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The Role of Preoperative CONUT Score in Prognosis in Patients With Radical Cystectomy

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ABSTRACT

Background: We evaluated the prognostic significance of the controlling nutritional status (CONUT) score, which was evaluated preoperatively, on survival. We aimed to evaluate prognostic signifcance of preoperatively assessed controlling nutritional status (CONUT) score on survival in bladder cancer (BC) patients underwent radical cystectomy (RC). **Materials and Methods:** The clinical and pathological data of 232 patients who underwent RC for BC between January 2006 and January 2019 at a tertiary level hospital were evaluated respectively. The data of the patients participating in the study were collected retrospectively from the patient records. All patients gave consent during hospitalization so that their information could be used. The potential prognostic value of CONUT score was assessed by using ROC curve analysis. The Kaplan–Meier method and Cox regression hazard models were used to analyzed the effect of CONUT score for patients' disease-specifc survival (DSS) and overall survival (OAS). **Results:** Totally, we had 232 BC patients. Mean age was 62,98 ± 9,3 years. Only 14 (6%) of the patients were female. According to ROC analysis, optimal threshold of CONUT score for DSS was 3,50. In Kaplan–Meier analyses, the high CONUT score group showed worse progression in DSS and OAS (all parameters, $p < 0.05$). On Cox regression models of clinical and pathological parameters to predict DSS, age (HR 1.04, 95% CI 1.01–1.07;p=0.009), pathological T stage (HR 5.53, 95% CI 2.09–14.46;$p < 0.001$) CONUT score (HR 5.44, 95% CI 2.48-11.92;$p<0.001$); and to predict OAS, only age (HR 1.04, 95% CI 1.01–1.07; $p = 0.004$) were determined as independent prognostic factors. **Conclusions:** Preoperative elevated CONUT score could be an independent prognostic factor in BC patients underwent RC.

Keywords: Bladder Cancer, CONUT score, Urothelial Carcinoma, Predictor.

INTRODUCTION

Bladder cancer (BC) is the 7th most commonly diagnosed cancer in males, whilst it drops to 10th position when both genders are considered

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[1]. Epithelial tumors constitute 95% of all bladder tumors, and approximately 80–85% is transitional epithelial cell carcinomas [2]. About 75% of patients with BC present with disease confined to the mucosa (stage Ta, carcinoma in situ [CIS]) or submucosa (stage T1), while the remainder present with muscle-invasive disease and more advanced stages [3]. For the treatment of these tumors, the first treatment stage is Transurethral Bladder Tumor Resection (TUR-B), which is accepted the optimum treatment approach. Around 70% of bladder tumors recur, and 20–30% progress to a more advanced or pathological grade [4]. Because of the poor prognosis in patients with metastatic and muscle-invasive bladder cancer (MIBC), it is important to control the progression of non-muscle-invasive bladder cancer (NMIBC). For this purpose, intracavitary treatments are used today. Because of all these, early diagnosis and treatment in bladder cancer is of great importance. Various nomograms have been used to estimate the prognosis of individuals by calculating scores for a large number of variables. The two scoring models of the European Agency for Research and Treatment of Cancer (EORTC) and the Spanish Association of Urology for Oncological Treatment (CUETO) are the most commonly used individual prognostic models of bladder cancer [5]. Today, although it has valuable clinical values, it is important to focus on the tumor characteristics of the patient and not include some hematological parameters. However, more precise nomograms are needed to predict prognosis in patients with MIBC.

Nutritional status can be impaired by cancer-induced chronic inflammation. Recently, a number of studies have reported that nutritional status and systemic inflammatory response have an impact on the prognosis of cancer patients. Accordingly, several systemic inflammatory or nutritional factors have been identified for prediction of patient survival and tolerability of surgery in various types of cancer [6,7]. Controlling Nutritional Status (CONUT) score is a scoring that shows both nutritional and immune status, which is calculated from the measurement of serum albumin level, total cholesterol level, and total peripheral blood lymphocyte count of patients. The CONUT score is a scoring that has been shown to be associated with prognosis in different types of cancer. Colorectal cancers, esophageal cancer, lung cancer and pancreatic cancer are just a few of the cancer types for which this scoring is used [8-11].

In the present study, we aimed to evaluate prognostic signifcance of preoperatively assessed CONUT score on survival in BC patients underwent radical cystectomy (RC).

MATERIALS AND METHOD

This study was carried out in the Urology Clinic of the İzmir Katip Çelebi University Atatürk Training and Research Hospital with the approval of the Local Ethics Committee.

Our study was designed retrospectively. In the study, while obtaining patient information, data in a database, where informed consent was obtained from each patient, were used. The clinical and pathological data of patients who underwent RC for BC in the Urology Clinic of the İzmir Katip Çelebi University Atatürk Training and Research Hospital between January 2006 and January 2019 at a tertiary level were analyzed retrospectively. A total of 232 patients who underwent RC for BC were included in the study.

Demographic and clinical data of patients, clinicopathological parameters as predictors of disease-specifc survival (DSS) and overall survival (OAS) were examined. Patients with preoperative data on serum albumin concentration, total cholesterol concentration, and total peripheral lymphocyte count, no history of other systemic autoimmune disease or cancer, no previous neoadjuvant chemotherapy or radiotherapy, any distant metastases, and full follow-up data was included in the study. Based on the previous study, the scoring criteria of CONUT are illustrated in Table 1 [12].

Table 1. Assessment of Undernutrition Degree by CONUT [12].

Parameter	Undernutrition Degree			
	Normal	Light	Moderate	Severe
Serum Albumin (g/dl)	3.5-4.5	3.0-3.49	2.5 - 2.9	<2.5
Score	**0**	**2**	**4**	**6**
Total Lymphocytes/ml	> 1600	1200-1599	800-1199	<800
Score	**0**	**1**	**2**	**3**
Cholesterol (mg/dl)	>180	140-180	100-139	< 100
Score	**0**	**1**	**2**	**3**
Screening Total Score	0-1	2-4	5-8	9-12

Statistical analyses were perfomed using the SPSS software demo version 22. All variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov Smirnov/Shapiro-Wilk's test) to determine whether or not they are normally distributed. Descriptive analyses were presented using means (±standard deviations) and medians (min-max) for scale variables and using frequencies for ordinal variables.

The potential prognostic value of the CONUT score was assessed by using ROC curve analysis. The effect of the CONUT score on patient disease-specific survival (DSS) and overall survival (OAS) was analyzed by the Kaplan-Meier method and log rank test was conducted to compare these parameters. To assess the effect of patient gender age, pathological T stage, tumor grade, lymphovascular invasion, lymph node involvement and CONUT score, Cox regression hazard models were used for univariate and multivariate analyses. A 5% type-I error level was used to infer statistical significance.

RESULTS

We included 232 patients to the study. The mean age was 62,98 ± 9,3 years. Only 14 (6%) of the patients were female. The mean CONUT score was 1.28±0.40. The most common pathological T stage was T3 (31.5%) and grade was G2 (70%). Only 34.9% of the patients had lymphovascular invasion and 35.6% of all had lymph node involvement. The demographic, clinical and laboratory parameters were summarized in Table 2.

Table 2. Demographic and clinical data of patients.

Age (Mean±SD)	62.98± 9.30 years
Sex(%)	
Female	14(6)
Male	218(94)
Diabetes mellitus	
Negative	201(86,6)
Positive	31(13,4)
Hypertension	
Negative	135(58,2)
Positive	97(41,8)
Coronary artery disease	
Negative	155(66,8)
Positive	77(33,2)
Smoking (Mean±SD)	37.03±20.31 package/year
Lymphovascular invasion (%)	
Negative	151(65.1)
Positive	81(34.9)
Lymph node involvement (%)	
Negative	154(66,4)
Positive	78(33,6)

Pathological T stage (%)	
T0	1(0.4)
T1	49(21,1)
T2	65(28)
T3	73(31,5)
T4	44(19)
Tumor grade (%)	
G0	1(0.4)
G1	20(8,6)
G2	211(90)
Metastasis (%)	
Negative	96(64.4)
Positive	53(35.6)
Lymphocyte(Mean±SD)	2,06±0,68 Lym/ml
Albumin (Mean±SD)	3,25±0,75 (g/dl)
Total cholesterol (Mean±SD)	154,61±46,46 (mg/dl)
CONUT Score (Mean±SD)	1.28±0.40
CONUT Score (%)	
Normal	36(15.5)
Light	115(49.6)
Moderate	33(14.2)
Severe	48(20.7)

We performed an ROC analysis to determine whether the preoperative CONUT score has diagnostic value of the patient's clinical prognosis and which cutoff value could predict this for the DSS. According to ROC analysis, optimal threshold of CONUT score for DSS was 3.50 (Figure 1;AUC:0,752 95% CI:0.681-0.823; p<0,001).

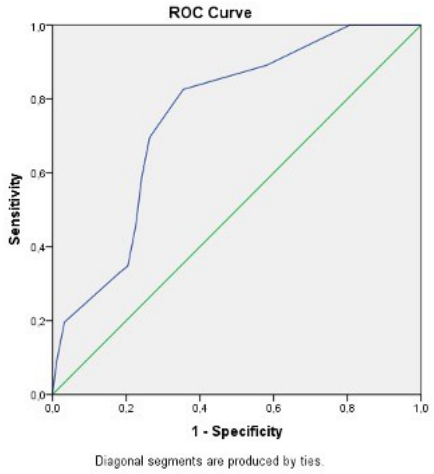

Figure 1. ROC analysis for DSS preoperative CONUT score.

In Kaplan-Meier analyses the high CONUT score group showed worse progression in DSS and OAS (p <0.001 and p=0,022, respectively) (Figure 2 and 3). 93.8% (120) of the patients with an CONUT score 3.5 or less than 3.5 and 60.7% (37) of the patients with an CONUT score greater than 3.5 are alive among DSS. 82% (105) of the patients with an CONUT score 3.5 or less than 3.5 and 71.2% (74) of the patients with an CONUT score greater than 3.5 are alive among OAS.

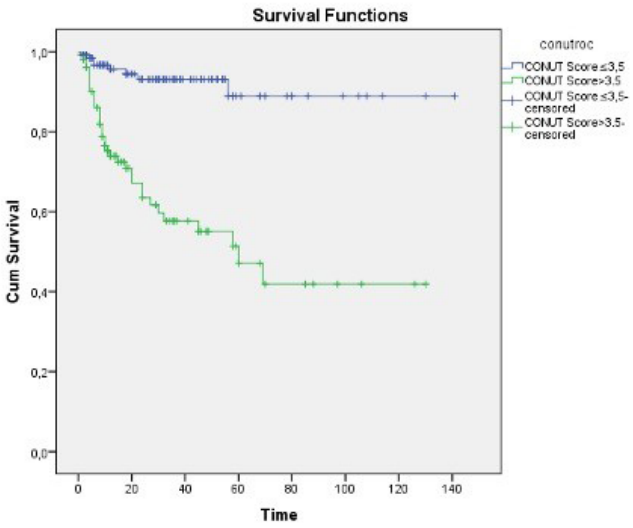

Figure 2. Kaplan Meier Analysis of Disease Spesific Survival According to CONUT Score After Cystectomy.

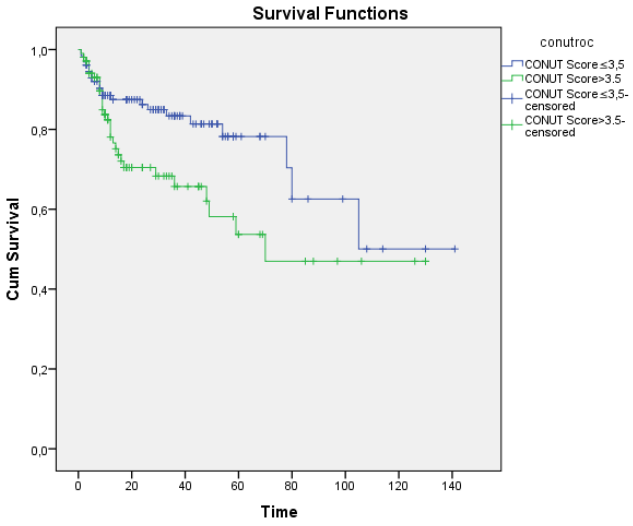

Figure 3. Kaplan Meier Analysis of Overall Survival According to CONUT Score After Cystectomy.

On univariate analyses predicting DSS age (HR:1.01, 95% CI:1.00-1.07, p=0.012), CONUT score (HR:6.82, 95% CI:3.17-14.66, p<0.001), pathological T stage (HR:9.98 95% CI:4.36-22.83, p<0.001), lymphovasculer invasion (HR:4.13, 95% CI:2.23-7.67, p<0.001), lymph node involvement (HR:4.66, 95% CI:2.18-9.94, p<0.001) and to predict OAS age (HR:1.04, 95% CI:1.01-1.07, p=0.002), pathological T stage (HR:2.27, 95% CI:1.28-4.02 p=0.004), lymphovasculer invasion (HR:2.31 95% CI:1.30-4.13, p=0.004) CONUT score (HR:1.86, 95% CI:1.08-3.21, p=0.024)) are defined as significant predictors (Table 3).

Table 3. Univariate analyses of various parameters for DSS and OAS.

	DSS		OAS	
	HR(95%CI)	**P Value**	**HR(95%CI)**	**P Value**
Age	1.012(1.009-1.074)	0,012	1.048(1.018-1.079)	0.002
Sex (male vs female)	2.074(0.815-5.278)	0.126	1.047(0.325-3.374)	0.938
Lymphovascular invasion (negative vs.positive)	4.137(2.230-7.678)	<0.001	2.317(1.300-4.130)	0.004
Pathological T stage (T1-T2 vs. T3-T4)	9.984(4.365-22.837)	<0.001	2.278(1.288-4.029)	0.004
Tumor grade (G0-G1vs. G2)	2.422(0.586-10.006)	0.222	1.116(0.443-2.816)	0.815
Lymph node involvement (negative vs positive)	4.661(2.186-9.941)	<0.001	1.721(0.980-3.023)	0.059
CONUT Score (<3.5 vs. 3.5 ≤)	6.827(3.179-14.662)	<0.001	1.864(1.081-3.215)	0.024

On multivariate Cox regression models of clinicopathological parameters to predict DSS, age (HR:1.04, 95% CI:1.01-1.07; p=0,009), pathological T stage (HR:5.53, 95%CI: 2.09-14.46; p =0,001), CONUT score (HR:5.44, 95% CI:2.48-11.92); and to predict OAS age (HR:1.04, 95% CI: 1.01-1.07; p=0,004) were determined as independent prognostic factors (Table 4).

Table 4. Multivariate Cox models of clinicopathological parameters as predictors of DSS and OAS.

	DSS		OS	
	HR(95%CI)	**P Value**	**HR(95%CI)**	**P Value**
Age	1.043(1.011-1.076)	0,009	1.045(1.014-1.077)	0.004
Sex				
Male	l(referent)	0.500	l(referent)	0.460
Female	0.718(0.274-1.882)		0.636(0.191-2.114)	
Lymphovascular invasion				
Negative	l(referent)	0.152	l(referent)	0.122
Positive	1.746(0.508-2.483)		1.766(0.859-3.631)	
Pathological T stage				
T1-T2	l(referent)	0.001	l(referent)	0.137
T3-T4	5.535(2.091-14.468)		1.700(0.844-3.421)	
Tumor grade				
G0-G1	l(referent)	0.824	l(referent)	0.933
G2	0.837(0.175-4.013)		0.958(0.360-2.623)	
Lymph node involvement				
Negative	l(referent)	0.083	l(referent)	0.754
Positive	1.932(0.918-4.066)		1.116(0.563-2.213)	
CONUT Score				
3.50 or less than	l(referent)	<0.001	l(referent)	0.050
greater than 3.50	5.447(2.488-11.928)		1.765(0.999-3.118)	

DISCUSSION

In EAU Guidelines nomograms on CSS following RC have been developed and externally validated, but their wider use cannot be recommended until further data become available [13]. Today, there are searches for prognostic markers regarding the survival of patients who underwent RC for BC. The CONUT score is a value calculated from serum albumin concentration, total lymphocyte count, and total cholesterol concentration. Serum albumin level, which is an important component of serum total protein, reflects nutrition and inflammation status. Lymphocytes suppress cancer cell growth and migration, as well as promote apoptosis of cancer cells. Serum cholesterol levels have been shown to be a predictive or prognostic factor in cancer, but how it does so has not been demonstrated [14-16]. In this study revealed that DSS and OAS following RC for BC were significantly shorter in patients with high CONUT score than in those with low CONUT score. Multivariate analysis further showed that the CONUT score was an independent factor for these survival outcomes.

These findings showed us that the CONUT score is significantly associated with survival in BC patients undergoing RC. In the literature, the relationship between CONUT score and prognosis was investigated in some urological cancers as well as in different clinical branches. In a study conducted by Chen et al. involving 3529 patients, it was found that the CONUT score is a valuable preoperative index to predict the survival of patients with upper urinary tract urothelial cancer or renal cell carcinoma. undergoing nephrectomy [17]. Another study showed significantly shorter Relapse-free survival, cancer-specific survival and overall survival in the group with a high CONUT score than in the group with a low score [18]. The CONUT score was also an independent prognostic factor in prostate cancer with oligometastasis [19]. Another study showed the prognostic significance of the CONUT score in advanced urothelial carcinoma patients. The CONUT score indicates a patient's general condition from the aspect of nutritional status, and appears to be independent of performance status as a prognosticator [20].

CONCLUSIONS

In our study, the optimal threshold of the CONUT score for DSS was measured as 3.50 according to the ROC analysis. However, the higher CONUT score group showed worse progression in DSS and OAS. These results were supported by literature data. Considering that the CONUT score can be easily evaluated using blood samples taken in daily clinical practice, it may be a less invasive and effective predictor.

A high preoperative CONUT score may be an independent prognostic factor in BC patients undergoing RC.

STATEMENTS AND DECLARATIONS

All methods were carried out in accordance with the relevant guidelines and regulations in the 'DECLARATION' section of the article. Informed consent was obtained from all subjects for participation in the study.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was carried out in the urology clinic of İzmir Katip Çelebi University Atatürk Training and Research Hospital with the approval of the Local Ethics Committee. Izmir Katip Celebi University Ethics Committee Decision Number: 0140.

CONSENT FOR PUBLICATION

Informed consent was obtained from all subjects for participation in the study.

COMPETING INTERESTS

The authors declare that they have no competing interests.

FUNDING

Not applicable.

AUTHORS' CONTRIBUTIONS

EMY determined the hypothesis of the study. In addition, as the main author, he analyzed and interpreted the data of patients who underwent Radical Cystectomy for bladder cancer. SNG contributed to the evaluation of the resulting data. OK made the statistics of the study and interpreted the results. YA compared the results found in the study with the literature data. SO significantly revised the study.

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Not applicable.

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