

Can the Cancer of the Bladder Risk Assessment (COBRA) Score be used in Radical Cystectomy Patients with Non-urothelial Pathology?

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What's known on the subject? and What does the study add?

The Cancer of the Bladder Risk Assessment (COBRA) score is a useful tool for predicting prognosis in urothelial bladder cancer. However, the COBRA score has not been used in non-urothelial bladder cancers, and sufficient data has not yet been provided. Our study results showed that the COBRA score is not sufficiently effective in non-urothelial cancers.

Abstract

Objective: The Cancer of the Bladder Risk Assessment (COBRA) score is a practical and validated prognostic tool for estimating survival outcomes in patients undergoing radical cystectomy. In this study, for the first time, we aimed to compare survival outcomes and risk stratification between patients with urothelial and non-urothelial histological subtypes using the COBRA score.

Materials and Methods: A total of 1,017 patients from the Turkish Urooncology Association database who underwent radical cystectomy were retrospectively analyzed. Of these, 923 had urothelial carcinoma (Group 1) and 94 had non-urothelial bladder cancer (Group 2). Patients were classified based on tumor stage, and lymph node (TLN) involvement. Cancer-specific mortality and overall survival were evaluated according to both TLN classification and COBRA scores.

Results: There was no statistically significant difference in cancer-specific survival between the two groups. However, median COBRA score, lymph node density, lymphovascular invasion, and metastasis rates were significantly higher in Group 1 compared to Group 2 ($p \leq 0.001$, $p \leq 0.05$, $p \leq 0.05$, and $p \leq 0.05$, respectively). In Group 1, both cancer-specific and overall survival differed significantly according to COBRA scores and TLN classification ($p < 0.001$ for both), whereas in Group 2, no such association was observed (COBRA score: $p = 0.213$ and $p = 0.225$; TLN classification: $p = 0.505$ and $p = 0.481$). Additionally, in contrast to Group 1, no stepwise increase in cancer-related mortality was noted across COBRA score increments in Group 2.

Conclusion: Among patients with urothelial carcinoma, higher COBRA scores and advanced TLN classifications were associated with worse prognosis. However, in the non-urothelial group, no significant prognostic value of the COBRA score was identified.

Keywords: Prognosis, radical cystectomy, risk assessment, urothelial

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Introduction

Radical cystectomy combined with bilateral pelvic lymphadenectomy and neoadjuvant chemotherapy represents the standard of care for patients diagnosed with muscle-invasive bladder cancer, with a reported five-year overall survival rate of approximately 50%. Postoperative survival is influenced by several demographic factors, such as age and sex, and by pathological variables, most notably tumor stage, depth of invasion, and lymph node involvement. In a large population-based study, the 10-year disease-free survival and overall survival rates were reported as 35% and 58%, respectively (1). However, among patients with lymph node-positive disease undergoing cystectomy, the five-year overall survival rate was markedly lower, at only 18% (2). Although several nomograms have been developed to estimate survival outcomes following radical cystectomy, their implementation in routine clinical practice remains limited. This is primarily due to the inclusion of numerous parameters and the complexity involved in data collection and interpretation (3,4). In an effort to provide a more user-friendly and clinically applicable model, Welty et al. (5) proposed the Cancer of the Bladder Risk Assessment (COBRA) score—a prognostic tool that incorporates three core variables: patient age, pathological tumor stage, and lymph node (TLN) involvement ratio. This scoring system offers a practical and reproducible means of estimating survival after cystectomy. This scoring system was immediately highlighted as a rapid tool to assist clinicians in counseling patients after cystectomy (6).

Our research group was the first in our country to report outcomes using the COBRA score, and our clinical experience has demonstrated its feasibility and practicality in real-world settings (7). In contrast to previous studies, which focused solely on urothelial carcinoma, our analysis included patients with non-urothelial bladder tumors (8-11). Although pure non-urothelial bladder cancers are rare—comprising approximately 5% of all bladder malignancies—they represent a heterogeneous group with distinct biological behaviour and prognostic implications (12).

In this study, we aimed to compare demographic, pathological, and survival outcomes between patients with urothelial and non-urothelial bladder cancer using our previously updated data.

Materials and Methods

Patients who underwent radical cystectomy and bilateral pelvic lymphadenectomy and were followed for at least three months were retrospectively identified in the Turkish Urooncology Association Bladder Cancer Database. The study aimed to classify patients according to TLN involvement and

the COBRA score. Additionally, mortality rates and survival times were analyzed according to these classifications, with separate analyses for urothelial and non-urothelial subgroups.

The COBRA score, as originally described by Welty et al. (5), incorporates three key prognostic parameters: patient age, TLN density. Lymph node density is calculated as the ratio of the number of positive lymph nodes to the total number of lymph nodes removed. Patients younger than eighty receive a score of 0, while those aged eighty or older receive a score of 1. Depending on the tumor stage in radical cystectomy pathology, 0 points are given for those with T1 and below, 1 point for T2, and 3 points for T3 and T4. Those with a lymph node density of 0 are given 0 points, those with >0.33 are given 1 point, those with $\geq 0.33-0.5$ are given 2 points, and those with $\geq 0.5-1$ points are given 3 points. The scores obtained are summed to obtain a minimum of 0 and a maximum of 7 points. TLN classification was determined as $<T2$ node negative, $<T2$ node positive; $T2$ node negative; $T2$ node positive, $T3-T4$ node negative; and $T3-T4$ node positive. The COBRA score and the TLN classes were determined and recorded by the researchers using information from the database.

In our bladder cancer database, non-urothelial tumors were categorized as squamous cell carcinoma, adenocarcinoma, or other or unspecified histological subtypes. Patients were excluded from the analysis if they lacked data on the total number of lymph nodes removed or on the number of positive nodes, had incomplete pathological information, or had postoperative follow-up of less than three months. Since variant histology or divergent differentiation information was available for a limited number of patients in our database, patients with this variant histology or divergent differentiation were not included in the study. Ethical approval for the study was obtained from the Marmara University Clinical Research Ethics Committee (approval number: 09.2020.909, date: 24.07.2020).

Study data were collected and managed using REDCap (Research Electronic Data Capture) tools hosted by the Turkish Urooncology Association. REDCap is a secure, web-based platform specifically designed to facilitate data collection for research purposes (13,14). It offers: (1) an intuitive interface for validated data entry, (2) audit trails to monitor data manipulation and export activities, (3) automated export functions to enable seamless transfer of data to common statistical software, and (4) procedures to support data integration and interoperability with external systems.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics version 22 (IBM Corp., Armonk, NY, USA). Descriptive statistics (mean, standard deviation, and frequency) were used to summarize the data. The chi-square test and the Fisher-

Freeman-Halton exact test were used to compare categorical variables. For multivariate analysis, Cox proportional hazards regression was used. Survival analyses were conducted using the Kaplan-Meier method, and comparisons between survival curves were made using the log-rank test. A p-value of less than 0.05 was considered statistically significant.

Results

A total of 1,017 patients who underwent radical cystectomy were identified in the Turkish Urooncology Association database and included in the study. Among them, 923 patients had urothelial carcinoma (Group 1), and 94 had non-urothelial histologies (Group 2). The non-urothelial group comprised 30 patients with squamous cell carcinoma, 8 with adenocarcinoma, and 56 with other histological subtypes. The mean follow-up durations were 34.09 months in Group 1 and 38.86 months in Group 2. In our study, the proportions of male and female patients are similar. Table 1 presents the overall distribution of demographic and clinicopathological characteristics, including age, sex, histological subtype, number of lymph nodes removed, number of positive lymph nodes, COBRA scores, and TLN classification.

Preoperative imaging (computed tomography or magnetic resonance imaging) revealed lymph node involvement in 176 patients (20.66%). Regarding the surgical approach, 87.8% of patients underwent open cystectomy, 7.28% underwent laparoscopic cystectomy, and 4.92% underwent robot-assisted laparoscopic surgery. An ileal loop was applied to 91.4% of patients. Lymphovascular invasion was detected in 35.23% in the general patient population, and carcinoma in situ (CIS) was identified in 21.27% of cystectomy specimens. While 36.88% of the patients received adjuvant chemotherapy, 8.32% received adjuvant radiotherapy. Metastasis was reported in 28.55% of patients; 33.3% of patients died, including 20.65% who died of cancer.

No statistically significant differences between the two groups were observed with respect to age, sex, follow-up duration, smoking status, number of lymph nodes removed, or cancer-specific mortality. Moreover, there were no differences between the groups in terms of preoperative Bacillus Calmette-Guérin (BCG) induction history, CIS, and high-grade histology on cystectomy pathology. Although no difference was found between the two groups regarding adjuvant radiotherapy, Group 1 had a higher rate of adjuvant chemotherapy ($p=0.035$). However, Group 1 exhibited significantly higher median COBRA scores, higher rates of lymphovascular invasion, higher lymph node density, higher metastasis rates, and higher overall mortality ($p<0.001$, $p<0.05$, $p<0.05$, $p<0.05$, and $p<0.05$, respectively). In contrast, the neoadjuvant chemotherapy rate was significantly higher in Group 2 ($p<0.05$) (Table 2).

Table 1. Demographic and clinicopathological characteristics of the study population, including COBRA scores, and TLN classifications

		n	%
Sex	Men	539	53.95
	Women	478	47.05
Age	<60	299	29.40
	60-69	424	41.69
	70+	294	28.91
Histological type	Urothelial	923	90.94
	Squamous	30	2.96
	Adenocancer	8	0.79
	Other	54	5.32
Number of total removed nodes	0-5	71	6.98
	6-10	173	17.1
	11-15	262	25.76
	16-20	213	20.94
	21-25	130	12.78
	≥ 26	168	16.52
Number of positive lymph nodes	0	715	70.30
	1	102	10.03
	2-4	111	10.91
	5+	89	8.75
Lymphovascular invasion	Yes	346	35.3
	No	636	64.7
Adjuvant chemotherapy	Yes	354	36.8
	No	606	63.1
Adjuvant radiotherapy	Yes	79	8.32
	No	870	91.6
Metastasis	Yes	219	28.5
	No	548	71.45
COBRA score	0	237	23.30
	1	243	23.89
	2	63	6.19
	3	228	22.42
	4	182	17.90
	5	31	3.05
	6	32	3.15
	7	1	0.10
TLN classification	<T2 node-	247	24.29
	<T2 node+	16	1.57
	T2 node-	231	22.71
	T2 node+	61	6.0
	T3-T4 node-	234	23.01
	T3-T4 node+	228	22.42

COBRA: Cancer of the Bladder Risk Assessment, TLN: Tumor stage and lymph node

In Group 1, cancer-specific and overall survival rates, stratified by COBRA scores and TLN classification, differed significantly by the log-rank test ($p < 0.001$ for both) (Figures 1 and 2). In Group 2, no differences were observed in either overall or cancer-specific survival according to the COBRA Score. Moreover, in Group 2, no differences were found overall or cancer-specific survival according to the TLN classification (Figure 2). Unlike Group 1, Group 2 showed no significant association between each one-unit increase in the COBRA score and either overall survival or cancer-specific survival.

In Group 1, a COBRA score ≥ 3 was significantly associated with worse overall survival and cancer-specific survival compared to COBRA score 0. Pairwise comparisons revealed statistically significant differences between COBRA scores 3 and 4, and between scores 4 and 5 (Table 3). Each one-point increase in the COBRA score was associated with approximately a 1.2-fold increase in risk. In contrast, results for Group 2 did not reach statistical significance.

In Group 1, patients classified as TLN T3-T4 node-negative or higher had significantly reduced overall survival compared to patients classified as $<T2$ node-negative. Similarly, TLN T3-T4

node-positive status was associated with worse cancer-specific survival compared to $<T2$ node-negative status. Furthermore, within Group 1, a significant difference was observed between T3-T4 node-positive and T3-T4 node-negative classifications. Each incremental increase in TLN class corresponded to an approximately 1.1-fold increase in risk. For Group 2, no consistent or statistically significant patterns were identified ($p = 0.751$). In group 2, there is a weak association between $<T2$ node-positive and $<T2$ node-negative with respect to cancer-specific survival ($p < 0.05$).

Discussion

The COBRA scoring system constitutes a practical and evidence-based approach for estimating postoperative survival in patients with bladder cancer. The COBRA score provides clinicians with a streamlined, accessible prognostic model that facilitates risk stratification without the complexity of traditional nomograms (3,4,12,15). Its simplicity enables widespread use in routine clinical practice, aiding in personalized decision-making, particularly in identifying high-risk patients who may benefit from intensified follow-up or adjuvant therapy. Moreover, its

Table 2. Comparison of clinical and pathological data between patients with two groups

		Group 1	Group 2	p
		n (%)	n (%)	
Sex (n=1017)	Men	484 (52.49)	54 (57.45)	0.359 ^x
	Women	438 (47.51)	40 (42.55)	
Age (n=1017)	<60	273 (29.58)	26 (27.66)	0.905 ^x
	60-69	383 (41.50)	41 (43.62)	
	70+	267 (28.93)	27 (28.72)	
Smoking cigarette	Yes	406 (59.27)	34 (51.52)	0.396 ^x
	No	160 (33.36)	20 (30.30)	
	Stopped	119 (17.37)	12 (18.18)	
Neoadjuvant chemotherapy	Yes	112 (12.92)	22 (24.18)	0.003 ^{**}
	No	755 (87.08)	69 (75.82)	
Lymphovascular invasion	Yes	324 (36.45)	22 (23.66)	0.014 ^{**x}
	No	565 (63.55)	71 (76.34)	
Lymph node density	Median (IQR)	0.00 (0.00-0.06)	0.00 (0.00-0.00)	0.007 ^{*u}
Adjuvant chemotherapy	Yes	330 (37.93)	24 (26.67)	0.035 ^{**x}
	No	540 (62.07)	66 (73.33)	
Metastasis	Yes	210 (30.26)	9 (12.33)	0.001 ^{**x}
	No	484 (69.74)	64 (87.67)	
Mortality	Alive	605 (65.69)	72 (76.60)	0.033 ^{**x}
	Dead	316 (34.31)	22 (23.40)	
Cancer spesific death	Yes	165 (21.37)	12 (14.12)	0.117 ^x
	No	607 (78.63)	73 (85.88)	

^xChi-square test, ^uMann-Whitney U, ^{*} $p < 0.05$, IQR: Interquartile range

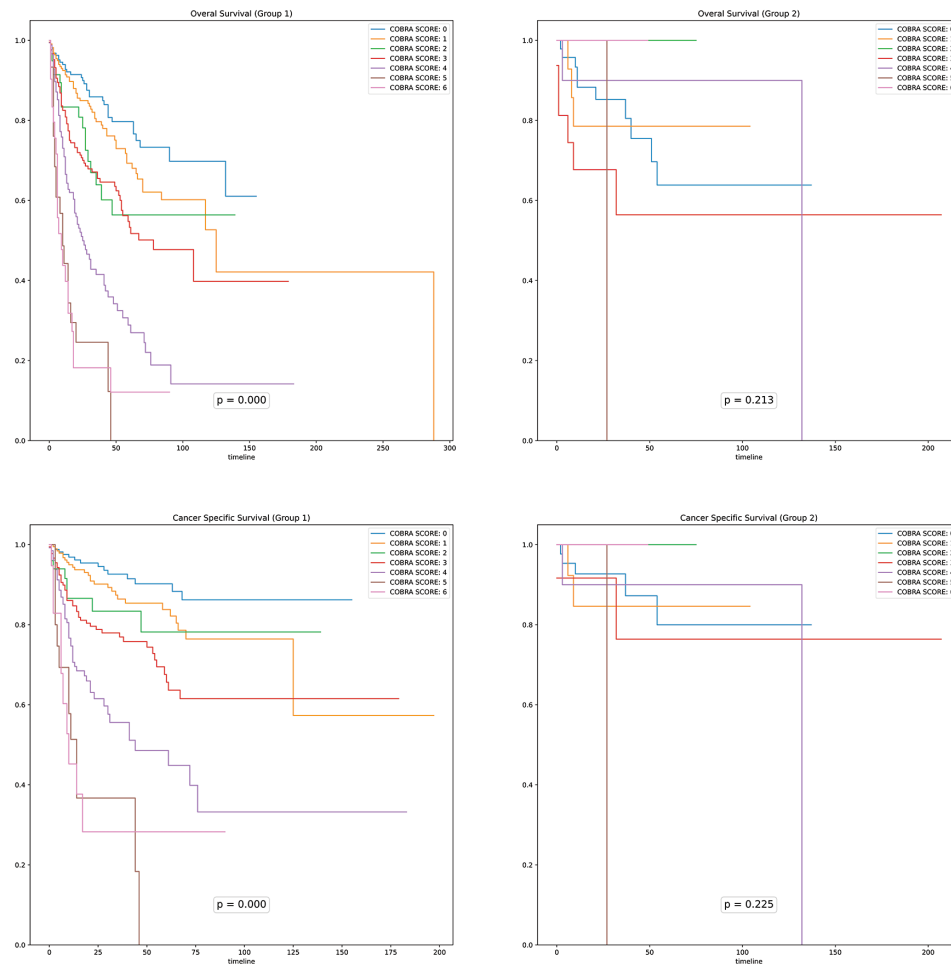


Figure 1. The survival curves stratified by COBRA scores

COBRA: Cancer of the Bladder Risk Assessment, CSS: Cancer specific survival, OS: Overall survival

applicability across multicenter datasets supports its external validity and potential integration into international clinical guidelines (15,16).

To date, only a limited number of studies have investigated the prognostic value of the COBRA scoring system in patients with variant histologies of bladder cancer. In our study, we specifically addressed this gap by evaluating the applicability and predictive performance of the COBRA score in this subgroup. In this study, we applied the COBRA scoring system to non-urothelial bladder cancers and performed a detailed comparison with urothelial carcinoma cases. Overall, our findings indicate that in non-urothelial subtypes, the COBRA score did not demonstrate the same prognostic alignment with survival risk as observed in pure urothelial carcinomas.

In our previous study, we demonstrated that the COBRA score is a valuable prognostic tool for patients undergoing radical cystectomy (7). This updated analysis included 1,017 patients, with particular emphasis on those with non-

urothelial histological subtypes. Notably, we were the first to report survival outcomes using the COBRA scoring system, incorporating non-urothelial bladder cancer cases alongside urothelial carcinoma cases. The inclusion of non-urothelial tumors did not substantially alter the overall results, and the predictive consistency of the COBRA score was preserved. Importantly, in the current dataset, the COBRA score did not demonstrate a significant association with either cancer-specific or overall survival in the non-urothelial group.

Chappidi et al. (17) reported that basal, luminal-infiltrating, and luminal-papillary molecular subtypes with high COBRA scores were associated with significantly increased mortality in the Cancer Genome Atlas (TCGA) Bladder Cancer Cohort. Similarly, Suartz et al. (18) evaluated the applicability of the COBRA scoring system in variant histologies of urothelial carcinoma and concluded that the score was compatible across diverse subtypes—including squamous, glandular, sarcomatoid, and nested variants—demonstrating particular utility in the micropapillary subtype. They suggested that the COBRA score

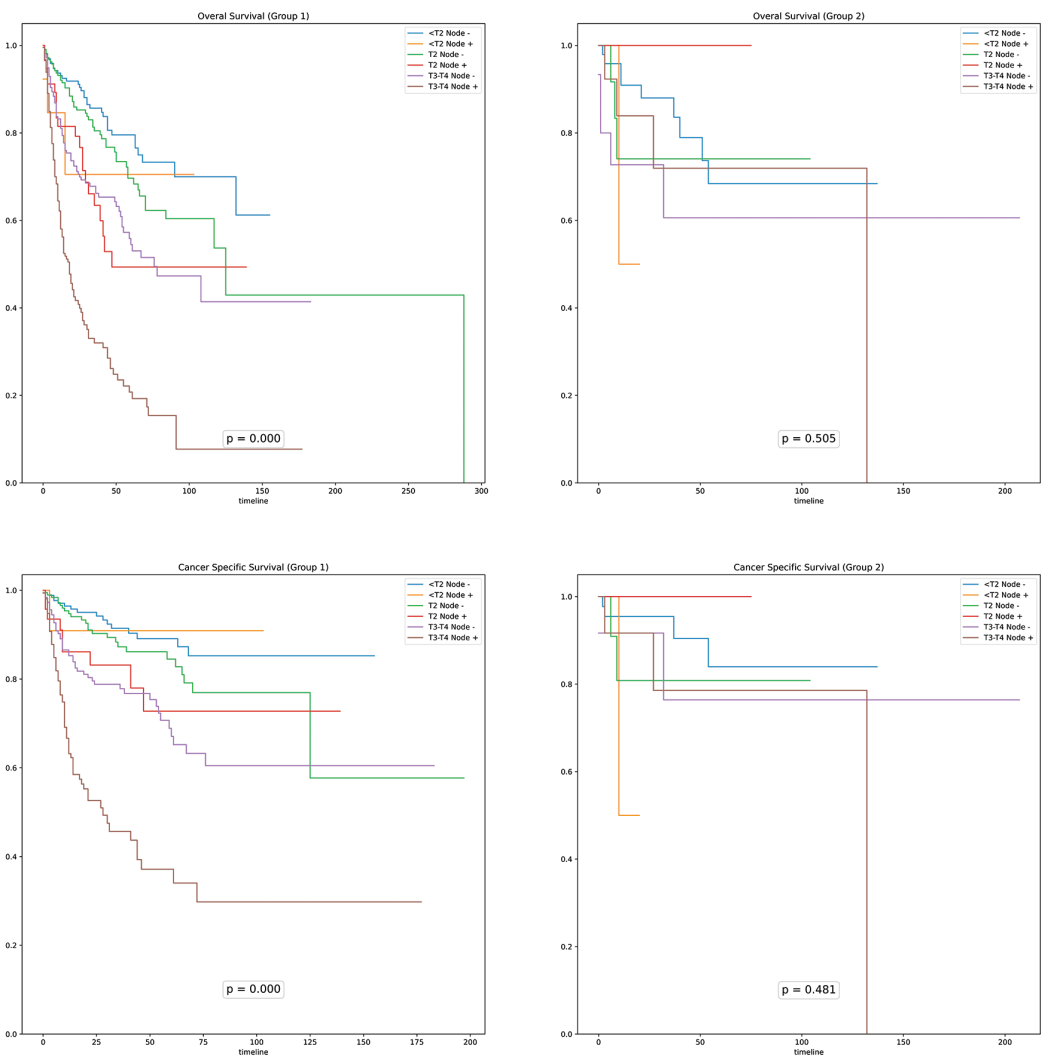


Figure 2. The survival curves based on TLN classification
TLN: Tumor stage and lymph node, CSS: Cancer specific survival, OS: Overall survival

Table 3. Cox regression analysis results for cancer-related death according to COBRA scores in Group 1								
	Compared with COBRA: 0 95% CI				Compared with prior COBRA level 95% CI			
	HR	Lower	Upper	p	HR	Lower	Upper	p
Continuous	1.177	1.125	1.232	<0.001				
COBRA (0)	Ref	-	-	-				
COBRA (1)	1.118	0.910	1.373	0.286	1.118	0.910	1.373	0.286
COBRA (2)	1.231	0.897	1.688	0.197	1.101	0.807	1.502	0.543
COBRA (3)	1.295	1.050	1.599	<0.05	1.052	0.768	1.440	0.749
COBRA (4)	1.974	1.568	2.486	<0.001	1.523	1.215	1.910	<0.001
COBRA (5)	3.630	2.293	5.748	<0.001	1.838	1.157	2.921	<0.05
COBRA (6)	2.867	1.782	4.614	<0.001	0.789	0.423	1.472	0.458

COBRA: Cancer of the Bladder Risk Assessment, CI: Confidence interval, HR: Hazard ratio

is an effective tool for risk stratification in variant urothelial carcinomas (18). In our study, we determined that subgroup analyses within the non-urothelial group were underpowered. Therefore, variant or subtype pathologies were not analyzed separately; only non-urothelial histological types were included in the evaluation.

Upon comparison of the two groups, no statistically significant differences were identified in terms of age, gender, or smoking status. Notably, the administration of neoadjuvant chemotherapy was significantly more frequent in Group 2 ($p<0.05$). This finding may be attributable to ongoing clinical trials within our Uro-Oncology Association Study Group, which specifically focus on the application of neoadjuvant therapy in non-urothelial bladder cancer subtypes (19).

In contrast, Suartz et al. (18) reported no significant difference in neoadjuvant chemotherapy utilization among variant histological subtypes, although their study was limited by the relatively small subgroup sizes. Furthermore, Chappidi et al. (17) did not provide a detailed stratification of rates of neoadjuvant chemotherapy across molecular subgroups in their analysis of the TCGA Bladder Cancer dataset (17).

In our cohort, final pathology revealed a significantly higher rate of lymphovascular invasion and a higher lymph node density in Group 1 ($p=0.014$ and $p=0.007$, respectively). Accordingly, COBRA scores were significantly elevated in Group 1. Contrary to our initial expectations, the incidence of lymph node metastasis was lower in the non-urothelial group. However, this finding is consistent with previous literature reporting that squamous cell carcinoma of the bladder typically presents at an earlier stage and has lower rates of lymph node involvement (20).

In Muilwijk et al.'s (9) study, in addition to COBRA scoring, a modified risk stratification was used by dividing patients into low (0-1 points), intermediate (2-4 points), and high (5-7 points) risk groups according to the COBRA score value, and a good predictive fit was reported in parallel with the classical COBRA scoring. It is called modified COBRA scoring. Another study reported that adding lymphovascular invasion to the COBRA score provided stronger agreement for predicting survival than the COBRA score alone, and the authors recommended using it in this way (11). Although we examined the lymphovascular invasion rate between the groups, we did not use the modified COBRA scoring. This study was specifically designed to evaluate the prognostic utility of the COBRA scoring system across urothelial and non-urothelial bladder cancer subtypes.

An analysis of metastasis rates revealed a higher incidence in Group 1 than in Group 2. Although the difference in cancer-specific mortality between the groups did not reach statistical significance, the overall mortality rate was notably higher in Group 1. This discrepancy may be partially attributed to the

relatively shorter follow-up duration in our cohort compared to certain previously published studies (8,10). In the present study, the mean follow-up period was 34.7 months; the median follow-up durations were 23 and 25 months for Groups 1 and 2, respectively. Nonetheless, our follow-up interval was comparable to that of the original COBRA score validation study (5). The cancer-specific mortality rate in Group 1 was 21.37%, which is lower than rates reported in prior studies, where values have ranged from 25% to 32% (5,8-11).

When both groups were stratified according to COBRA scores and TLN classifications, statistically significant differences in both overall survival and cancer-specific survival were observed exclusively in Group 1 ($p<0.005$) (Figures 1 and 2). In Group 1, a significant increase in cancer-specific mortality was noted between COBRA scores 3 and 4 and between 4 and 5, which aligns with our previously published findings (Table 3) (7). Welty et al. (5) demonstrated that, compared with COBRA score 0, each incremental increase in COBRA score was associated with a statistically significant increase in cancer-specific mortality; this result was also supported by De Nunzio et al. (10). In contrast, Muilwijk et al. (9) reported that scores 1 and 2 differed significantly from COBRA 0 (9). Similarly, Kim et al. (8) found significant differences in cancer-specific mortality between COBRA scores of 0-1 and higher scores, but did not observe consistent differences between successive categories.

In our cohort, the COBRA score failed to demonstrate a survival risk gradient in the non-urothelial group, whereas it demonstrated such a gradient in the urothelial subgroup. Specifically, each one-unit increase in the COBRA score was associated with a 1.2-fold increase in cancer-specific mortality in Group 1. This is slightly lower than the hazard ratio (HR) reported in the original COBRA study ($HR=1.61$) (5). In our previous study, this rate was 1.54 times higher. Muilwijk et al. (9) and Kim et al. (8) reported similar estimates ($HR=1.52$ and 1.50 , respectively). Notably, Kim et al. (8) reported that patients with a COBRA score of 6 had an 11-fold increased risk of cancer-specific death, a finding consistent with our results ($HR=11.29$).

The urothelial group demonstrated statistically significant differences in both overall and cancer-specific survival based on COBRA scores and TLN classification, in contrast to the non-urothelial group. Furthermore, our findings are consistent with Welty et al. (5) and Kim et al. (8), who reported that the survival curve of patients with T2 node-positive disease closely resembled that of T3-T4 node-negative patients. Our Group 1 analysis also supported this observation.

Study Limitations

This study has several limitations. First, its retrospective design inherently limits causal inference. Second, although the

multicenter nature of the study enhances its generalizability, it may also introduce inter-institutional variability in treatment protocols and pathological assessments; however, all centers in our study are experienced in uro-oncological procedures in Türkiye. Furthermore, our database lacked detailed subclassification of non-urothelial histologies beyond squamous cell carcinoma and adenocarcinoma. Patients with variant histology were not included in the study. Finally, while lymphovascular invasion was included in our analysis, the modified COBRA scoring system integrating this variable was not applied. Overall biological heterogeneity, small subgroup size, and the fact that the COBRA score was initially developed for urothelial carcinoma may explain the model's failure in the non-urothelial group.

Conclusion

In the urothelial carcinoma group, increases in COBRA score and TLN classification were associated with poorer prognosis. However, no statistically significant differences were observed in the non-urothelial group based on COBRA score or TLN classification. These findings suggest that the COBRA scoring system may have limited utility in predicting survival outcomes for patients with non-urothelial bladder cancer. Future studies incorporating larger cohorts within specific non-urothelial subtypes (e.g., squamous cell carcinoma, adenocarcinoma) may provide more robust comparative data.

Ethics

Ethics Committee Approval: Ethical approval for the study was obtained from the Marmara University Clinical Research Ethics Committee (approval number: 09.2020.909, date: 24.07.2020).

Informed Consent: Retrospective study.

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Footnotes

Authorship Contributions

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

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