ORIGINAL RESEARCH

High Preoperative Controlling Nutritional Status Score Predicts a Poor Prognosis in Patients with Localized Upper Tract Urothelial Cancer: A Propensity Score Matching Study in a Large Chinese Center

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Purpose: The aim of this study was to elucidate the prognostic value of the preoperative controlling nutritional status (CONUT) score, a new index based on the total lymphocyte count, serum albumin concentration and total cholesterol concentration, in patients with localized upper tract urothelial cancer (UTUC) after radical nephroureterectomy (RNU) using propensity score matching (PSM) analysis.

Methods: We retrospectively reviewed 908 consecutive patients with localized UTUC who underwent RNU between 1999 and 2015. Patients were divided into two groups according to the optimal cutoff value of the preoperative CONUT score. Relationships between the CONUT score with clinicopathological characteristics, overall survival (OS), cancer-specific survival (CSS), and disease-free survival (DFS) were analyzed before and after 1:1 PSM.

Results: A high preoperative CONUT score was significantly correlated with older age, low body mass index (BMI), poor American Statistical Association (ASA) score, advanced pathological T stage, and tumor squamous or glandular differentiation (all p<0.05). Kaplan-Meier curves showed poor OS, CSS, and DFS for patients with a high CONUT score before and after PSM (all p<0.001). Furthermore, multivariate analyses revealed that a high preoperative CONUT score was an independent risk factor for poor DFS (hazard ratio [HR] 1.418, 95% confidence interval [CI] 1.132–1.776, p=0.002) before PSM and an independent risk factor for poor DFS (HR 1.333, 95% CI 1.010–1.760, p=0.042) and OS (HR 1.459, 95% CI 1.010–2.107, p=0.044) after PSM.

Conclusion: A high preoperative CONUT score is an independent prognostic factor for poor outcomes in patients with localized UTUC after RNU.

Keywords: controlling nutritional status score, upper tract urothelial carcinoma, propensity score matching, prognosis

Introduction

Upper tract urothelial carcinoma (UTUC) is relatively rare, with an approximate annual incidence of almost 2 cases per 100,000 individuals in Western countries, and accounts for only 5–10% of all urothelial carcinomas (UCs).[1,2] Radical nephroureterectomy (RNU) with excision of the bladder cuff is the standard treatment for high-risk UTUCs,[3,4] and kidney-sparing surgery can be the primary option for patients with

low-risk tumors.[1,5] Although the diagnosis and treatment for UTUC have significantly improved, the clinical outcome remains poor, as 5-year specific survival is less than 50% for patients with pT2/pT3 and less than 10% for patients with pT4.[6–8] Therefore, it is necessary to identify biomarkers that have the potential to predict prognosis and individualize adjuvant therapy based on the stratification of risks.

There is accumulating evidence that the preoperative immune-nutritional status plays crucial roles in human cancer development and progression.[9,10] Recently, several biomarkers, such as serum sodium, hemoglobin, C-reactive protein (CRP), albumin, albumin to globulin ratio (AGR), plasma fibrinogen, neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), lymphocyte to monocyte ratio (LMR), body mass index (BMI), sarcopenia and prognostic nutritional index (PNI), have been reported to be independent prognostic factors in many human malignancies, including UTUC.[11,12]

The controlling nutritional status (CONUT) score, a new index calculated from three peripheral blood parameters (total lymphocyte count [TLC], serum albumin concentration and total cholesterol concentration [TCC]), was originally reported as an early screening tool to detect a poor nutritional status in 2005 (Table 1).[13] The CONUT score was proposed as a comprehensive index that could assess the immune response status and long-term nutritional effect of the host. Recently, the prognostic value of the preoperative CONUT score has been reported in many types of malignancies, such as colorectal cancer, esophageal cancer, gastric cancer, and renal cell carcinoma.[14–17] However, there are few studies on UTUC. Shihara and Xu reported that the CONUT score is an independent prognostic factor in UTUC patients treated with surgery.[18,19] However, their studies were limited by the presence of selection bias, a short follow-up interval, a small sample size and limited covariates.

Table 1 CONUT Score System

Parameter	None	Light	Moderate	Severe
Serum albumin, g/dl Score	≥3.50 0	3.00–3.49 2	2.50–2.99 4	<2.50 6
TLC,/mm^3 Score	≥1600 0	1200-1599 1	800-1199 2	<800 3
TCC$^\#$, mg/dl Score	≥180 0	140-179 1	100-139 2	<100 3

Abbreviations: CONUT, controlling nutritional status; TLC, Total lymphocyte count; TCC, total cholesterol concentration.

The aim of this study was to elucidate the prognostic value of the preoperative CONUT score in patients with localized UTUC treated with RNU using propensity score matching (PSM) analysis based on a nationwide high-volume cohort in China.

Materials and Methods
Patient Enrollment and Evaluation

After obtaining approval by the internal ethics review board of Peking University First Hospital (approval no. 2015[977]), we retrospectively collected the records of 908 consecutive patients with localized UTUC who received surgical treatment at Peking University First Hospital between 1999 and 2015. A total of 154 patients were excluded from this study because of accompanying colorectal cancer, breast cancer or other malignancies (n=16), receiving adjuvant chemotherapy (n=44), missing clinicopathological data or follow-up data (n=90), or hepatitis (n=4). Ultimately, 754 patients were enrolled (Figure 1). All patients were treated with standard RNU with bladder cuff resection without any preoperative treatment. Routine lymph node dissection was performed in selected patients with enlarged lymph nodes that were found intraoperatively or by preoperative imaging.

The clinicopathological and follow-up data were collected from a database containing the comprehensive medical records of UTUC patients. Staging was assessed according to the 2002 Union for International Cancer Control (UICC) TNM classification guidelines. Patients were graded based on the World Health Organization (WHO) 1973 grading system. Blood samples were obtained and measured within one week before the operation as regular preoperative laboratory tests. Exposure to aristolochic acids (AAs) was defined as a history of long-term exposure (>3 months) of intermittent intake of regular doses of AA-containing traditional Chinese medicine. All procedures performed in this study were in accordance with the 1964 Declaration of Helsinki and its later amendments, and written informed consent was obtained from all patients.

For patients who were followed at our institute, their follow-up regimen included cystoscopy every 3 months for the first 3 years. The cystoscopy interval was extended to 1 year thereafter. Chest X-ray, urine cytology, serum creatinine tests, and abdominal ultrasound or CT/MRI evaluation were performed at the same time. Overall survival (OS) was determined by a review of patient medical records or data obtained from the Chinese National Statistical Office database. Cancer-specific survival (CSS)
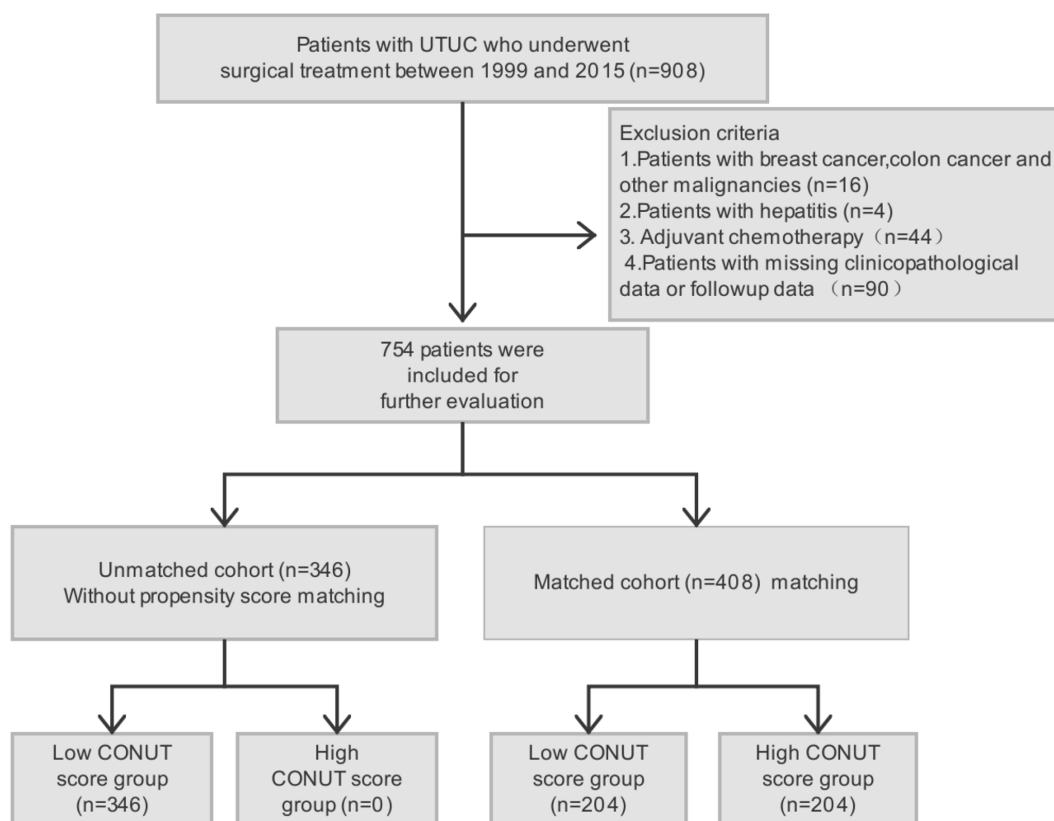
Figure 1 Workflow of this study.

and disease-free survival (DFS) were determined at the last follow-up based on examination results.

As a study in a single center, bias is inevitable. Therefore, all patient variables were adjusted using 1:1 PSM analysis to minimize selection bias.

Statistical Analysis

All statistical tests were performed with SPSS 22.0 (IBM Corp., Armonk, NY, USA) or SAS 9.4 (SAS institute Inc., USA), and statistical significance was set at p<0.05. To determine the optimum cutoff value for the preoperative CONT score, the receiver operating characteristic (ROC) curve of the CONUT score for DFS was analyzed, and the cutoff value for the preoperative CONUT score was defined by the maximum Youden index value. Patients with a preoperative CONUT score over the cutoff value were as assigned to the high CONUT score group, while the remaining patients (CONUT score less than the cutoff value) were assigned to the low CONUT score group.

Several preoperative characteristics, such as age, BMI, American Statistical Association (ASA) score and hydronephrosis, were notably different between the low and high CONUT score patient cohorts (all p<0.1). These preoperative characteristics might have an important impact on the CONUT score. To minimize bias, we performed PSM. The propensity scores were evaluated by nonparsimonious multivariate logistic regression according to the preoperative characteristics. In total, 204 patients with a high CONUT score were matched to 204 patients with a low CONUT score at a ratio of 1:1 using the nearest-neighbor method of PSM with a caliber of 0.1 (Figure 1). After PSM, the differences in preoperative characteristics between the low and high CONUT score groups were acceptable (Figure 2 and Table 3).

Pearson's test and the chi-square test were used to determine the distribution of categorical variables, and the Mann–Whitney U-test was used for continuous variables. OS, CSS and DFS curves were plotted using the Kaplan-Meier method and analyzed by the Log rank test. The univariate analysis was assessed by the Log rank test, and the multivariate analysis was evaluated using the Cox proportional hazard regression model. Only those variables that were identified as significant (p<0.05) in the univariate analysis were included in the multivariate analysis. Sensitivity analyses were also used to measure the potential effect of an unmeasured confounder on the relationship between preoperative CONUT score and the oncological outcomes.
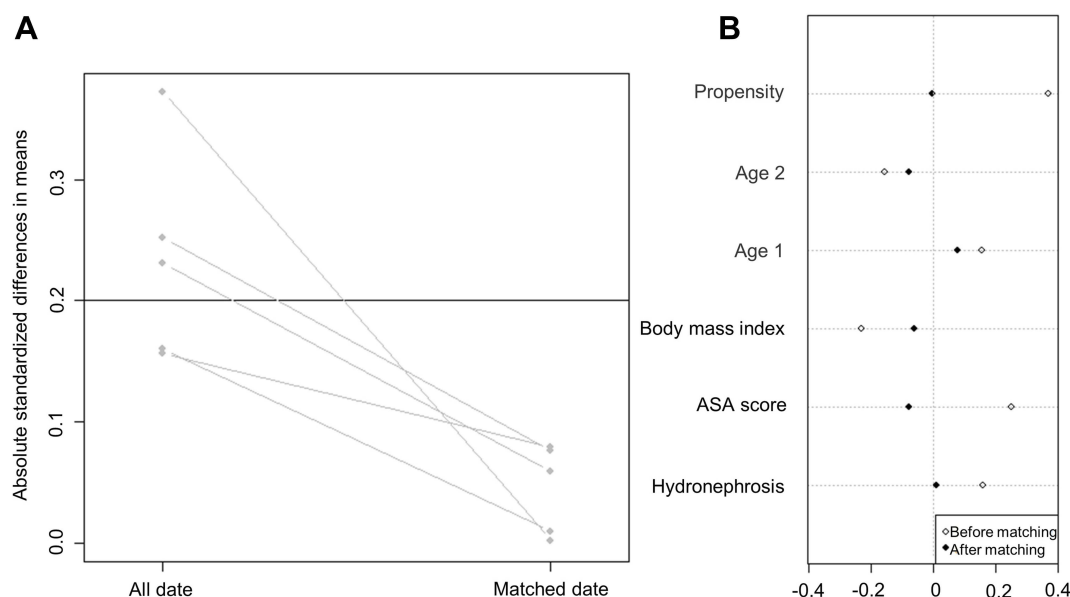
Figure 2 Line plot of individual differences (**A**) and dot-plot of standardized mean differences (**B**) in propensity score matching.

Results

Patient Characteristics

Given that a CONUT score of 3 had a maximum Youden index value, the cutoff value for the CONUT score was set as 3 (Figure 3). Patients with a CONUT score ≥3 were assigned to the high CONUT score group, and those with a CONUT score<3 were assigned to the low CONUT score group. Of the 754 UTUC patients, 204 (27.1%) had a high CONUT score. The patient clinicopathological characteristics before and after PSM are described in Tables 2 and 3, respectively. The median patient age was 69 years (interquartile range [IQR] 61–74 years), and the median follow-up duration was 61 months (IQR 45–105 months). Patients in the high CONUT score group were significantly older (p=0.018), had a lower BMI (p=0.005), had a high ASA score (p<0.001) and were more likely to have hydronephrosis (p=0.055, 53.5% vs 61.3%). These patients were also more likely to have advanced pathological T stage (p=0.001), squamous differentiation (p=0.013) and glandular differentiation (p=0.043) compared with the low CONUT score group. These patients also tended to have an advanced cellular grade (≥G3, p=0.098, 40.4% vs 47.1%) and sessile tumors (p=0.090, 18.9% vs 24.5%) compared with the low CONUT score group.

Survival Outcomes
Before PSM

After a median (IQR) of 32 (19–56) months postoperatively, 234 (31.0%) patients died from any cause.
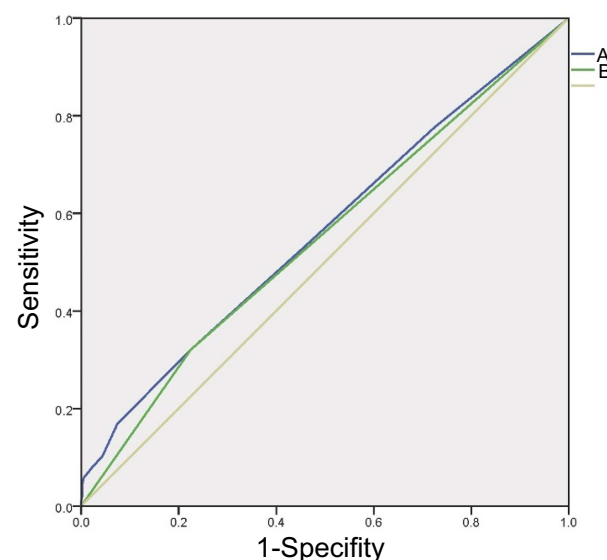
Figure 3 ROC curves used to predict DFS according to the preoperative CONUT score (A-continuous, AUC = 0.563; B-stratified by cutoff=3, AUC = 0.548). **Abbreviations:** DFS, disease-free survival; ROC, receiver operating characteristic; CONUT, controlling nutritional status; AUC, area under the curve.

Postoperatively, 165 (21.5%) patients experienced cancer-specific mortality after a median (IQR) of 26 (16–44) months, and 362 (48.0%) patients experienced disease progression after a median (IQR) of 21 (11–39) months. The Kaplan-Meier curves showed significantly poor OS (p=0.021), CSS (p=0.028), and DFS (p<0.001) for patients with a high preoperative CONUT score (Figure 4A, C and E). A high preoperative CONUT

Table 2 Associations Between CONUT[#] Score and Clinicopathological Characteristics of the Patients According to CONUT Score (CONUT Score<3 are Low Group, Otherwise High Group) Before Propensity Score Matching

Characteristics	Entire Cohort	Low CONUT Score	High CONUT Score	p
No. of subjects	754	550	204	
Preoperative characteristics				
Age, years	67.01±10.46	66.46±10.61	68.49±9.90	0.018*
Age (≥69)	386 (51.2%)	270 (49.1%)	116 (56.9%)	0.058
Gender (male)	342 (45.4%)	240 (43.6%)	102 (50.0%)	0.119
BMI[#]	24.29±3.57	24.51±3.50	23.68±3.71	0.005*
BMI (≥24.19 kg/m^2)	350 (46.4%)	271 (49.3%)	79 (38.7%)	0.010*
Diabetes	146 (19.4%)	106 (19.3%)	40 (19.6%)	0.918
Hypertension	333 (44.2%)	241 (43.8%)	92 (45.1%)	0.753
Coronary disease	129 (17.1%)	96 (17.5%)	33 (16.2%)	0.679
Bladder tumor history	34 (4.5%)	26 (4.7%)	8 (3.9%)	0.636
ASA[#] score (≥3)	145 (19.2%)	89 (16.2%)	56 (27.5%)	<0.001*
Alcohol	89 (11.8%)	63 (11.5%)	26 (12.7%)	0.626
Tobacco	136 (18.0%)	98 (17.8%)	38 (18.6%)	0.797
Exposure of AA[#]	63 (8.4%)	43 (7.8%)	20 (9.8%)	0.381
Hydronephrosis	419 (55.6%)	294 (53.5%)	125 (61.3%)	0.055
The largest tumor location (pelvis)	339 (45.0%)	239 (43.5%)	100 (49.0%)	0.172
Postoperative characteristics				
Pathological T stage (T2-4)	481 (63.8%)	332 (60.4%)	149 (73.0%)	0.001*
Lymph node status (N1)	49 (6.5%)	36 (6.5%)	13 (6.4%)	0.932
Tumor grade (G3)	318 (42.2%)	222 (40.4%)	96 (47.1%)	0.098
LVI[#]	47 (6.2%)	33 (6.0%)	14 (6.9%)	0.663
Multifocality	160 (21.2%)	123 (22.4%)	37 (18.1%)	0.207
The largest tumor size	3.59±2.47	3.36±2.15	3.66±2.26	0.095
The largest tumor size (≥3 cm)	304 (40.3%)	219 (39.8%)	85 (41.7%)	0.646
Tumor architecture (sessile)	154 (20.4%)	104 (18.9%)	50 (24.5%)	0.090
Squamous differentiation	77 (10.2%)	47 (8.5%)	30 (14.7%)	0.013*
Sarcomatoid differentiation	34 (4.5%)	26 (4.7%)	8 (3.9%)	0.636
Glandular differentiation	36 (4.8%)	21 (3.8%)	15 (7.4%)	0.043*

Note: *Statistically significant
Abbreviations: [#]CONUT, controlling nutritional status; BMI, body mass index; ASA, American statistical association; AA, aristolochic acids; LVI, lymphovascular invasion.

score was found to be an independent risk factor for DFS (hazard ratio [HR] 1.418, 95% confidence interval [CI] 1.132–1.776, p=0.002) but not OS (HR 1.273, 95% CI 0.960–1.686, p=0.093) or CSS (HR 1.328, 95% CI 0.954–1.847, p=0.092) based on multivariate Cox regression analyses when adjusted for clinicopathological parameters, as shown in Table 4. For OS, patient sex, hypertension, ASA score ≥3, pathological T and N stages, tumor size, and glandular differentiation were significant co-predictors (all p<0.05). Moreover, patient sex, hypertension, pathologic T and N stages, and tumor size were proved to be independent co-predictors of postoperative CSS and DFS (all p<0.05). Tumor glandular differentiation (p=0.011) significantly predicted DFS but not CSS (Table 4).

After PSM

After a median (IQR) of 30 (18–53) months postoperatively, 127 (31.1%) patients died from any cause. Preoperatively, 90 (22.1%) patients experienced cancer-specific mortality after a median (IQR) of 24 (15–41) months, and 213 (52.2%) patients experienced disease progression after a median (IQR) of 19 (10–39) months. The Kaplan-Meier curves showed significantly inferior OS (p=0.017), CSS (p=0.020), and DFS (p=0.004) for patients with a high preoperative CONUT score (Figure 4B, D and F). Multivariate Cox regression analyses demonstrated that a high CONUT score was an independent risk factor for OS (HR 1.459, 95% CI 1.010–2.107, p=0.044) and DFS (HR 1.333, 95% CI 1.010–1.760, p=0.042) but not CSS (HR 1.336, 95% CI 0.863–2.067, p=0.194), as shown in Table 5. For OS, patient sex,

Table 3 Associations Between CONUT[#] Score and Clinicopathological Characteristics of the Patients According to CONUT Score (CONUT Score<3 are Low Group, Otherwise High Group) After Propensity Score Matching

Characteristics	Entire Cohort	Low CONUT Score	High CONUT Score	p
No. of subjects	408	204	204	
Preoperative characteristics				
Age, years	67.81±10.39	67.12±10.84	68.49±9.90	0.184
Age (≥69)	224 (54.9%)	108 (52.9%)	116 (56.9%)	0.426
Gender (male)	182 (47.1%)	80 (39.2%)	102 (50.0%)	0.058
BMI[#]	24.00±3.82	24.31±3.92	23.68±3.71	0.095
BMI (≥24.19 kg/m^2)	176 (43.1%)	97 (44.6%)	79 (38.7%)	0.549
Diabetes	81 (19.9%)	41 (20.1%)	40 (19.6%)	0.901
Hypertension	188 (44.2%)	96 (47.1%)	92 (45.1%)	0.691
Coronary disease	74 (18.1%)	43 (21.1%)	33 (16.2%)	0.438
Bladder tumor history	18 (4.4%)	10 (4.9%)	8 (3.9%)	0.630
ASA[#] score (≥3)	119 (29.2%)	63 (30.9%)	56 (27.5%)	0.446
Alcohol	47 (11.5%)	21 (10.3%)	26 (12.7%)	0.438
Tobacco	72 (17.6%)	34 (16.7%)	38 (18.6%)	0.603
Exposure of AA[#]	42 (10.3%)	22 (710.8%)	20 (9.8%)	0.745
Hydronephrosis	249 (61.0%)	124 (60.8%)	125 (61.3%)	0.919
The largest tumor location (pelvis)	195 (47.8%)	95 (46.6%)	100 (49.0%)	0.620
Postoperative characteristics				
Pathological T stage (T2-4)	267 (65.4%)	118 (57.8%)	149 (73.0%)	0.001*
Lymph node status (N1)	23 (5.6%)	10 (4.9%)	13 (6.4%)	0.520
Tumor grade (G3)	173 (42.4%)	77 (37.7%)	96 (47.1%)	0.057
LVI[#]	27 (6.6%)	13 (6.4%)	14 (6.9%)	0.842
Multifocality	84 (20.6%)	47 (23.0%)	37 (18.1%)	0.221
The largest tumor size	3.54±2.30	3.41±2.34	3.66±2.26	0.262
The largest tumor size (≥3 cm)	164 (40.2%)	79 (38.7%)	85 (41.7%)	0.545
Tumor architecture (sessile)	84 (20.6%)	34 (16.7%)	50 (24.5%)	0.093
Squamous differentiation	47 (11.5%)	17 (8.3%)	30 (14.7%)	0.044*
Sarcomatoid differentiation	20 (4.9%)	12 (5.9%)	8 (3.9%)	0.359
Glandular differentiation	23 (5.6%)	8 (3.9%)	15 (7.4%)	0.133

Note: *Statistically significant
Abbreviations: [#]CONUT, controlling nutritional status; BMI, body mass index; ASA, American statistical association; AA, aristolochic acids; LVI, lymphovascular invasion.

hypertension, ASA score ≥3, pathological T and N stages and glandular differentiation were significant co-predictors. Moreover, patient sex, pathological N stage and tumor glandular differentiation were revealed as independent co-predictors of postoperative CSS and DFS (all p<0.05). Pathological T stage (p<0.001) significantly predicted CSS but not DFS in the propensity score-matched cohort (Table 5).

Sensitivity analyses revealed that the relationship between preoperative CONUT score and the oncological outcomes was maintained (data not shown).

Discussion

Based on patients with localized UTUC treated with RNU from a nationwide high-volume cohort in China, we found that a high preoperative CONUT score was significantly related to certain adverse clinical and pathological characteristics, and a high CONUT score was associated with poor oncological outcomes before and after PSM. These results suggest that a high preoperative CONUT score is a robust independent predictor for localized UTUC.

The optimum cutoff value of the CONUT score vary from study to study. In our study, it was 3 according to the ROC curve, which was in accordance with previous studies.[19–21] PSM analysis has been used in many studies to balance subgroups across selected factors.[22] In our study, to balance the baseline characteristics of preoperative covariates between the two groups, we used the PSM method. The differences in preoperative covariates between the low and high CONUT score groups were acceptable.

Before PSM

After PSM
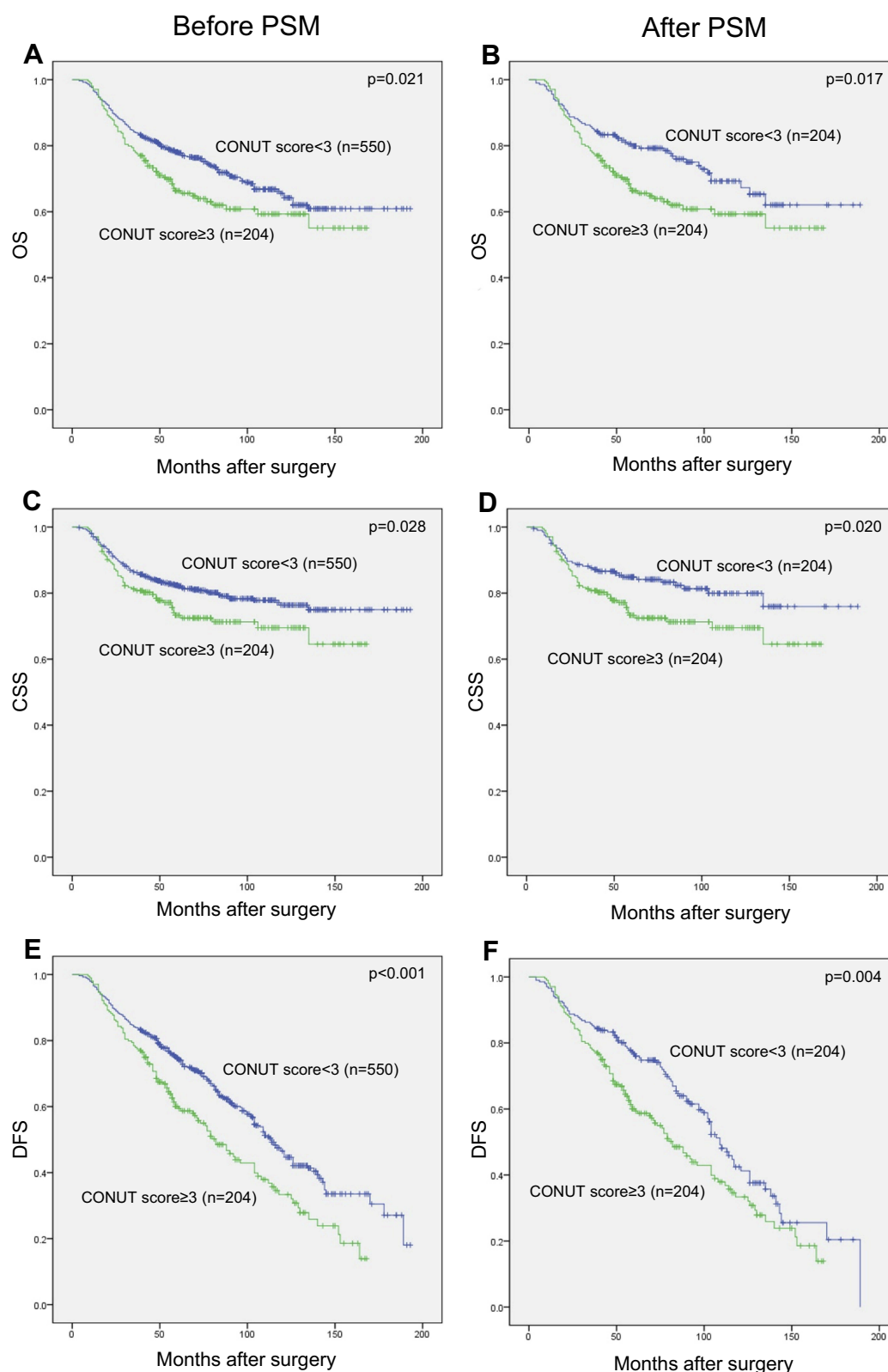
Figure 4 OS (**A**), CSS (**C**) and DFS (**E**) of the 754 patients with localized UTUC according to the preoperative CONUT score before propensity score matching; OS (**B**), CSS (**D**) and DFS (**F**) of the 408 patients with localized UTUC according to the preoperative CONUT score after propensity score matching.
Abbreviations: OS, overall survival; CSS, cancer-specific survival; DFS, disease-free survival; UTUC: upper tract urothelial carcinoma; CONUT: controlling nutritional status.

Table 4 Univariate and Multivariate Analyses of the Relationship Between Preoperative CONUT[#] Score and Oncological Outcome in Patients with Localized UTUC Before Propensity Score Matching

Characteristics	Overall Survival		Cancer-Specific Survival		Disease-Free Survival	
	Univariate Analyses	Multivariate Analyses	Univariate Analyses	Multivariate Analyses	Univariate Analyses	Multivariate Analyses
	HR[#] (95% CI[#]), p	HR (95% CI), p	HR (95% CI), p	HR (95% CI), p	HR (95% CI), p	HR (95% CI), p
CONUT score (≥3)	1.383 (1.048–1.824), 0.022*	1.273 (0.960–1.686), 0.093	1.435 (1.036–1.988), 0.030*	1.328 (0.954–1.847), 0.092	1.540 (1.234–1.922), <0.001*	1.418 (1.132–1.776), 0.002*
Age (≥69)	1.257 (0.972–1.627), 0.082		1.205 (0.887–1.638), 0.233		1.229 (0.999–1.512), 0.052	
Gender (male)	1.550 (1.199–2.005), 0.001*	1.443 (1.113–1.872), 0.006*	1.799 (1.321–2.451), <0.001*	1.637 (1.198–2.237), 0.002*	1.467 (1.193–1.804), <0.001*	1.436 (1.165–1.771), 0.001*
BMI[#] (≥24.19 kg/m^2)	0.908 (0.702–1.175), 0.464		0.751 (0.550–1.025), 0.071		0.877 (0.713–1.079), 0.214	
Diabetes	0.902 (0.646–1.259), 0.544		0.907 (0.610–1.347), 0.627		1.030 (0.794–1.338), 0.822	
Hypertension	1.452 (1.123–1.878), 0.004*	1.371 (1.049–1.790), 0.021*	1.388 (1.022–1.884), 0.036*	1.433 (1.051–1.953), 0.023*	1.349 (1.095–1.661), 0.005*	1.337 (1.078–1.658), 0.008*
Coronary disease	0.933 (0.742–1.173), 0.552		0.787 (0.507–1.223), 0.288		1.084 (0.825–1.423), 0.562	
Bladder tumor history	0.529 (0.235–1.190), 0.124		0.364 (0.116–1.142), 0.083		1.093 (0.679–1.759), 0.715	
ASA[#] score (≥3)	1.740 (1.311–2.310), <0.001*	1.539 (1.146–2.067), 0.004*	1.419 (0.997–2.020), 0.052		1.417 (1.113–1.804), 0.005*	1.271 (0.988–1.634), 0.062
Alcohol	1.163 (0.801–1.690), 0.427		0.906 (0.555–1.478), 0.692		1.000 (0.731–1.367), 1.000	
Tobacco	1.300 (0.953–1.773), 0.097		1.250 (0.860–1.815), 0.242		1.058 (0.813–1.378), 0.674	
Exposure of AA[#]	0.458 (0.243–0.863), 0.016*	0.547 (0.289–1.037), 0.065	0.314 (0.129–0.765), 0.011*	0.413 (0.169–1.010), 0.052	1.211 (0.853–1.719), 0.285	
Hydronephrosis	1.165 (0.899–1.512), 0.248		1.274 (0.932–1.742), 0.128		1.209 (0.981–1.491), 0.075	
Pathological T stage (T2-4)	2.671 (1.929–3.698), <0.001*	2.072 (1.455–2.951), <0.001*	4.125 (2.633–6.463), <0.001*	3.019 (1.867–4.882), <0.001*	1.614 (1.282–2.032), <0.001*	1.349 (1.049–1.734), 0.020*
Lymph node status (N1)	2.474 (1.655–3.097), <0.001*	2.029 (1.329–3.099), 0.001*	2.938 (1.890–4.567), <0.001*	2.100 (1.309–3.371), 0.002*	1.839 (1.257–2.691), 0.002*	1.725 (1.167–2.551), 0.006*
Tumor grade (G3)	1.611 (1.246–2.082), <0.001*	1.028 (0.767–1.378), 0.853	1.831 (1.347–2.489), 0.001*	1.010 (0.686–1.486), 0.959	1.285 (1.044–1.581), 0.018*	0.979 (0.774–1.239), 0.860

(*Continued*)

Table 4 (Continued).

Characteristics	Overall Survival		Cancer-Specific Survival		Disease-Free Survival	
	Univariate Analyses	Multivariate Analyses	Univariate Analyses	Multivariate Analyses	Univariate Analyses	Multivariate Analyses
	HR[#] (95% CI[#]), p	HR (95% CI), p	HR (95% CI), p	HR (95% CI), p	HR (95% CI), p	HR (95% CI), p
LVI[#]	1.114 (0.660–1.880), 0.686		1.375 (0.780–2.424), 0.270		1.122 (0.734–1.713), 0.596	
Multifocality	1.044 (0.770–1.416), 0.783		1.152 (0.806–1.645), 0.437		1.015 (0.797–1.293), 0.905	
Tumor architecture (sessile)	1.077 (0.955–1.214), 0.226		2.012 (1.446–2.800), <0.001*	1.258 (0.840–1.885), 0.265	1.091 (0.988–1.206), 0.086	
The largest tumor size (≥3 cm)	1.521 (1.177–1.966), 0.001*	1.314 (1.011–1.707), 0.041*	1.707 (1.258–2.317), 0.001*	1.411 (1.031–1.930), 0.031*	1.313 (1.066–1.616), 0.010*	1.253 (1.012–1.550), 0.039*
Squamous differentiation	1.432 (0.958–2.142), 0.080		1.508 (0.953–2.386), 0.080		1.537 (1.101–2.148), 0.012*	1.342 (0.942–1.911), 0.103
Sarcomatoid differentiation	2.144 (1.308–3.514), 0.002*	1.284 (0.759–2.171), 0.352	2.314 (1.313–4.078), 0.004*	1.207 (0.659–2.209), 0.524	1.451 (0.891–2.364), 0.134	
Glandular differentiation	2.408 (1.488–3.897), <0.001*	2.026 (1.236–3.321), 0.005*	2.388 (1.354–4.210), 0.003*	1.743 (0.968–3.139), 0.064	2.082 (1.351–3.207), 0.001*	1.789 (1.145–2.794), 0.011*

Note: *Statistically significant.
Abbreviations: [#]CONUT, controlling nutritional status; UTUC, upper tract urothelial carcinoma; HR, hazard ratio; CI, confidence interval; BMI, body mass index; ASA, American statistical association; AA, aristolochic acids; LVI, lymphovascular invasion.

Ideal cancer predictors should be objective, inexpensive, quickly measured, simple to use, and available before surgery. Similar to objective data assessment (ODA) and subjective global assessment (SGA), the CONUT score has been reported to be a simple and cost-effective method of comprehensively and objectively detecting and controlling hospital malnutrition.[13] It is comprised of the TLC, serum albumin concentration and TCC, reflecting immune function, host protein metabolism, and lipid metabolism, respectively.[13] Thus, the CONUT score reflects not only the host status of nutrition but also systemic inflammation and the immune response. The combination of these three parameters can conceal their individual weaknesses and emphasize the advantage of each parameter. The mechanism underlying the association between a high CONUT score and a poor prognosis in human cancer remains unclear. The prognostic value of the preoperative CONUT score in UTUC patients might be explained by the functions of these three parameters.

The TLC, an indicator of the immunological status,[11] plays important roles in inhibiting tumor cell malignant phenotypes, such as cell proliferation, invasion, and migration, by initiating a cytotoxic immune response.[10] The number of tumor infiltrating lymphocytes (TILs) in the tumor microenvironment has a crucial impact on the prognosis and immunotherapy outcome of various human tumors.[23,24] A previous study indicated that TILs might affect the host response to neoadjuvant chemotherapy in bladder cancer.[23] The TLC in the peripheral blood may indicate the number of TILs. Several biomarkers based on the TLC, such as NLR and PLR, were proven to be indexes for the immune status and serve as prognostic predictors for UTUC.[11,25,26]

As a reliable indicator of the status of host nutrition and systematic inflammation, serum albumin can be influenced not only by the production of proinflammatory cytokines,[27] such as interleukin-6 and tumor necrosis factor-alpha, but also by body fluid retention and damage to hepatocytes.[28,29] Previous studies revealed that hypoalbuminemia was associated with immune deficiency. Furthermore, hypoalbuminemia was demonstrated to be associated with poor outcomes in UTUC patients.[30]

Table 5 Univariate and Multivariate Analyses of the Relationship Between Preoperative CONUT[#] Score and Oncological Outcome in Patients with Localized UTUC[#] After Propensity Score Matching

Characteristics	Overall Survival		Cancer-Specific Survival		Disease-Free Survival	
	Univariate Analyses	Multivariate Analyses	Univariate Analyses	Multivariate Analyses	Univariate Analyses	Multivariate Analyses
	HR[#] (95% CI[#]), p	HR (95% CI), p	HR (95% CI), p	HR (95% CI), p	HR (95% CI), p	HR (95% CI), p
CONUT score (≥3)	1.530 (1.075–2.177), 0.018*	1.459 (1.010–2.107), 0.044*	1.644 (1.077–2.509), 0.021*	1.336 (0.863–2.067), 0.194	1.479 (1.127–1.942), 0.005*	1.333 (1.010–1.760), 0.042*
Age (≥69)	1.069 (0.754–1.518), 0.707		1.080 (0.712–1.637), 0.718		1.082 (0.825–1.420), 0.568	
Gender (male)	1.771 (1.247–2.513), 0.001*	1.519 (1.049–2.198), 0.027*	2.233 (1.461–3.414), <0.001*	2.057 (1.338–3.161), 0.001*	1.655 (1.263–2.169), <0.001*	1.641 (1.246–2.163), <0.001*
BMI[#] (≥24.19 kg/m^2)	0.882 (0.620–1.254), 0.483		0.729 (0.476–1.116), 0.145		0.775 (0.589–1.020), 0.069	
Diabetes	0.887 (0.569–1.383), 0.596		0.955 (0.570–1.602), 0.863		0.958 (0.683–1.344), 0.804	
Hypertension	1.148 (0.810–1.628), 0.437	1.371 (1.049–1.790), 0.021*	1.058 (0.699–1.602), 0.790		1.141 (0.868–1.499), 0.344	
Coronary disease	0.896 (0.672–1.196), 0.456		0.734 (0.431–1.250), 0.255		0.991 (0.850–1.154), 0.905	
Bladder tumor history	0.628 (0.232–1.700), 0.360		0.217 (0.030–1.561), 0.129		1.191 (0.667–2.145), 0.549	
ASA[#] score (≥3)	1.821 (1.281–2.589), 0.001*	2.094 (1.459–3.005), <0.001*	1.488 (0.972–2.279), 0.068		1.304 (0.981–1.734), 0.067	
Alcohol	1.511 (0.937–2.435), 0.091		1.365 (0.758–2.456), 0.300		1.246 (0.841–1.845), 0.273	
Tobacco	1.552 (1.030–2.435), 0.036*	1.405 (0.904–2.184), 0.131	1.605 (0.992–2.597), 0.054		1.129 (0.799–1.595), 0.493	
Exposure of AA[#]	0.465 (0.217–0.998), 0.049*	0.566 (0.263–1.220), 0.146	0.275 (0.087–0.869), 0.028*	0.350 (0.110–1.110), 0.075	1.108 (0.723–1.698), 0.638	
Hydronephrosis	0.943 (0.662–1.344), 0.746		1.238 (0.801–1.913), 0.336		1.075 (0.815–1.418), 0.608	
Pathological T stage (T2-4)	2.647 (1.685–4.160), <0.001*	2.093 (1.290–3.395), 0.003*	4.658 (2.413–8.991), <0.001*	3.432 (1.727–6.820), <0.001*	1.385 (1.027–1.866), 0.033*	1.128 (0.826–1.541), 0.448
Lymph node status (N1)	2.533 (1.395–4.599), 0.002*	2.450 (1.306–4.595), 0.005*	3.522 (1.915–6.480), <0.001*	3.084 (1.601–5.941), 0.001*	2.117 (1.227–3.653), 0.007*	1.990 (1.139–3.478), 0.016*
Tumor grade (G3)	1.462 (1.032–2.071), 0.033*	0.910 (0.601–1.377), 0.655	1.850 (1.220–2.805), 0.004*	1.055 (0.656–1.695), 0.826	1.260 (0.961–1.652), 0.095	
LVI#	0.866 (0.404–1.856), 0.711		1.067 (0.466–2.444), 0.878		1.020 (0.593–1.756), 0.942	
Multifocality	1.226 (0.817–1.840), 0.324		1.484 (0.935–2.356), 0.094		1.191 (0.874–1.756), 0.269	
Tumor architecture (sessile)	1.071 (0.880–1.304), 0.493		1.083 (0.870–1.349), 0.476		1.141 (1.006–1.294), 0.040*	1.112 (0.936–1.323), 0.227

(Continued)

Table 5 (Continued).

Characteristics	Overall Survival		Cancer-Specific Survival		Disease-Free Survival	
	Univariate Analyses	Multivariate Analyses	Univariate Analyses	Multivariate Analyses	Univariate Analyses	Multivariate Analyses
	HR[#] (95% CI[#]), p	HR (95% CI), p	HR (95% CI), p	HR (95% CI), p	HR (95% CI), p	HR (95% CI), p
The largest tumor size (≥3 cm)	1.521 (1.173–2.155), 0.018*	1.365 (0.955–1.951), 0.087	1.695 (1.121–2.563), 0.012*	1.432 (0.939–2.182), 0.095	1.180 0.898–1.552), 0.235	
Squamous differentiation	1.740 (1.066–2.838), 0.027*	1.258 (0.743–2.130), 0.394	1.747 (0.986–3.096), 0.056		1.733 (1.161–2.585), 0.007*	1.394 (0.917–2.119), 0.121
Sarcomatoid differentiation	2.144 (1.308–4.331), 0.013*	1.514 (0.751–3.052), 0.247	2.215 (1.023–4.796), 0.044*	1.223 (0.538–2.781), 0.630	1.445 (0.765–2.730), 0.257	
Glandular differentiation	2.346 (1.262–4.358), 0.007*	2.165 (1.113–4.211), 0.023*	2.698 (1.353–5.382), 0.005*	2.497 (1.192–5.230), 0.015*	2.112 (1.247–3.577), 0.005*	1.859 (1.074–3.219), 0.027*

Note: *Statistically significant.
Abbreviations: [#]CONUT, controlling nutritional status; UTUC, upper tract urothelial carcinoma; HR, hazard ratio; CI, confidence interval; BMI, body mass index; ASA, American statistical association; AA, aristolochic acids; LVI, lymphovescular invasion.

Finally, as an important component of human cell membranes, cholesterol plays an essential role in maintaining the membrane structure, fluidity and membrane protein activity.[31,32] Thus, hypocholesterolemia may affect the mobility of cell surface receptors and their value in transmitting transmembrane signals. Increasing evidence has revealed an inverse association between the TCC in the blood and cancer incidence and mortality.[33,34] Abnormal lipid metabolism has been demonstrated to be closely related to cancer development. The increased mRNA expression of low-density lipoprotein (LDL) receptor was found in colorectal tumor tissue compared to normal tissue, resulting in a high intake of LDL, which increases tumor growth.[35] A previous study revealed that chronic cholesterol depletion promoted tumor cell proliferation by inducing NFkB activation.[36] Furthermore, hypocholesterolemia was shown to be associated with a poor prognosis in many cancer patients.[37,38]

Previous studies indicated that nutritional intervention could reduce postoperative complications and improve the tolerance of patients to anticancer treatment.[39,40] However, the effects of nutritional intervention on the long-term oncological outcomes in patients with cancer-related malnutrition have not been confirmed. Our results remind us of the importance of perioperative nutritional support in UTUC patients. In addition, immunotherapy is becoming a promising strategy for the management of UTUC. The CONUT score may be a useful index for the selection of patients who need perioperative nutritional intervention in UTUC treatment.

Although important discoveries were revealed, our study had certain limitations. First, it was a retrospective single-center and single-race study. Therefore, we matched the patient preoperative variables between the high and low CONUT score groups using PSM analysis, which made the differences in preoperative covariates between the two groups acceptable. However, further multicenter interracial prospective studies are needed to clarify the prognostic role of the preoperative CONUT score in UTUC patients. Second, the CONUT score might have been biased by medicine or the presence of undetected conditions that affect the TLC, serum albumin concentration or TCC. Third, we did not obtain information on the CONUT score or nutritional support after surgery, which might influence our results. Finally, the mechanism by which the CONUT score affects the survival of patients with UTUC should be further explored using basic studies. Despite these limitations, we revealed that the preoperative CONUT score was correlated with oncological outcome in patients with UTUC.

Conclusion

Our study revealed that the preoperative CONUT score is a convenient and effective factor for predicting prognosis in patients with localized UTUC after RNU. Perioperative nutritional intervention should be emphasized in UTUC patients.

Abbreviations

CONUT, controlling nutritional status; UTUC, upper tract urothelial cancer; RNU, radical nephroureterectomy; PSM,

propensity score matching; OS: overall survival; CSS, cancer-specific survival; DFS, disease-free survival; ASA, American Statistical Association; HR, hazard ratio; CI, confidence interval; AGR, albumin to globulin ratio; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; LMR, lymphocyte to monocyte ratio; BMI, body mass index; PNI, prognostic nutritional index; TLC, total lymphocyte count; TCC, total cholesterol concentration; UICC, Union for International Cancer Control; WHO, World Health Organization; AA, aristolochic acid; ROC, receiver operating characteristic; IQR, interquartile range; ODA, objective data assessment; SGA, subjective global assessment; TILs, tumor infiltrating lymphocytes; LDL, low-density lipoprotein.

Data Sharing Statment

Supporting data are available from the first author, Zhengqing Bao E-mail: baozq1101@bjmu.edu.cn.

Acknowledgments

Author Contributions

Zhengqing Bao, Yifan Li and Bao Guan carried out the study, participated in the data analysis, and drafted the manuscript. Gengyan Xiong, Lei Zhang, Qi Tang and Tianyu Wang collected the data. Zhengqing Bao and Xuesong Li conceived and designed the study. Dong Fang and Liqun Zhou initiated this study and participated in revising the manuscript critically for important intellectual content. All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors have stated that they have no conflicts of interest.

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