	1.11 (0.85–1.46)	0.442
Tumor size (≥3 cm vs. <3 cm)	1.54 (1.08–2.20)	<b>0.017</b>	1.47 (1.11–1.96)	<b>0.008</b>	1.47 (1.11–1.96)	<b>0.008</b>
Tumor grade (high vs. low)	2.01 (1.19–3.40)	<b>0.009</b>	1.39 (0.97–2.00)	0.076	1.33 (0.93–1.91)	0.122
Pathological T stage		<b>0.001</b>		<b>&lt;0.001</b>		<b>&lt;0.001</b>
TaTisT1	Ref.		Ref.		Ref.	
T2	1.15 (0.63–2.09)	0.645	1.25 (0.80–1.94)	0.334	1.27 (0.82–1.99)	0.289
T3	1.95 (1.14–3.32)	<b>0.015</b>	1.98 (1.32–2.98)	<b>0.001</b>	2.10 (1.40–3.15)	<b>&lt;0.001</b>
T4	3.04 (1.62–5.72)	<b>0.001</b>	3.38 (2.05–5.59)	<b>&lt;0.001</b>	3.66 (2.22–6.04)	<b>&lt;0.001</b>
Lymph node status (pN+ vs. pN0/x)	1.76 (1.17–2.63)	<b>0.006</b>	1.87 (1.30–2.68)	<b>0.001</b>	1.85 (1.29–2.66)	<b>0.001</b>
lymphovascular invasion (yes vs. no)	1.14 (0.79–1.64)	0.487	0.96 (0.69–1.32)	0.782	0.97 (0.70–1.34)	0.851
Positive surgical margins (yes vs. no)	1.18 (0.74–1.87)	0.491	1.04 (0.69–1.59)	0.842	0.99 (0.65–1.50)	0.958
Tumor architecture (Sessile vs. Papillary)	1.82 (1.13–2.93)	<b>0.014</b>	1.44 (1.01–2.04)	<b>0.042</b>	1.38 (0.97–1.97)	0.07
Concomitant variant histology (yes vs. no)	1.38 (1.00–1.89)	<b>0.048</b>	1.20 (0.92–1.59)	0.185	1.22 (0.92–1.60)	0.164
MetS (yes vs. no)	1.38 (1.01–1.88)	<b>0.042</b>	1.27 (0.97–1.67)	0.078	1.24 (0.95–1.62)	0.121

CI = confidence interval; HR = hazard ratio; MetS = metabolic syndrome. Bold values indicated statistical significance.

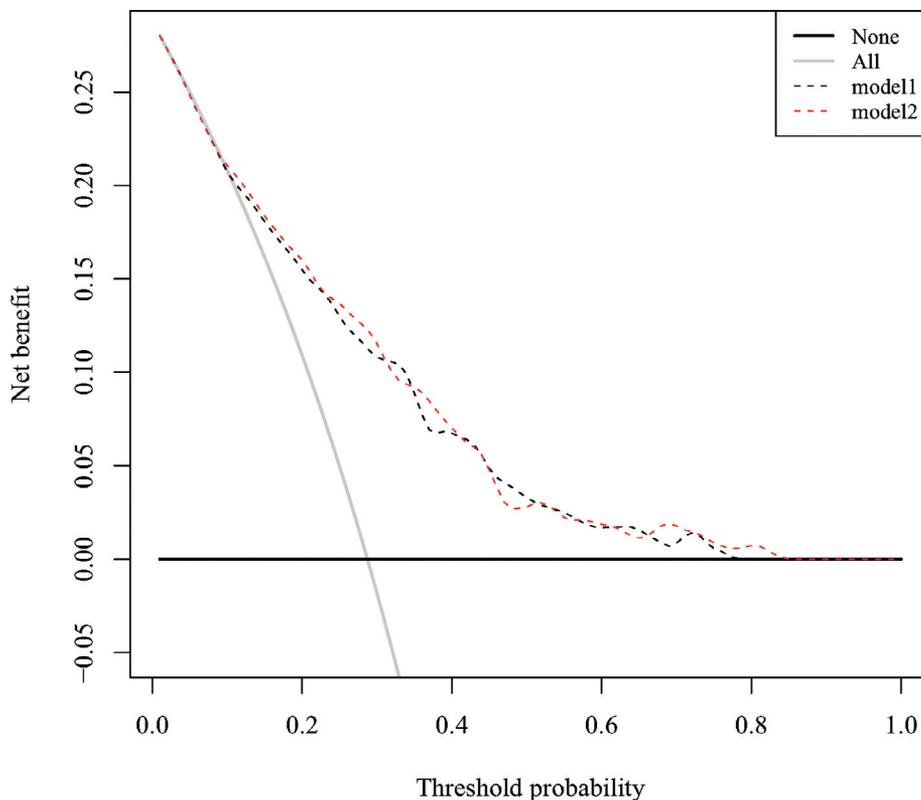


Fig. 2. Decision curve analysis. Model 1: including age, tumor size, tumor grade, tumor stage, lymph node status, tumor architecture, and CVH and model 2: model 1 + MetS. CVH =concomitant variant histology.

59.0% in the Non-MetS group, as compared with 49.6%, 44.6%, and 30.8% in the MetS group.

Kaplan–Meier curves demonstrated that MetS patients had significantly lower CSS, RFS, and OS than those without MetS (Fig. 1).

Univariate Cox proportional hazards regression analyses showed that MetS was associated with decreased CSS, RFS, and OS (all  $P < 0.01$ ; Table 3). After adjusting clinical confounders, multivariate Cox regression analysis showed that MetS was an independent factor for worse CSS (hazard ratio [HR]: 1.38, 95% CI: 1.01–1.89,  $P = 0.042$ ) but not for RFS (HR: 1.27, 95% CI: 0.97–1.67,  $P = 0.078$ ), and OS (HR: 1.24, 95% CI: 0.95–1.62,  $P = 0.121$ ; Table 4). Besides, each component of MetS for survival outcomes in patients with UTUC was also estimated (Table A.2, Supplementary Material). The results indicated that hypertriglyceridemia was independently associated with better CSS (HR: 0.54, 95% CI: 0.35–0.82,  $P = 0.004$ ) and OS (HR: 0.53, 95% CI: 0.36–0.77,  $P = 0.001$ ) while not for RFS (HR: 0.65, 95% CI: 0.47–0.91,  $P = 0.011$ , Bonferroni correction). However, obesity, hypertension impaired fasting glucose or diabetes, and low HDL-cholesterol were not independently associated with CSS, RFS, and OS (all  $P > 0.01$ ).

### 3.4. Benefit of the multivariate models

Given the results from the multivariate cox regression analysis, we selected the factors with a  $P$  value  $< 0.1$  in the

multivariate analysis to develop the predictive models for CSS. Model 1 included age, tumor size, tumor grade, tumor stage, lymph node status, tumor architecture, and CVH. Model 2 included the factors in the model 1 in addition to MetS. Decision curve analysis showed that when the threshold probability was 0.1 to 0.4, both the models can achieve the relative high net benefit (Fig. 2). In addition, we also calculated the predictive accuracies of the 2 models. The results showed that the predictive accuracy was 76.3% for model 1, and 76.9% for model 2 (data not shown), suggesting that when MetS was added to the predictive model, the predictive accuracy of the model was slightly improved.

### 3.5. Subgroup analysis

To best select which population with MetS had worse survival outcomes, all patients were further stratified according to tumor stage, tumor grade, and tumor size in order to compare MetS and non-MetS in different UTUC subgroups. Patients with MetS had decreased CSS ( $P = 0.019$ ), RFS ( $P = 0.047$ ), and OS ( $P = 0.011$ ) in nonmuscle-invasive UTUC compared with patients without MetS (Fig. 3). Additionally, patients with MetS had decreased CSS ( $P = 0.025$ ) and OS ( $P = 0.0039$ ) in those with high-grade carcinoma. While in those with low-grade carcinoma, the associations of MetS and CSS ( $P = 0.0087$ ), RFS ( $P = 0.29$ ), and OS ( $P = 0.071$ ) did not remain significant (Fig. 4). When taking tumor size into

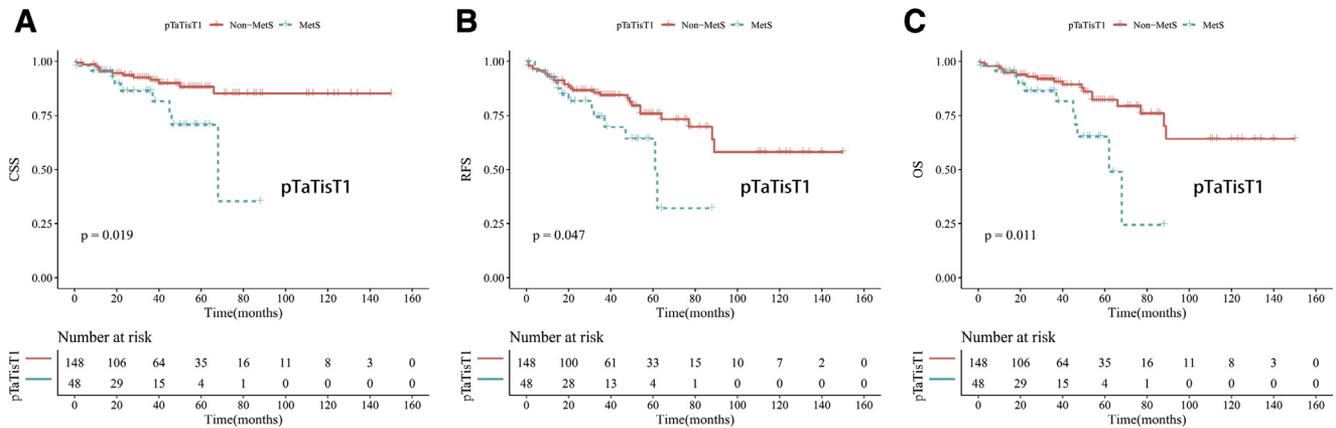


Fig. 3. Kaplan–Meier curves for survival in UTUC patients with nonmuscle-invasive UTUC (TaTisT1) according to the presence of MetS. (A) CSS, cancer-specific survival, (B) RFS, disease recurrence-free survival and (C) OS, overall survival. UTUC = upper tract urothelial carcinoma.

consideration, patients with MetS had significant shorter CSS ( $P = 0.0015$ ), RFS ( $P = 0.011$ ), and OS ( $P = 0.0029$ ) than non-MetS in those with large tumor size. While this association was attenuated in patients with low tumor size (Fig.5).

#### 4. Discussion

In the present single-center study, we enrolled 644 patients with UTUC treated with RNU and observed the negative impact of MetS on both pathological and survival

outcomes in UTUC. Additionally, we performed detailed subgroup analyses regarding tumor size, tumor grade, and stage. The results revealed that the presence of MetS would increase the hazard of death among those with large tumor size, nonmuscle-invasive UTUC and high-grade carcinoma. To the best of our knowledge, our study is the first to explore whether MetS or its components would influence the oncological outcomes in patients with UTUC.

MetS has been reported to be associated with increased risk of several cancers [14]. Cumulating evidence suggested

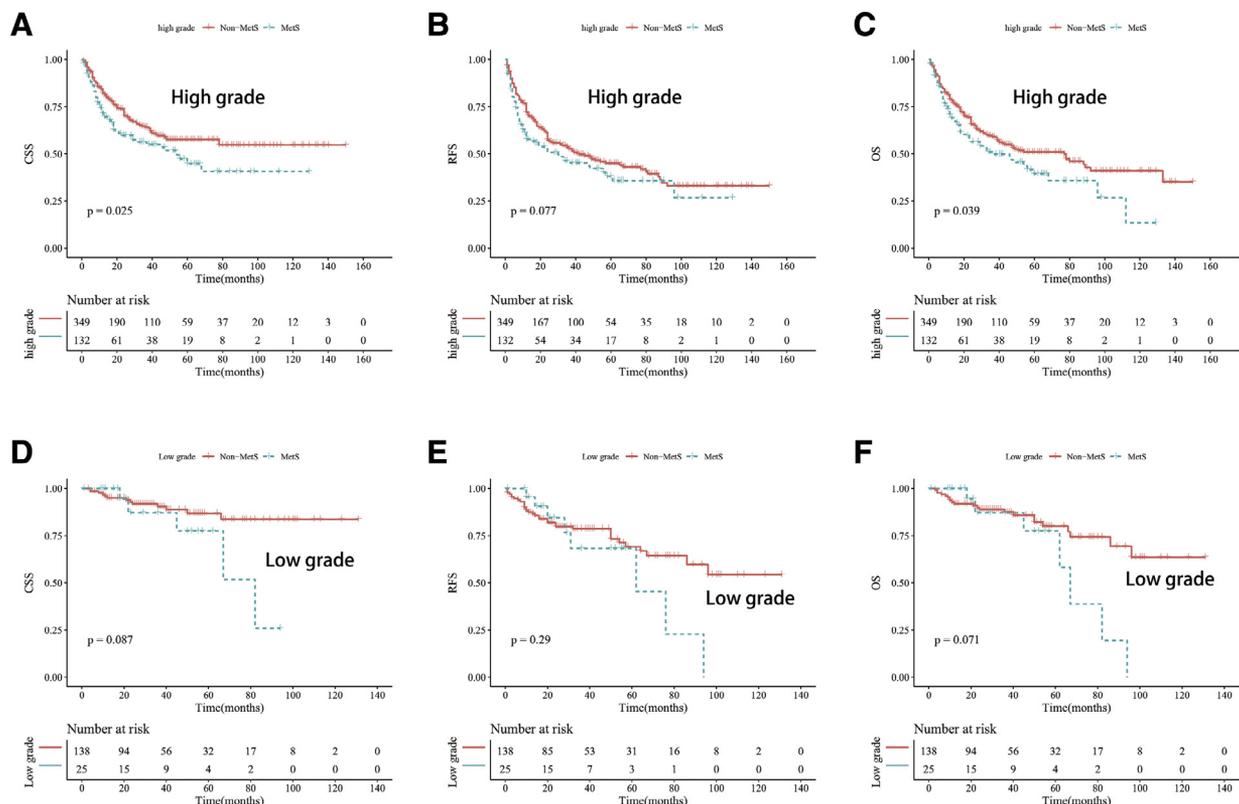


Fig. 4. Kaplan–Meier curves for cancer-specific survival, disease recurrence-free survival, and overall survival stratified by MetS in UTUC patients with high-grade carcinoma (A–C) and low-grade carcinoma (D–F). UTUC = upper tract urothelial carcinoma.

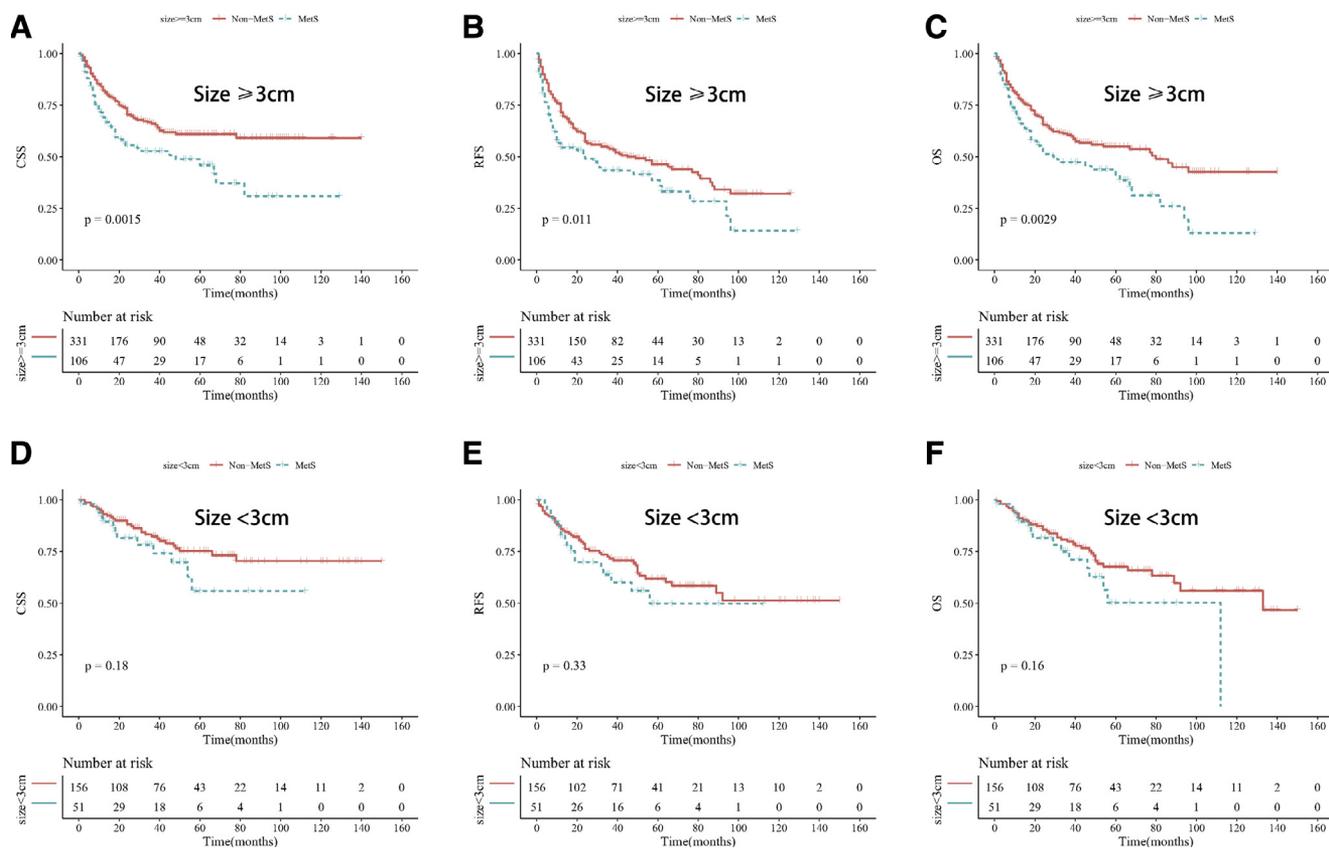


Fig. 5. Kaplan–Meier curves for cancer-specific survival, disease recurrence-free survival, and overall survival stratified by MetS in UTUC patients with tumor size  $\geq 3$ cm (A–C) and tumor size  $< 3$ cm (D–F). UTUC = upper tract urothelial carcinoma.

that MetS was an independent factor for worse pathological outcomes in bladder cancer [15,16] and prostate cancer [17,18]. Likewise, our research also showed that MetS was an independent factor for higher tumor stage, grade, and lymphovascular invasion in UTUC. In line with previous studies which have investigated the relationship between MetS and cancer survival [8,9,19], our study revealed that MetS would decrease UTUC patients' CSS rate. However, data were not always consistent. In a retrospective study from US which included 831 patients with very low-risk prostate cancer (who were potentially eligible for active surveillance), their results did not reveal the association of MetS and biochemical failure or overall death [20]. By contrast, our study showed that even though patients were diagnosed with nonmuscle-invasive UTUC ( $\leq pT1$ ), their hazards of deaths increased when combining MetS.

Obesity, a major component of MetS, was described to be associated with worse outcomes in UTUC [10,11,21]. Whereas our results showed that obesity was not an independent factor for both adverse pathological and survival outcomes in UTUC whether in univariate analysis or multivariate analysis. A possible explanation could be that the differences in population may result different conclusions. Besides, these studies defined obesity as BMI  $\geq 30$  kg/m<sup>2</sup> based on patients from Western countries while we

considered obesity as BMI  $\geq 28$  kg/m<sup>2</sup> mainly based on the Chinese population [13]. Only 92 (14.3%) of 644 patients were diagnosed with obesity which prevented us from performing further subgroup analysis according to obesity. Also, sarcopenic obesity was proved to be associated with several clinicopathological factors in a study with 100 UTUC patients [22]. While multivariate logistic regression analyses were unable to perform in their study due to the limited sample size. Further large studies regarding this topic are still warranted.

As this is the first clinical research for MetS in UTUC, the mechanism of MetS affecting the pathologic features and decreasing the UTUC-related survival still remains unclear. Evidence for other cancer types showed that IGF-1 and insulin might play an important role in tumor progression [23]. Insulin resistance, a significant characteristic of MetS, has been associated with worse outcomes in various cancers [24]. In vitro studies revealed that increased insulin and IGF-I can activate the phosphatidylinositol 3'-kinase and mitogen-activated protein kinase pathways and promote tumor growth [25]. Our preliminary results showed that MetS had negative influence in UTUC patients especially in those with nonmuscle-invasive UTUC (typically with better prognosis), suggesting that especial attention should be paid to this population when MetS was added.

Further studies are required to validate our conclusions and to evaluate whether therapeutic drugs for MetS can improve patients' outcomes.

In the process of analyzing the impact of MetS components on UTUC outcomes, we found that preoperative low HDL-cholesterol was associated with more aggressive tumor characteristics and worse survival end points, suggesting that low HDL might be the main factor that drives the associations between MetS and adverse UTUC outcomes. Existing evidence suggests the interaction between lipid metabolism and cancer cell behavior [26]. Low HDL is capable of inducing inflammation (pro-inflammatory cytokine production), oxidation, and apoptosis, which might contribute to cancer progression [27]. Also, the associations of low HDL-cholesterol with cancer outcomes have been studied in varied cancer types such as prostate, breast, colorectal, and lung cancers [27], while their results were still inconclusive. Further studies are demanded to elucidate the role of HDL in UTUC and examine whether targeting HDL would improve UTUC outcomes.

Interestingly, the conventional adverse factors including diabetes and hypertriglyceridemia showed positive influence on some pathological features and patients' survival in present study. In a previous study conducted by Li et al. [28], they incorporated 1,044 breast cancer patients and showed that a high TG level was associated with better disease-free survival (HR: 0.569,  $P=0.010$ ). Another study with large multiethnic population also demonstrated diabetes <10 years predicted better colorectal CSS (HR: 0.61, 95% CI: 0.46–0.82) [29]. Possible reasons for ours and these results might be explained as the duration and the type of medication used for diabetes (metformin or insulin) might affect the final results [30].

Limitations should be noticed as well. First, this study was predominantly limited by its retrospective design which might lead to selection bias. As some medication such as statins or metformin were not measured in this study due to lack of information, as these drugs might have influence on the survival outcomes. Second, we adopted BMI  $\geq 28$  kg/m<sup>2</sup> rather than BMI  $\geq 30$  kg/m<sup>2</sup> (widely used) or waist circumferences to define obesity which might lead to misclassification. Third, as this study mainly focused on Chinese population which might affect the extension of our results. The role of MetS in UTUC in other races or ethnicities still remains to be explored. Last but not least, the specific dose, duration, and regimens of postoperative chemotherapies were incomplete, which prevented us from analyzing their potential influence on survival outcomes. Though our risk model showed the little improvement when MetS was added, this result should be clarified in further large, prospective, multicenter studies.

## 5. Conclusions

Our results demonstrated that patients with MetS had worse outcomes in UTUC, especially in those with

nonmuscle-invasive UTUC, high-grade disease, and large tumor size, suggesting that preoperative interventions might be warranted to offset the negative impact of MetS in UTUC. This topic is still an area of interest in UTUC and demands future research.

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## Conflict of interest

The authors declare that they have no conflicts of interest.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.urolonc.2018.12.005](https://doi.org/10.1016/j.urolonc.2018.12.005).

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