Original Article

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The Cancer of the Bladder Risk Assessment Score and Mortality-Survival Relationship Among Patients Who Have Undergone Radical Cystectomy in the Turkish Urooncology Association Database

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Abstract

Objective: The Cancer of the Bladder Risk Assessment (COBRA) score is a practical method that can be used to predict survival in patients who have undergone radical cystectomy (RC). We aimed to evaluate COBRA scores in our patient group.

Materials and Methods: Patients were classified according to tumor stage and lymph node (TLN) involvement; mortality rates and survival were analyzed according to both the TLN classification and COBRA score from the Turkish Urooncology Association database. The chi-square test and Fisher-Freeman-Halton Exact chi-square test were used to compare qualitative data as well as descriptive statistical methods. Cox regression analysis was used for multivariate analysis. Kaplan-Meier and log-rank tests were used for survival analysis.

Results: There was a statistically significant difference between the COBRA scores and survival rates in terms of cancer-specific mortality according to TLN classification (p=0.000; p<0.05). A COBRA score of 6 was associated with a lower mortality rate than a COBRA score of 5. In the Cox regression analysis of cancer-related death, a one-unit increase in the COBRA score increased the cancer-related death rate 1.54-fold [hazard ratio (HR)=1.540; 95% confidence interval (CI)=1.402-1.691] (p<0.05). When the COBRA score was compared to 0, the highest risk was observed for COBRA 5. If the COBRA score was 5, the risk of cancer-related death increased 14.63 times (HR=14.627; 95% CI=7.041-30.385) (p<0.05). If the COBRA score was 6, the risk of cancer-related death increased by 11.54 times (HR=11.547; 95% CI=5.270-25.278) (p<0.05).

Conclusion: The COBRA score increased, the prognosis worsened, and our results are consistent with the first validated study.

Keywords: Bladder cancer, cystectomy, prognosis.

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Introduction

Bladder cancer (BC) is the sixth most common cancer in men and the eleventh most common cancer in both sexes, and BC is the eighth most common lethal cancer in men (1). Seventy-five percent of patients with BC are non-muscle-invasive upon diagnosis, whereas the rest are muscle-invasive patients (2). The standard treatments for muscle-invasive BC are radical cystectomy (RC) and bilateral pelvic lymphadenectomy, which have a 5-year survival rate of 50%. Cisplatin-based neoadjuvant chemotherapy (NAC) has been used since the 1980s to improve survival (2). Postoperative survival is related to tumor stage, tumor invasion depth, and lymph node (LN) involvement (3). Additionally, other histopathological parameters, such as tumor location and lymphovascular invasion, were associated with prognosis in previous studies (4-6).

Determining postoperative patient prognosis may affect adjuvant treatment for patients with muscle-invasive BC. Although nomograms predicting survival after cystectomy have been developed previously, the necessity of a large number of parameters, and the difficulty of recording evaluation, these nomograms are not widely used in clinic (7,8). For this purpose, in 2017, Welty et al. (9) reported the Cancer of the Bladder Risk Assessment (COBRA) score, which is a more practical scoring system that includes age, tumor stage and LN involvement rate, which predicts survival after cystectomy.

Materials and Methods

Patients

Patients who underwent RC and lymphadenectomy and had at least 3 months of follow-up were identified from the Turkish Urooncology Association BC database and were included in this retrospective study. Patients were recruited from 16 different centers with experience in the field of urooncology. It was planned to classify patients according to tumor stage and lymph node (TLN) involvement; and also we aimed to analyze mortality rates and survival periods according to both the TLN classification and the COBRA score. Our database does not contain information about the type of LN dissection, whether standard or extended.

COBRA scores are based on patient age, tumor stage, and LN density. LN density was calculated as the total number of positive lymph nodes divided by the total number of removed lymph nodes. Briefly, patients under the age of 80 are given a score of 0, while those aged 80 and over are given a score of 1. Depending on the tumor stage in RC pathology, 0 pans are given to those with T1 and below, 1 pan is given to those with T2, and 3 pans are given to those with T3 and T4. Those with a LN density of 0 are given 0 points; those with ≥0-0.33 are given 1 point; those with ≥0.333-0.5 are given 2 points; and those with ≥0.5-1 points are given 3 points. The obtained scores were summed to obtain a minimum of 0 and a maximum of 7 points (9). Ethical Committee approval (protocol no: 09.2020.909, date: 24.07.2020) was received from Marmara University.

Patients with missing information regarding the total number of removed LNs, number of positive lymph nodes, incomplete pathological data, and duration of postoperative follow-up 3 months were excluded from the study.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics 22 program. The chi-square test and Fisher's freeman's Halton exact chi-square test were used to compare qualitative data as well as descriptive statistical methods (mean, standard deviation, frequency). Cox regression analysis was used for multivariate analysis. Kaplan-Meier and log-rank tests were used for survival analysis. Significant differences were evaluated at the $p<0.05$ level.

Results

A total of 910 cases, 450 (49.5%) male and 460 (50.5%) female, aged 34-98 years were included in the study who underwent cystectomy and pelvic LN dissection between 2002 and 2021. The median follow-up period was 24 months. In Table 1, general distribution of age, sex, histological type, history of NAC, number of lymph nodes removed, number of positive lymph nodes, COBRA scores, and TLN classification of the patients. We have only 36 patients aged over 80 years. Histological types in cystectomy pathology were urothelial in 92.3% of cases, squamous in 3%, adenocarcinoma in 0.9%, and other in 3.8%.

There was no statistical difference between patients with positive and negative lymph nodes in terms of age, gender, smoking status, histological type, and number of positive lymph nodes (Table 2). The mortality rate in patients with positive lymph nodes (49.1%) was significantly higher than that in patients with negative lymph nodes (26.9%) ($p=0.000$; $p<0.05$). The cancer-specific death rate in those with positive lymph nodes (33.8%) was statistically significantly higher than those with negative lymph nodes (16.6%) ($p=0.000$; $p<0.05$). The lymphovascular invasion rate in lymph node-positive patients (64.6%) was significantly higher than LN negative (20.2%) ($p=0.000$; $p<0.05$). There was a statistically significant correlation between LN positivity and COBRA score ($p=0.000$; $p<0.05$). Although the rates of COBRA scores of 0 (33%), 1 (32.3%), and 3 (31.2%) in LN (-) patients were high; the rates of COBRA scores of 2 (17.2%), 4 (53.4%), 5 (10.4%), and 6 (10.8%) in LN (+) patients are high (Table 2).

There was a statistically significant difference in cancer-specific death rates among COBRA scores ($p=0.000$; $p<0.05$). The cancer-specific death rate was 61.9% in score 5 score; and this is significantly higher than score 0 (9.1%), score 1 (14.8%), score 2 (15.7%), 3 (26.1%), and 4 (34.4%) ($p<0.05$). The cancer-specific death rate at score 6 (50%) was significantly higher than that at scores 0, 1, 2, and 3 ($p<0.05$). The incidence of cancer-specific death was significantly higher for score 4 (34.4%) than for scores 0, 1, and 2 ($p<0.05$). The incidence of cancer-specific death was significantly higher for score 3 (34.4%) than for scores 0 and score 1 ($p<0.05$). There were no significant differences among the other COBRA scores ($p>0.05$) (Table 3).

There was a statistically significant difference in cancer-specific death rates between the TLN groups ($p=0.000$; $p<0.05$). The cancer-specific death rate was 41% in the T3-T4 LN-positive group, which was significantly higher than <T2 LN-negative

(9.4%), <T2 LN-positive (7.7%), T2 LN-negative (14.8%), T2 LN-positive (19.1%), and T3-T4 LN-negative (25.7%) classes (p<0.05). The cancer-specific death rate was 25.7% in the T3-T4 LN-negative group, which was significantly higher than <T2 LN-negative, <T2 LN-positive, and T2 LN-negative groups is high (p<0.05). There were no significant differences between the other TLN groups (p>0.05) (Table 4).

Table 1. General distribution of age, sex, histological type, number of lymph nodes removed, number of positive lymph nodes, COBRA Scores, and TLN classification of the patients included in the study

		n	%
Sex	**Men**	**450**	**49.5**
	Women	460	50.5
Age	<60	271	29.8
	60-69	381	41.9
	70+	258	28.4
Histological type	Urotelial	840	92.3
	Squamous	27	3.0
	Adenocancer	8	0.9
	Other	35	3.8
Neoadjuvant chemotherapy	Yes	91	10
	No	764	84
	NA	55	6
Number of total removed nodes	0-5	62	6.8
	6-10	155	17
	11-15	229	25.2
	16-20	193	21.2
	21-25	119	13.1
	≥26	152	16.7
Number of positive lymph nodes	0	631	69.3
	1	96	10.5
	2-4	104	11.4
	5+	79	8.7
COBRA score	0	209	23.0
	1	216	23.7
	2	59	6.5
	3	206	22.6
	4	160	17.6
	5	29	3.2
	6	30	3.3
	7	1	0.1
TLN classification	<T2 node -	214	23.5
	<T2 node +	15	1.6
	T2 node	209	23.0
	T2 node +	57	6.3
	T3-T4 node -	207	22.7
	T3-T4 node +	208	22.9

NA: Not available, COBRA: Cancer of the Bladder Risk Assessment, TLN: Tumor stage and lymph node

Cancer-specific death was observed in 73 (33.8%) of 215 cases with (+) lymph nodes, whereas cancer-specific death was observed in 92 (16.6%) of 553 cases with LN (-). As expected, evaluated using the log-rank test, the survival rates of patients with LN (+) were significantly lower than those with LN (-) (p=0.000; p<0.05) (Figure 1).

When survival rates were evaluated using the log-rank test according to the COBRA score, a statistically significant difference was found between them (p=0.000; p<0.05). Survival rates were significantly higher in people with a COBRA score of 0 than in those with a score of 3 (p=0.000), 4 (p=0.000), 5 (p=0.000) and 6 (p=0.000) (p<0.05). Survival rates were significantly higher for people with a COBRA score of 1 than for those with a score of 3 (p=0.005), 4 (p=0.000), 5 (p=0.000) and 6 (p=0.000) (p<0.05). Survival rates were significantly higher in individuals with a COBRA score of 2 than in those with 4 (p=0.007), 5 (p=0.000) and 6 (p=0.000) (p<0.05). Survival rates were significantly higher in individuals with a COBRA score of 3 than in those with 4 (p=0.020), 5 (p=0.000) and 6 (p=0.000) (p<0.05). Survival rates were significantly higher for people with a COBRA score of 4 than for those with a score of 5 (p=0.002) and significantly lower than those with a 6 (p=0.032) score (p<0.05). There were no significant differences between the other scores (p>0.05) (Figure 2).

When the survival rates according to the TLN group were evaluated using the log-rank test, a statistically significant difference was found between them (p=0.000; p<0.05). The survival rate of cases with T3-T4 LN positivity was significantly lower than that of the cases (p<0.05), <T2 node (-) (p=0.000), <T2 node (+) (p=0.036), T2 node (-) (p=0.000), T2 node (+) (p=0.001), and T3-T4 node (-) (p=0.000). The survival rate of cases with <T2 node (-) were significantly higher than that of cases (p<0.05), T2 node (-) (p=0.044), T2 node (+) (p=0.033),

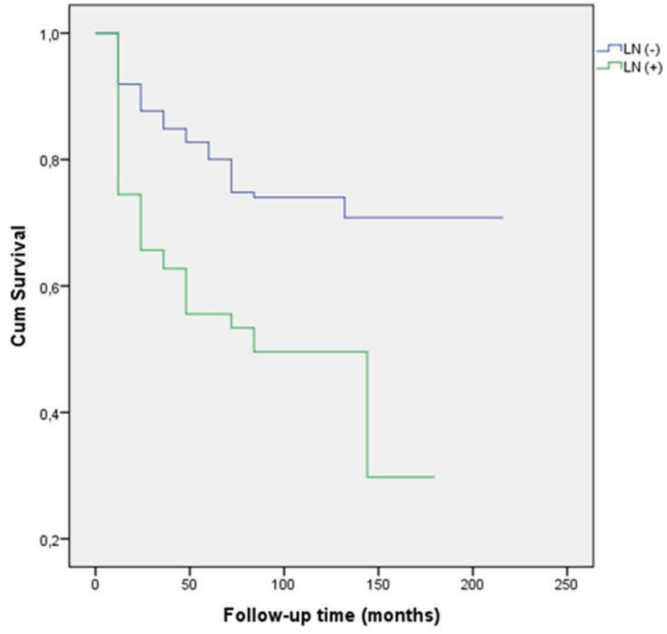

Figure 1. Graph of survival for cancer-related death according to lymph node positivity

Table 2. Comparison of clinical and pathological data between patients with positive and negative lymph nodes					
		LN (-)	LN (+)	Total	
		n (%)	n (%)	n (%)	p-value
Sex (n=910)	Men	303 (48%)	147 (52.7%)	450 (49.5%)	0.194
	Women	328 (52%)	132 (47.3%)	460 (50.5%)	
Age (n=910)	<60	195 (30.9%)	76 (27.2%)	271 (29.8%)	0.530
	60-69	259 (41%)	122 (43.7%)	381 (41.9%)	
	70+	177 (28.1%)	81 (29%)	258 (28.4%)	
Smoking cigarette(n=645)	Yes	266 (61.6%)	136 (63.8%)	402 (62.3%)	0.613
	No	92 (21.3%)	47 (22.1%)	139 (21.6%)	
	Stopped	74 (17.1%)	30 (14.1%)	104 (16.1%)	
Histological type (n=910)	Urotelial	576 (91.3%)	264 (94.6%)	840 (92.3%)	0.089
	Squamose	19 (3%)	8 (2.9%)	27 (3%)	
	Adenocancer	5 (0.8%)	3 (1.1%)	8 (0.9%)	
	Other	31 (4.9%)	4 (1.4%)	35 (3.8%)	
Tumor stage (n=901)	T0	77 (12.4%)	6 (2.2%)	83 (9.2%)	0.000*
	TA	25 (4%)	2 (0.7%)	27 (3%)	
	It is	21 (3.4%)	1 (0.4%)	22 (2.4%)	
	T1	84 (13.5%)	5 (1.8%)	89 (9.9%)	
	T2	208 (33.4%)	57 (20.5%)	265 (29.4%)	
	T3	141 (22.6%)	135 (48.6%)	276 (30.6%)	
	T4	67 (10.8%)	72 (25.9%)	139 (15.4%)	
Lymphovascular invasion (n=879)	Yes	122 (20.2%)	177 (64.6%)	299 (34%)	0.000*
	No	483 (79.8%)	97 (35.4%)	580 (66%)	
Number of positive lymph nodes (n=910)	0	631 (100%)	0 (0%)	631 (69.3%)	0.000*
	1	0 (0%)	96 (34.4%)	96 (10.5%)	
	2-4	0 (0%)	104 (37.3%)	104 (11.4%)	
	5+	0 (0%)	79 (28.3%)	79 (8.7%)	
COBRA score (n=910)	0	208 (33%)	1 (0.4%)	209 (23%)	0.000*
	1	204 (32.3%)	12 (4.3%)	216 (23.7%)	
	2	11 (1.7%)	48 (17.2%)	59 (6.5%)	
	3	197 (31.2%)	9 (3.2%)	206 (22.6%)	
	4	11 (1.7%)	149 (53.4%)	160 (17.6%)	
	5	0 (0%)	29 (10.4%)	29 (3.2%)	
	6	0 (0%)	30 (10.8%)	30 (3.3%)	
	7	0 (0%)	1 (0.4%)	1 (0.1%)	
Mortality (n=910)	Alive	461 (73.1%)	142 (50.9%)	603 (66.3%)	0.000*
	Dead	170 (26.9%)	137 (49.1%)	307 (33.7%)	
Cancer spesific death (n=769)	Yes	92 (16.6%)	73 (33.8%)	165 (21.5%)	0.000*
	No	461 (83.4%)	143 (66.2%)	604 (78.5%)	

Chi-square test, +Fisher Freeman-Halton Exact test, *p<0.05
LN: Lymph node, COBRA: Cancer of the Bladder Risk Assessment, TLN: Tumor stage and lymph node

T3-T4 node (-) (p=0.000) and T3-T4 node (+) (p=0.000). There were no significant differences between the other TLN classes (p>0.05) (Figure 3).

In total, a one-unit increase in the COBRA score increased the cancer-specific death rate 1.54 times (HR=1.540; 95% CI=1.402-1.691) (p<0.05). Compared with COBRA 0, the highest risk is observed with COBRA 5. If the COBRA score is 5, the risk of cancer-related death increases by 14.63-fold (HR=14.627; 95% CI=7.041-30.385) (p<0.05). This is followed by the COBRA 6 score. If the COBRA score was 6, the risk of cancer-related death increased by 11.54 times (HR=11.547; 95% CI=5.270-25.278) (p<0.05). When evaluated according to the previous COBRA score, the significant scores were the COBRA 4 and 5 scores (p<0.05) (Table 5).

Discussion

Our study revealed that the COBRA score can be a practical prognostic tool in RC patients. As the COBRA score increases, the prognosis worsens.

The study included 910 patients. After the COBRA score study by Welty et al.'s (9), 4 more studies using this scoring were reported (10-13). The number of patients in these studies ranged from 412 to 2395. The number of patients in our study was comparable with that of other studies. While the Korean study was conducted at a single center, the study by Muilwijk et al. (11) included patients from 2 different centers (13). Moreover, the cancer genome atlas project was conducted using patient data from 36 different centers, and the study by De Nunzio

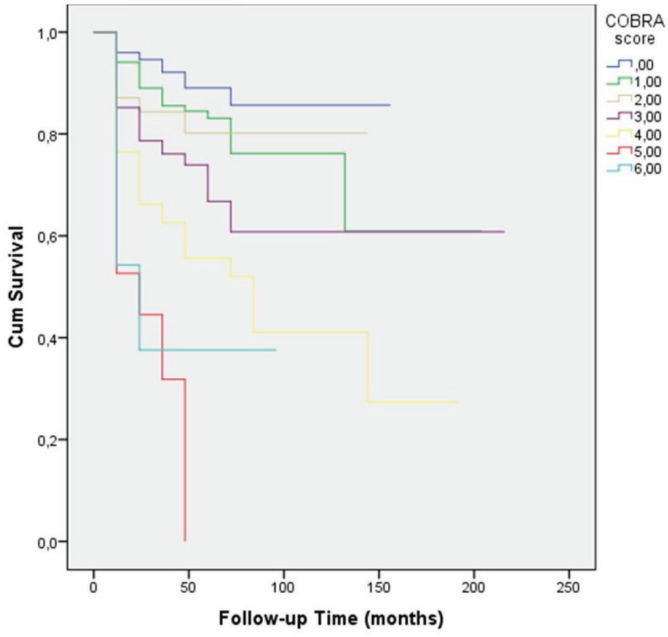

Figure 2. Graph of survival for cancer-related death according to COBRA score
COBRA: Cancer of the Bladder Risk Assessment

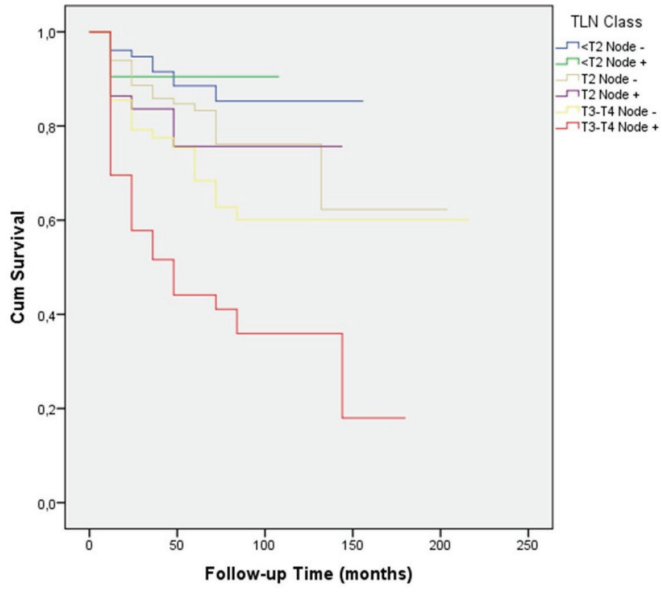

Figure 3. Survival graph for cancer-related death by TLN group
TLN: Tumor stage and lymph node

Table 3. Cancer specific death rates according to COBRA scores

Cancer-specific death	COBRA score							
	0	1	2	3	4	5	6	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	p-value
No	169 (90.9%)	161 (85.2%)	43 (84.3%)	130 (73.9%)	82 (65.6%)	8 (38.1%)	10 (50%)	0.000*
Yes	17 (9.1%)	28 (14.8%)	8 (15.7%)	46 (26.1%)	43 (34.4%)	13 (61.9%)	10 (50%)	

COBRA: Cancer of the Bladder Risk Assessment

Table 4. Cancer-specific death rates according to TLN classifications

Cancer-specific death	TLN classification						
	<T2 node -	<T2 node +	T2 node	T2 node +	T3-T4 node -	T3-T4 node +	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	p-value
No	173 (90.6%)	12 (92.3%)	156 (85.2%)	38 (80.9%)	133 (74.3%)	92 (59%)	0.000*
Yes	18 (9.4%)	1 (7.7%)	27 (14.8%)	9 (19.1%)	46 (25.7%)	64 (41%)	

TLN: Tumor stage and lymph node

Table 5. Cox regression analysis results for cancer-related death according to COBRA scores								
		Compared with COBRA:0			Compared with prior COBRA levels			
		95% CI				95% CI		
	HR	Lower	Upper	p-value	HR	Lower	Upper	p-value
Continuous	1.540	1.402	1.691	0.001*				
COBRA (0)	Ref	-	-	-				
COBRA (1)	1.772	0.969	3.238	0.063	1.797	0.982	3.289	0.057
COBRA (2)	2.028	0.875	4.701	0.099	1.142	0.520	2.506	0.741
COBRA (3)	3.409	1.954	5.948	0.001*	1.698	0.801	3.597	0.167
COBRA (4)	5.658	3.221	9.939	0.001*	1.631	1.073	2.477	0.022*
COBRA (5)	14.627	7.041	30.385	0.001*	2.607	1.384	4.910	0.003*
COBRA (6)	11.542	5.27	25.278	0.001*	0.878	0.381	2.025	0.760
COBRA: Cancer of the Bladder Risk Assessment, CI: Confidence interval, HR: Hazard ratio								

et al. (12) was conducted using data from 4 different centers (10). Our study included patients from 16 different experienced Urooncology centers and reflected the Turkish BC database results.

Importantly, our study differs from previous studies by including patients with non-urothelial histological type (9,11-13). In our study, there was no statistically significant difference between patients with negative and positive lymph nodes according to histological type (p=0.089). Chappidi et al. (10) investigated the association between the COBRA score and survival in subtypes of urothelial histology in BC patients with the cancer genome atlas. According to the results of their study, basal, luminal-infiltrated, and luminal papillary tumors with high COBRA scores had significantly higher mortality rates.

In our study, the mortality rate (49.1%) was significantly higher in those with positive lymph nodes than in those with negative lymph nodes (26.9%) (p=0.000; p<0.05). The cancer-related death rate (33.8%) was significantly higher in those with positive lymph nodes than in those with negative lymph nodes (16.6%) (p=0.000; p<0.05). The overall mortality rate was 33.7%, and cancer-related mortality was 18.1% in our study, which is close to the rate reported as 31% in the study of Welty et al. (9). Cancer-related mortality rates were 25% in the study of Kim et al. (13), 27% in the study of De Nunzio et al. (12), and %32 in the Muilwijk (11) study (13).

In a pioneer study, a one-unit increase in the COBRA score was reported to be associated with cancer-related death by 1.61 times (9). In our study, a one-unit increase in the COBRA score increased the cancer-related death rate 1.54 times (HR=1.540; 95% CI=1.402-1.691) (p<0.05). This rate was reported as 1.52 in the study of Muilwijk et al. (11). In the study of Kim et al. (13), the rate of cancer-related death was 1.50, and when the highest COBRA score was 6, cancer-related death increased 11 times (13). In our study, a COBRA score of 5 increased the risk of death due to cancer 14.63 times (HR=14.627; 95% CI=7.041-30.385), and this was the highest risk score. De Nunzio et al. (12) reported that cancer-related death rates increased 1.54-fold with the COBRA score and that the risk of death increased 134-fold at the highest COBRA score of 7. Thus, all of these studies, including ours, revealed that increasing COBRA scores were associated with increased cancer-related death rates.

We also performed survival analysis according to the TLN classification. Welty et al. (9) reported that the survival curve of T2 node-positive patients was similar to that of T3-4 node-negative patients in their study and emphasized this situation. We, like Welty et al. (9), did not find any difference in survival between these two groups. There was no statistically significant difference between the mortality rate of T3-T4 N(-) (25.7%) and T2N(+) (19.1%) (p>0.05) (Table 4). Kim et al. (13) reported the same findings between T2N-positive patients and T3-4 node-negative patients (13). Muilwijk et al. (11) also analyzed the TLN classification, but they only concluded that node-positive patients had worse outcomes than expected. The other two studies did not provide any information about TLN classification (10,12).

Welty et al. (9) could not manage to perform any analysis regarding the effect of NAC because they used the SEER database, which had no information about the chemotherapy status (9). In the present study, 91 patients received NAC. There was no difference between the groups with and without LN positivity in terms of receiving NAC. NAC data were not given clearly in the Kim (13) and De Nunzio (12) studies, and NAC data were not included in the other two studies (10-13).

Study Limitations

The first current study was designed retrospectively. Second, the limits of pelvic lymphadenectomy at the centers were not clearly reported. Multicentricity may be considered as another limitation because the surgical techniques may differ from one center to another. However, all the centers in our study are experienced centers performing urooncological procedures in Turkey. Apart from these limitations, our study differs from previous studies in that it included histological types other than urothelial carcinoma.

Conclusions

The COBRA score can be used as a prognostic tool in RC patients. The prognosis worsened as the COBRA score increased, and our results are consistent with the first validated study. A one-unit increase in the COBRA score increased the cancer-specific death rate 1.54-fold in our cohort. Our study also included RC patients with histological type other than urothelial carcinoma, and the results should be evaluated in a larger series in the future.

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Ethics

Ethics Committee Approval: Ethical Committee approval (protocol no: 09.2020.909, date: 24.07.2020) was received from Marmara University.

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: H.H.T., Concept: H.H.T., S.B., B.Ş., Design: H.H.T., İ.T., S.B., Data Collection or Processing: H.H.T., İ.T., V.İ, S.B., K.T., E.S., U.Y., S.Y., S.A., B.Ş., Analysis or Interpretation: H.H.T., İ.T., V.İ, S.B., K.T., E.S., U.Y., S.Y., S.A., B.Ş., Literature Search: H.H.T., S.B., Writing: H.H.T., S.B.

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