Prognostic Significance of the Controlling Nutritional Status (CONUT) Score in Patients with Muscle-Invasive Bladder Cancer after Radical Cystectomy

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Purpose: To assess the impact of the The Controlling Nutritional Status (CONUT) score, an indicator of nutritional status, on the survival and prognosis after radical cystectomy.

Materials and Methods: The medical records of patients who underwent consecutive radical cystectomy operations with the diagnosis of muscle-invasive bladder cancer at our clinic were retrospectively examined. The patients were separated into two groups based on the cut-off CONUT score which was derived using the receiver operating characteristic (ROC) curve. The group with a CONUT score ≥ 3 was categorized as high CONUT, whereas the group with a CONUT score < 3 was categorized as low CONUT. The groups were compaired according to oncological outcomes and survival risk factors.

Results: Cancer-specific survival (CSS) and overall survival (OS) were statistically significantly lower in the High CONUT group compared to the Low CONUT group ($p < 0.001$, $p = 0.024$, respectively). Age (HR: 1.02, 95% CI: 1.006-1.04, $p = 0.011$) and CONUT score (HR: 3.92, 95% CI: 2.66-5.77, $p < 0.001$) were revealed to be independent prognostic variables in the multivariate analysis for OS.

Conclusion: The CONUT score was found to be an independent predictor of survival in patients with muscle-invasive bladder cancer in this study.

Keywords: bladder cancer; cancer-specific survival; cystectomy; overall survival; The Controlling Nutritional Status

INTRODUCTION

Bladder cancer is among the most prevalent malignancies of the urogenital system worldwide. It ranks fourth and eighth, respectively, among all malignancies affecting men in terms of new case and death rates.[1] At the time of diagnosis, 75% of bladder cancers are superficial bladder cancers, while 25% are muscle-invasive bladder cancers (MIBC). The gold standard treatment for patients with MIBC is radical cystectomy with or without preoperative systemic chemotherapy.[2] Prior to surgery, there is no conclusive parameter that can be used to forecast the prognosis and survival of these patients. The identification of novel prognostic biomarkers that can forecast the survival and prognosis of patients is of the utmost importance.

The impacts of nutritional factors in cancer patients on the prognosis or progression of the disease is complex due to the diversity of situations that may be encountered depending on the disease. Eating the right amount of protein and calories is important for healing, fighting infection, and having enough energy in cancer patients. Cancer-related malnutrition results from a combination of anorexia and metabolism alterations caused by the tumor itself or by its treatment and is characterized by inflammation, increased protein breakdown, and severe loss of skeletal muscle mass. Cancer cachexia negatively affects patients' anticancer treatment, outcomes, quality of life, and survival. Inflammation and catabolism caused by the tumor may cause muscle loss and weight loss and may impair food intake and absorption with symptoms such as dysphagia, pain, and vomiting. In addition, side effects of anticancer treatment such as nausea, vomiting, anorexia, early satiety, dysphagia with oral and intestinal mucositis, hemorrhoids, anal fissures, diarrhea and changes in smell and taste may compromise nutritional status by affecting not only total energy intake but also nutrient absorption. Moreover, the poor psychological state of cancer patients may affect their energy intake.[3]

Studies have established that the nutritional status of individuals plays a prominent role in the progression of the tumor and the survival of the patients.[4] The Controlling Nutritional Status (CONUT) score is a recommended assessment system for assessing patients' nutritional status. It is a simple, low-cost, and straightforward instrument that only requires blood test results. The calculation requires only three blood test results: the concentration of serum albumin, the total cholesterol level, and the total lymphocyte count.[5]

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Received June 2024 & Accepted November 2024

Table 1. The evaluation of the CONUT score.

Parameters		Nutritional status		
Serum albumin, g/dl	≥ 3.50	3.00-3.49	2.50-2.99	< 2.50
Score	0	2	4	6
Total lymphocyte count, /mm^3	≥ 1.600	1.200-1.599	800-1.199	< 800
Score	0	1	2	3
Total cholesterol, mg/dl	≥ 180	140-179	100-139	< 100
Score	0	1	2	3
CONUT score	0-1	2-4	5-8	9-12
CONUT score Groups	Normal	Light	Moderate	Severe

The existing body of literature on the relationship between the CONUT score and survival in patients with bladder cancer is limited. Due to research yielding inconsistent findings, the prognostic value of the CONUT score in bladder cancer remains unclear.[5]
The aim of this study is to assess the impact of the CONUT score, an indicator of nutritional status, on the survival and prognosis after radical cystectomy, patients diagnosed with MIBC.

MATERIALS AND METHODS

Study design and patients

The medical records of patients who underwent consecutive radical cystectomy operations with the diagnosis of MIBC in our clinic between January 2006 and March 2024 were retrospectively examined. The ethics review board (no: 20201/10-26) approved this study, which was conducted in accordance with the principles stated in the Declaration of Helsinki.
Patients excluded from our study included those who underwent nephroureterectomy or nephrectomy procedures in which other organs were also removed along with the cystectomy, patients with malignancies other than bladder cancer, concomitant rheumatological disease, autoimmune disease, active infectious disease, or patients with missing data. In the end, 262 patients were comprised of the study population. From the patient files, demographic information, tumor location and stage, pathological characteristics, and treatment details were recorded.
The patients were separated into two groups according

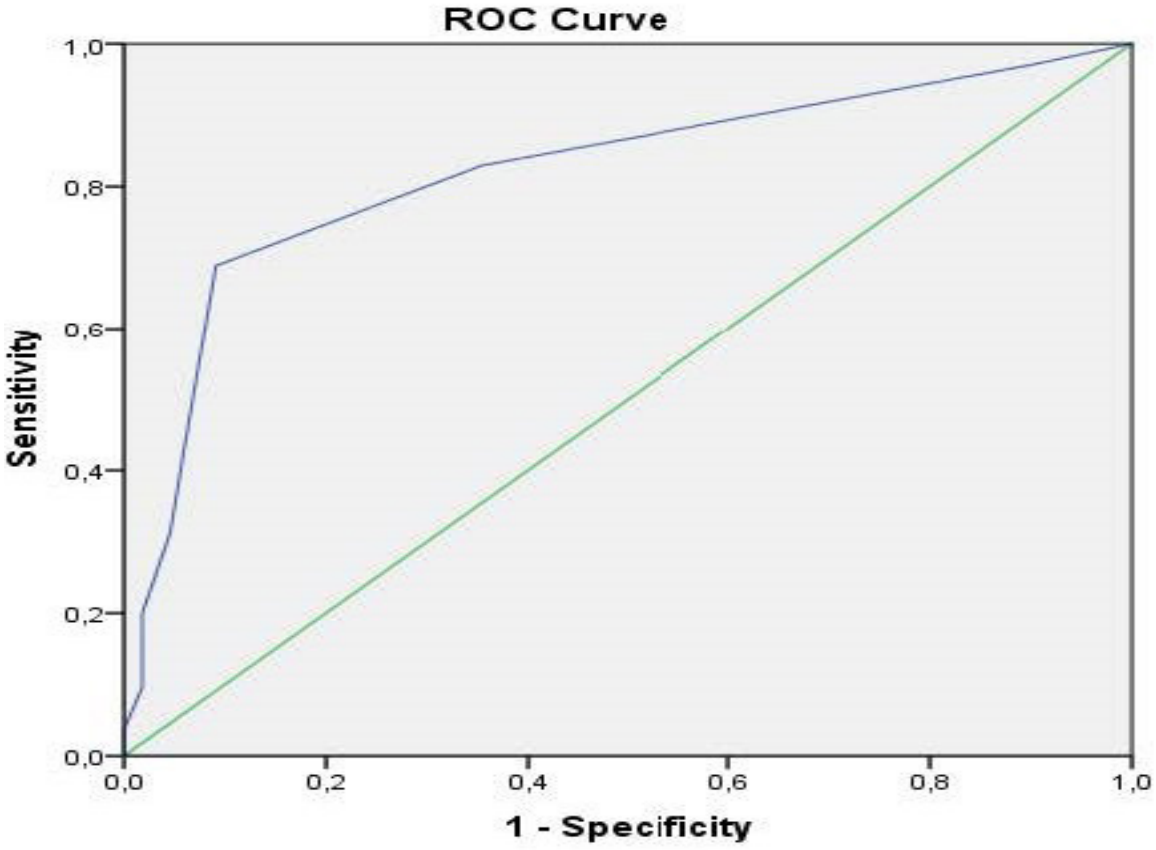

Figure 1. Receiver operating characteristic (ROC) analysis for CONUT score. The best cut-off value for CONUT score was determined via ROC analysis to be 3. Area under the curve (AUC)=0.831 95% CI=0.780-0.882, $p < 0.001$.

Table 2. Characteristic of Patients in Groups

Variables	High CONUT Group (score ≥ 3) (n=109)	Low CONUT Group (score ≤ 2) (n=153)	Overall (n=262)	*p* value
Age (years) (SD)	66.5 (9.3)	64.7 (9.1)	65.4 (9.1)	0.123
Gender (n,%)				0.488
Male	101 (92.6)	138 (90.1)	239 (91.2)	
Female	8 (7.3)	15 (9.8)	23 (8.7)	
Smoking (n,%)				0.786
No	46 (42.2)	62 (40.5)	108 (41.2)	
Yes	63 (57.7)	91 (59.4)	154 (58.7)	
ASA score (n,%)				< 0.001
1	10 (9.1)	32 (20.9)	42 (16.0)	
2	51 (46.7)	87 (56.8)	138 (52.6)	
3	47 (43.1)	33 (21.5)	80 (30.5)	
4	1 (0.9)	1 (0.6)	2 (0.7)	
Neoadjuvant Chemotherapy (n,%)				0.897
No	103 (94.4)	144 (94.1)	247 (94.2)	
Yes	6 (5.5)	9 (5.8)	15 (5.7)	
pT stage (n,%)				0.013
pT1	7 (6.4)	26 (16.9)	33 (12.5)	
pT2	33 (30.2)	49 (32.0)	82 (31.2)	
pT3	44 (40.3)	54 (35.2)	98 (37.4)	
p T4	25 (22.9)	24 (15.6)	49 (18.7)	
pN stage (n,%)				< 0.001
pN0	60 (55.0)	119 (77.7)	179 (68.3)	
pN1	21 (19.2)	24 (15.6)	45 (17.1)	
pN2	27 (24.7)	9 (5.8)	36 (13.7)	
pN3	1 (0.9)	1 (0.6)	2 (0.7)	
lymph nodes removed (median) (Q1-Q3)	12 (9-17)	12 (8-18)	12(8.75-18)	0.293
Positive surgical margin (n,%)				0.003
Negative	87 (79.8)	141 (92.1)	228 (87.0)	
Positive	22 (20.1)	12 (7.8)	34 (12.9)	
Concomitant CIS (n,%)				0.728
No	78 (71.5)	106 (69.2)	184 (70.2)	
Yes	31 (28.4)	47 (30.7)	78 (29.7)	
lymphovascular invasion (n,%)				0.004
No	41 (37.6)	85 (55.5)	126 (48)	
Yes	68 (62.3)	68 (44.4)	136 (51.9)	
Perineural invasion (n,%)				0.589
No	66 (60.5)	94 (61.4)	160 (61.0)	
Yes	43 (39.4)	59 (38.5)	102 (38.9)	
Adjuvant chemotherapy (n,%)				0.068
No	77 (70.6)	123 (80.3)	200 (76.3)	
Yes	32 (29.3)	30 (19.6)	62 (23.6)	
Overall Survival (n,%)				< 0.001
Alive	10 (9.1)	108 (70.5)	118 (45)	
Death	99 (90.8)	45 (29.4)	144 (54.9)	
Follow-up time, months (median) (Q1-Q3)	12 (5-21.5)	24 (11-36)	16 (8-36)	< 0.001
Recurrence (n,%)				0.243
None	72 (66.0)	119 (77.7)	191 (72.9)	
Local	13 (11.9)	14 (9.1)	27 (10.3)	
Metastatic	24 (22.0)	19 (12.4)	43 (16.4)	
Type of urinary diversion (n,%)				0.126
İleal	99 (90.8)	145 (94.7)	244 (93.1)	
Orthotopic	0 (0)	3 (1.9)	3 (1.1)	
Ureterocut-aneostomy	10 (9.1)	4 (2.6)	14 (5.3)	
Multiplicity (n,%)				0.260
Single	47 (43.1)	76 (50)	123 (46.9)	
Multiple	60 (55.0)	76 (50)	136 (51.9)	
Grade (n,%)				0.224
High	102 (93.5)	149 (97.3)	251 (95.8)	
Low	6 (5.5)	4 (2.6)	10 (3.8)	

Abbreviations: ASA: American Society of Anesthesiologists; pT: pathological tumor; pN: pathological node; CIS: carcinoma in situ; OS: overall survival

to the cut-off CONUT score, which was derived using the receiver operating characteristic (ROC) curve and the Youden index. The group with a CONUT score ≥ 3 was categorized as high CONUT, whereas the group with a CONUT score < 3 was categorized as low CONUT.

The groups were compared in terms of gender, age, American Society of Anesthesiologists score (ASA), smoking status, neoadjuvant chemotherapy history, grade and multiplicity, pathological tumor stage (pT), pathological node stage (pN), the presence of concomitant carcinoma in situ (CIS), number of lymph nodes removed, positive surgical margin, perineural invasion, lymphovascular invasion, history of adjuvant chemotherapy, relapse status and urinary diversion type. Oncological outcomes and survival risk factors, such as cancer-specific survival (CSS) and overall survival (OS), were also studied following radical cystectomy. The pathology outcome of a transurethral resection bladder tumor (TURBT) procedure was used to diag-

Table 3: Multivariate analyses of Variables

Variables	CSS HR (95% CI)	*p* value	OS HR (95% CI)	*p* value
Age	1.0 (0.9-1.03)	0.423	1.02 (1.006-1.04)	0.011
Smoking	1.1 (0.66-1.92)	0.654	1.209 (0.83-1.75)	0.318
CONUT	1.2 (0.71-2.14)	0.442	3.92 (2.66-5.77)	<0.001
pT stage	0.93 (0.31-2.73)	0.899	0.83 (0.53-1.30)	0.428
pN stage	0.45 (0.76-2.68)	0.383	0.54 (0.25-1.21)	0.138
Positive surgical margin	0.52 (0.27-1.0)	0.052	0.14 (0.03-0.68)	0.15
Concomittant CIS	0.17 (0.01-1.62)	0.125	0.15 (0.01-1.34)	0.175
Lymphovascular invasion	0.91 (0.50-1.65)	0.761	0.88 (0.57-1.34)	0.566
Grade	0.26 (0.09-0.70)	0.008	0.84 (0.34-2.05)	0.707
Lymph nodes removed	1.0 (0.96-1.04)	0.871	0.98 (0.96-1.01)	0.305

Abbreviations: pT: pathological tumor; pN: pathological node; CIS: carcinoma in situ; OS: overall survival; HR: hazard ratio; CSS : cancer-specific survival;

nose MIBC. The open approach was used for all cystectomy surgeries. With careful assessment of the patients' comorbidities, performance level, and desire to take chemotherapy, neoadjuvant chemotherapy was planned for patients with projected anti-tumor benefit who could endure the delay and toxicity in curative treatment.
Urinary diversion technique was mostly applied in the form of ileal conduit, orthotopic neobladder and ureterocutaneostomy. Before the cystectomy procedure, computer tomography (CT) was conducted for a thorough physical assessment and staging. Patients with suspected bone metastases took bone scintigraphy. At the time of surgery, none of the patients developed metastases. The obturator and iliac lymph nodes were dissected up to the point where the ureter crosses the common iliac lymph nodes. For clinical staging, the TNM staging system was employed. At least two experienced uropathologists conducted all pathological examinations. For pathological grade, the World Health Organization (WHO) grading system from 2004 was employed.

CONUT Score

The CONUT score, as previously stated, consists of three variables: total cholesterol, serum albumin concentration, and total lymphocyte count, all of which may be retrieved from a laboratory database. After fasting for at least 12 hours, all blood samples were obtained from the antecubital veins and tested in the same laboratory. One week before radical cystectomy, laboratory results were gathered. The scoring criteria for the CONUT score are shown in **Table 1**.

Oncological Outcomes and Follow-up

In accordance with the guidelines, postoperative follow-up was undertaken at specific intervals. The first control examination was done one month following sur-

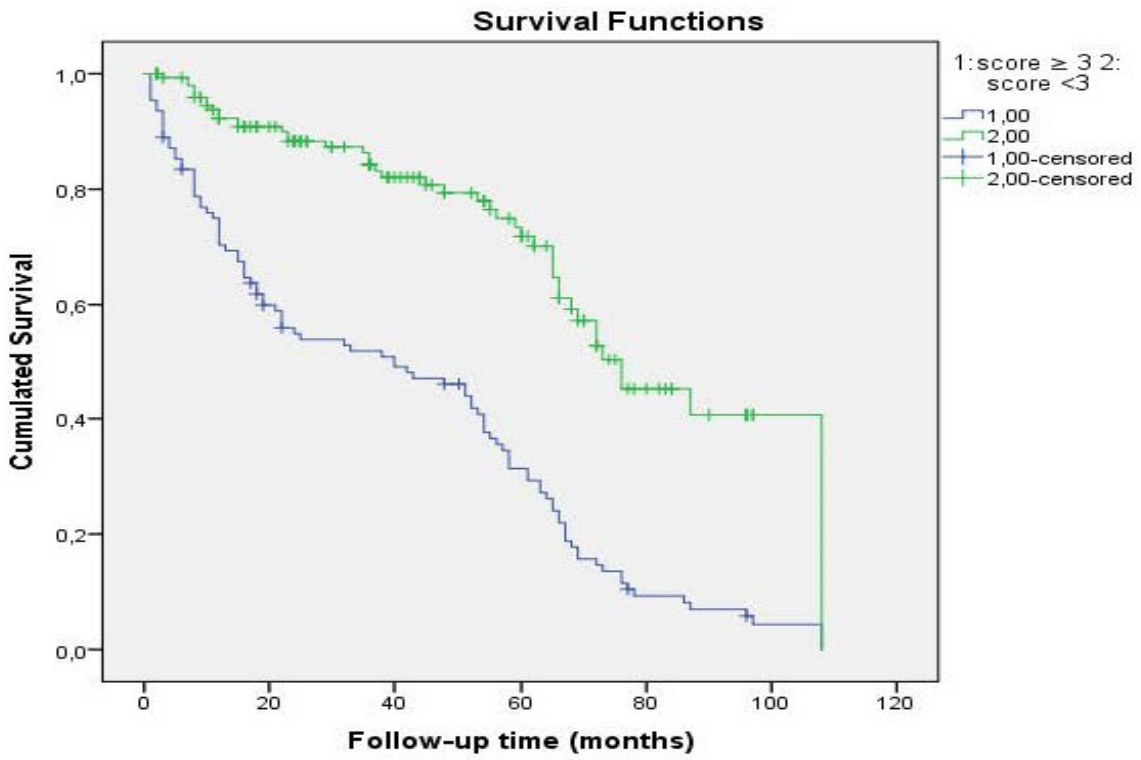

Figure 2. Cancer-specific survival (CSS) according to the CONUT score.

gery. Following that, CT scans were conducted every 6 months for up to three years. Annual controls were instituted three years later. The influence of CONUT score on survival following radical cystectomy was assessed using CSS and OS. The period from the date of surgery to the date of disease-specific death was defined as CSS, and the time from the date of surgery to the date of all-cause death was defined as OS.

Statistical analysis

Among the patients whose medical data were examined, those who met the inclusion criteria were included in the study. The minimum sample size was calculated at 184 to achieve a 95% confidence interval (CI). The suitability of the variables for normal distribution was determined using The Kolmogorov Smirnov Test along with the Q-Q plot visualization. Evaluating the relationship between two category variables, The Chi-square Test or Fisher's exact test was used. The Mann Whitney U Test was preferred to compare two independent means. ROC curve analysis and Youden Index Method were used to determine an optimal cut off value. For survival analysis, we defined the starting point as the date of diagnosis for patients who underwent radical cystectomy operations between 2006 and 2024, and the endpoint as the date of their last follow-up, which had a mean duration of 26.2 months. The Kaplan-Meier log-rank test was used to determine survival. CSS and OS were subjected to multivariate analysis utilizing the survival Cox proportional hazards regression model. Cox regression was performed after confirming that the hazard ratio (HR) is constant over time and the relationship between a quantitative predictor and the log hazard is linear. The variables for multivariable Cox regression model were selected from the parameters that are important in the oncological outcome of patients with MIBC. The effects of these variables on survival together with the CONUT variable were intended to be determined statistically.

The risk was reported as a HR with a 95% CI. The statistical package for the social sciences (SPSS Inc, Chicago, Illinois, USA) version 24.0 was used to analyze the data, and a p value < 0.05 was considered statistically significant.

RESULTS

The mean duration of follow-up was 26.2.8 ± 26.8 months. The best cut-off value for CONUT score was determined via ROC curve analysis to be 3. The area under the curve (AUC) was 0.831 ($p < .001$) (**Figure 1**). The high CONUT group had 109 patients while the low CONUT group had 153 patients. The mean age of the patients was 65.4 ± 9.1 years. The ileal conduit was the most commonly used diversion method in cystectomy (93.1%). The male: female ratio of the study's subjects was 91.2:8.7. The demographic data and clinicopathological features of the patients are shown in **Table 2**. There were 69 patients (63.2%) with pT3 and 4 stages in the high CONUT group, and 78 patients (50.8%) with pT3 and 4 stages in the low CONUT group. There were 28 patients (25.6%) in the high CONUT group with pN3 and 4 stages, and 10 patients (6.4%) with pN3 and 4 stages in the low CONUT group. In terms of the pT and pN stages, a statistical difference was determined between the groups ($p = .013$ and $p < .001$, respectively). Between the groups, there was also a statistical difference in terms of ASA score, positive sur-

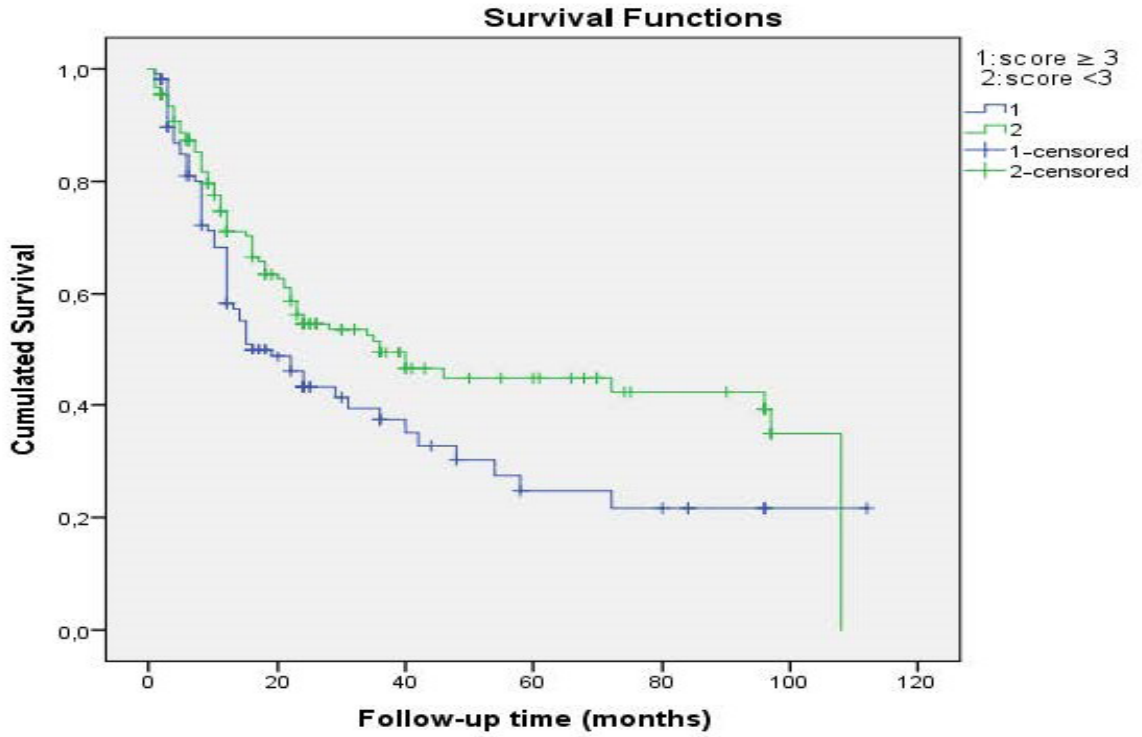

Figure 3. Overall survival (OS) according to the CONUT score.

gical margin, and lymphovascular invasion (**Table 2**). CSS was 46.6 months in the high CONUT group and 60.5 months in the low CONUT group, according to Kaplan Meier analysis (**Figure 2**). The high CONUT group had an OS of 40.2 months while the low CONUT group had an OS of 55.5 months (**Figure 3**). CSS and OS were statistically significantly lower in the High CONUT group compared to the Low CONUT group ($p < .001$, $p = .024$, respectively).

Only tumor grade (95% CI: 0.09-0.70, HR= .26, $P = .008$) was identified to be an independent prognostic factor for CSS in the multivariate analysis. Age (95% CI: 1.006-1.04, HR= 1.02, $P = .011$) and CONUT score (95% CI: 2.66-5.77, HR= 3.92, $P < .001$) were revealed to be independent prognostic variables in the multivariate analysis for OS. Table 3 shows the multivariate Cox proportional hazards regression model.

DISCUSSION

The CONUT score is a recently proposed scoring system for assessing patients' nutritional status. It is a simple, low-cost, and effective technology that simply requires blood test results. It can be easily calculated with 3 blood test results (total lymphocyte count, total cholesterol level and serum albumin concentration).[5,6] Serum albumin concentration is an essential component of serum total protein concentration.[7] It is an important indicator of liver synthesis capability, nutritional and inflammation status. The proinflammatory cytokines TNF- and IL-6 have been demonstrated to decrease albumin synthesis in many malignancies.[8] Although the significance of cholesterol levels in cancer formation is unclear, cholesterol plays an important role in cell protection. Reduced cholesterol levels cause cholesterol to be lost from the cell membrane, reducing the ability of immune system cells to combat cancer cells.[9] Lymphocytes, another component of the CONUT score, show anti-tumoral activity by inhibiting the development and migration of cancer cells by inducing apoptosis. It has been shown that lymphocyte level is related to survival in many kinds of cancer.[10]

In our study, patients with MIBC who had a high preoperative CONUT score had a lower OS and CSS following cystectomy than patients with a low CONUT score. Furthermore, multivariate analysis revealed that the CONUT score predicted overall survival independently. The results of this study indicated a substantial correlation between the CONUT score and the oncological prognosis of patients diagnosed with MIBC.

Previously, the prognostic significance of the CONUT score has been investigated in many organ cancers such as brain, esophagus, cervix, breast, etc., especially gastrointestinal tumors.[5,7,11] There aren't many studies that look at the prognostic value of the CONUT score in bladder cancer patients. Due to research yielding inconsistent findings, the prognostic value of the CONUT score in bladder cancer has not been firmly shown. Niu et al. conducted a meta-analysis of 12 research, revealing the predictive significance of the CONUT score in urological malignancies.[5] Only two articles pertaining to bladder cancer were incorporated into this research. Furthermore, they identified the fact that the majority of patients who participated in this research resided in Asian countries as a limitation of the study.

Nemoto et al. revealed that the CONUT score might predict survival in their study of 115 patients who had advanced bladder cancer.[9] Similarly, our study found that the CONUT score might predict survival.

In 185 patients with advanced urothelial carcinoma, Suzuki et al. explored the prognostic importance of the CONUT score.[8] In this study, only 56% of the patients had advanced bladder tumors. The remaining 81 patients (44%) had malignancies of the upper urinary tract. They discovered that a high CONUT score was linked to a poor OS. They discovered that individuals with a CONUT score of 3 had a median OS of 13.3 months, whereas those with a CONUT score ≥ 4 had a median OS of 7.7 months. High CONUT scores were shown to be related to poor OS in our study. Contrary to Suzuki et al.'s study, we ascribe the longer OS durations in our analysis to the fact that we only included bladder cancer patients and did not include upper urinary tract tumors, which have a poorer prognosis.

Contrary to our study, Tanabe et al., in their study of 133 patients in which they investigated the effect of CONUT score on the development of paralytic ileus after radical cystectomy, found no relationship between the CONUT score and oncologic prognosis.[12] Miyake et al. discovered that a high CONUT score was not connected with patient prognosis in their study of 117 muscle-invasive bladder cancer patients.[13] More studies are required to clearly establish the influence of the CONUT score on oncological survival due to studies yielding contradictory findings.

A growing body of evidence indicates that the host's nutritional status is linked to the immune system and plays a significant role in cancer progression and patient survival.[14] Proinflammatory cytokines such as TNF-, IL1, IL10, and IL-6 have been found to have a role in the development of cancer cachexia which is a hyper-catabolic state.[8] The discovery of a link between nutritional status and cancer prognosis implies that nutritional support may play a role improving prognosis. An oral nutritional supplement containing eicosapentanoic acid increased progression-free survival in patients with advanced non-small cell lung cancer according to a randomized study.[15] Studies on the effect of nutritional supplementation on the prognosis and quality of life of patients with muscle-invasive bladder cancer are needed.

There are some limitations of our study. One primary limitation is its retrospective nature. Another limitation of our study is that, despite the huge number of patients, it was a single-center study. The small number of patients who get neoadjuvant therapy can be considered a limitation. Another limitation is that the study excludes inflammatory and immune-nutrition markers such as C-reactive protein level, erythrocyte sedimentation rate, cytokine level, and weight loss. As a result, additional prospective and multicenter studies with more variables are required.

CONCLUSIONS

The CONUT score was found to be an independent predictor of survival in patients with MIBC in this study. Meta-analyses demonstrating the clinical significance of the CONUT score, encompassing just advanced bladder cancer patients, are needed to corroborate this conclusion. Patients with high CONUT scores may benefit from nutritional supplements. More prospective and multicenter studies are required to elucidate this issue.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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