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Clinical-Bladder cancer

The Cancer of the Bladder Risk Assessment (COBRA) score for predicting cancer-specific survival after radical cystectomy for urothelial carcinoma of the bladder: External validation in a cohort of Korean patients

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Abstract

Objectives: To validate the Cancer of the Bladder Risk Assessment (COBRA) score for predicting cancer-specific survival (CSS) in comparison with the American Joint Committee on Cancer (AJCC) staging system using an external cohort of urothelial carcinoma of the bladder (UCB) from South Korea.

Materials and Methods: The final validation cohort consisted of 855 patients who underwent radical cystectomy (RC) for UCB in a single institution. The impact of the COBRA score on CSS was estimated using Cox proportional hazard models. Discrimination accuracy was quantified with concordance index. Calibration plots were used to determine the relationship between model-predicted CSS and actual CSS at 2 years and 5 years after RC. Clinical usefulness of the COBRA score was assessed using decision curve analyses.

Results: One-point increase in the COBRA score (range, 0−6) was closely related to a 1.50-fold increase (95% confidence interval [CI]: 1.39−1.62) in the risk of death from UCB. Discrimination accuracies of the COBRA score and AJCC staging system for CSS at 5 years were 70.6% (95% CI: 67.2−74.0) and 68.3% (95% CI: 65.0−71.6), respectively. Compared to the AJCC staging system, the COBRA score was generally well-calibrated for predicting CSS at 2 and 5 years after RC. On decision curve analyses, the use of the COBRA score showed more clinical net benefits across a wide range of threshold probabilities than the AJCC staging system.

Conclusions: Our external validation results suggest that although the COBRA score is not perfectly accurate, it shows a reasonable level of discriminative ability, adequate calibration, and meaningful net benefit gain for predicting CSS after RC in a Korean UCB cohort.

Keywords: Urinary bladder neoplasms; Carcinoma; Transitional cell; Cystectomy; Prognosis

1. Introduction

Although radical cystectomy (RC) with pelvic lymph node dissection (PLND) is applied as the standard therapeutic modality for muscle-invasive and refractory high-risk nonmuscle invasive urothelial carcinoma of the bladder (UCB) without distant metastasis, postsurgical prognosis may vary depending on local status of tumor, including primary tumor stage and the level of loco-regional lymph node (LN) involvement [1−3]. Occult micro-metastasis that cannot be clinically detected in preoperative imaging study can also negatively affect postsurgical outcomes [4]. To enhance local tumor control and improve prognosis after RC, the use of additional treatment such as systemic chemotherapy in neoadjuvant and/or adjuvant setting and

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perioperative radiotherapy has been clinically considered according to current international guidelines [5−7].

To determine the necessity of additional treatment and enroll patients to relevant clinical trials in UCB, it is important to exactly predict the prognosis of patients after RC. The American Joint Commission on Cancer (AJCC) Tumor-Node-Metastasis staging system has been used as the gold standard predictive tool to estimate the prognosis of UCB patients after surgery [8,9]. However, the level of LN involvement classified in the AJCC Tumor-Node-Metastasis staging system has limitation in accurately predicting the prognosis of LN-positive UCB patients [10] Other than the AJCC staging system, several risk-stratification models and nomograms incorporating diverse clinical and pathological variables have been developed and validated by many investigators for predicting post-RC tumor recurrence and survival outcomes [11−17]. Although these tools have shown acceptable overall predictability, their application in clinical practice has been impeded owing to several limitations, including a large number of included factors and economic burden using a paper nomogram or electronic software.

Recently, the Cancer of the Bladder Risk Assessment (COBRA) score for predicting cancer-specific survival (CSS) after RC has been newly developed and validated using Surveillance, Epidemiology, and End Results cancer database. Additional validation of the COBRA score has been conducted using National Cancer Data Base in terms of CSS and overall survival prediction [18]. In summary, the COBRA score is a validated simplified risk-stratification tool that can exactly incorporate the relative contribution of both primary tumor stage and LN status into postsurgical prognosis after RC for UCB [18].

However, to our knowledge, the COBRA score has not been validated using an external patient cohort, especially in other races. Such external validation using different patient cohort is mandatory to gain widespread and generalized acceptance of developed prediction models [19]. Thus, the objective of this study was to externally validate the predictive accuracy and clinical usefulness of the COBRA score using a different cohort consisting of Korean UCB patients treated with RC compared to the AJCC staging system.

2. Materials and methods

2.1. Study population

We initially identified 903 patients who received RC with PLND for UCB in a single institution (Seoul National University Hospital) from 1991 to 2016 after obtaining approval from our Institutional Review Board. Several patients were excluded from the final validation cohort owing to the following reasons: pathologic subtype other than UC, incomplete information on patient age, pathologic tumor stage and LN status, or distant metastasis at the time of RC. Finally, a total of 855 patients were eligible for current analyses. Details concerning pathologic review, postoperative follow-up strategies, and definition of survival outcomes for these patients in our institution have already been reported previously [16].

2.2. The COBRA score

Finally incorporated variables for constructing the COBRA score included age (<80 or ≥80), tumor stage (≤T1, T2, T3/4), and LN density (0, <0.33, 0.33−0.5, ≥0.5) defined as the total number of positive LNs divided by total number of LNs removed (Supplemental Table 1) [18]. The COBRA score was calculated as a total sum of points allocated to each variable, ranging from 0 to 7. Consequently, each point increase in the COBRA score showed a close association with 1.61-fold increase in the risk of death from UCB. Each COBRA score appropriately stratified the risk of cancer-specific death with reliable internal validation results [18].

2.3. Statistical analyses

CSS depending on the COBRA score (range, 0−6) or combination of tumor stage (<T2, T2, T3/4) and nodal status (absence or presence) and the risk of cancer-specific death by the COBRA score in the current cohort were estimated with Kaplan−Meier analyses and Cox-proportional hazard models, respectively. Discriminative abilities of the COBRA score and the AJCC staging system between predicted and actual events were quantitatively evaluated and compared using concordance index (C-index) ranging from 50% to 100% [20]. A value of 100% implies perfect discrimination whereas 50% means no discriminative ability. The relationship between model-predicted CSS and actual CSS was graphically explored within calibration plots. We then compared the calibration between the COBRA score and the AJCC staging system by plotting predictions on the x-axis and observed outcomes on the y-axis using nonparametric method [21] In the calibration plot, a slope of 45 degree represented perfect prediction. The validation was performed with 200 bootstrap resamples to decrease overfit bias. Finally, to assess the clinical usefulness of the COBRA score for predicting CSS compared to the AJCC staging system, we performed a decision curve analyses (DCA) to quantify the theoretical relationship between threshold probability of an event and the relative value of false-positive and false-negative results to determine net benefits of a prediction tool [22]. For all statistical analyses, 2-sided P value <0.05 was considered statistically significant. All statistical calculations were conducted by using SPSS software, version 21.0 (SPSS, Chicago, IL) and R package 2.13.2 (R Development Core Team, Vienna, Austria; http://www.R-project.org).

3. Results

3.1. Baseline characteristics of the study cohort

Clinical and pathological variables of our validation cohort as well as the existing COBRA development cohort are summarized in Table 1. Similar to the COBRA cohort, there were no significant differences in the distribution of age or sex between LN-negative group ($n = 718$) and LN-positive group ($n = 137$). High grade and locally advanced stage (pT3/4) tumors were more distributed in the LN-positive group. The median number of removed LNs was 11 (interquartile range [IQR]: 4−20) in the LN-negative group and 13 (IQR: 6−22) in the LN-positive group. In the LN-positive group, median numbers of positive LNs and LN density were 3 (IQR: 1−5) and 0.2 (IQR: 0.1−0.3), respectively.

3.2. Results of survival analysis

The median follow-up duration in this cohort was 40.6 months (IQR: 16.6−97.6 months). Of the entire population, 214 (25.0%) patients died from UCB. When classifying patients by tumor stage and nodal status, Kaplan−Meier analyses demonstrated that there were significant differences in CSS depending on tumor stage in LN-negative status, but not in LN-positive status. Patients with LN-positive, organ confined disease (≤T2) showed similar CSS compared to those with LN-negative, locally advanced (pT3/4)

Table 1
Distribution of clinical and pathological variables among lymph-node-negative and lymph node-positive patients

	Score development cohort		External validation cohort	
Variables	Lymph node-negative N = 11,179	Lymph node-positive N = 3,649	Lymph node-negative N = 718	Lymph node-positive N = 137
Age, y				
<60	2,473 (22%)	894 (24%)	237 (33%)	43 (31%)
60−69	3,537 (32%)	1,175 (32%)	268 (37%)	52 (38%)
70−79	3,845 (34%)	1,152 (32%)	193 (27%)	37 (27%)
>80	1,324 (12%)	428 (12%)	20 (3%)	5 (4%)
Total	11,179 (100%)	3,649 (100%)	718 (100%)	137 (100%)
Sex				
Men	8,713 (78%)	2,699 (74%)	604 (84%)	116 (85%)
Women	2,466 (22%)	950 (26%)	114 (16%)	21 (15%)
Total	11,179 (100%)	3,649 (100%)	718 (100%)	137 (100%)
Tumor grade*				
Low	762 (7%)	863 (6%)	109 (17%)	6 (4%)
High	10,069 (93%)	13,546 (94%)	549 (83%)	131 (96%)
Total	10,831 (100%)	14,409 (100%)	657 (100%)	137 (100%)
Tumor stage				
Ta, Tis, T1	1,801 (16%)	68 (2%)	375 (52%)	15 (11(%)
T2	5,022 (46%)	783 (22%)	148 (21%)	28 (20%)
T3	2,783 (25%)	1,590 (45%)	168 (23%)	70 (51%)
T4	1,387 (13%)	1,123 (32%)	27 (4%)	24 (18%)
Total	10,993 (100%)	3,564 (100%)	718 (100%)	137 (100%)
No. of lymph nodes removed				
0−5	3,042 (27%)	847 (23%)	254 (35%)	18 (13%)
6−10	2,660 (24%)	872 (24%)	78 (11%)	17 (12%)
11−15	1,960 (18%)	648 (18%)	107 (15%)	26 (19%)
16-20	1,228 (11%)	481 (13%)	100 (14%)	17 (12%)
≥21	2,289 (20%)	801 (22%)	179 (25%)	59 (44%)
Total	11,179 (100%)	3,649 (100%)	718 (100%)	137 (100%)
No. of positive lymph nodes				
0	11,179 (100%)	0 (0%)	718 (100%)	0 (0%)
1	0 (0%)	1,497 (41%)	0 (0%)	51 (37%)
2−4	0 (0%)	1,448 (40%)	0 (0%)	51 (37%)
≥5	0 (0%)	704 (19%)	0 (0%)	35 (26%)
Total	11,179 (100%)	3,649 (100%)	718 (100%)	137 (100%)
Lymph node density[a]				
≤0.125	11,179 (100%)	1,184 (32%)	718 (100%)	1 (1%)
>0.125−0.25	0 (0%)	847 (23%)	0 (0%)	99 (72%)
>0.25−0.50	0 (0%)	881 (24%)	0 (0%)	17 (12%)
>0.50	0 (0%)	737 (20%)	0 (0%)	20 (15%)
Total	11,179 (100%)	3,649 (100%)	718 (100%)	137 (100%)

* Missing cases = 61
[a] Lymph node density is calculated as the total number of positive lymph nodes/total number of lymph nodes removed.

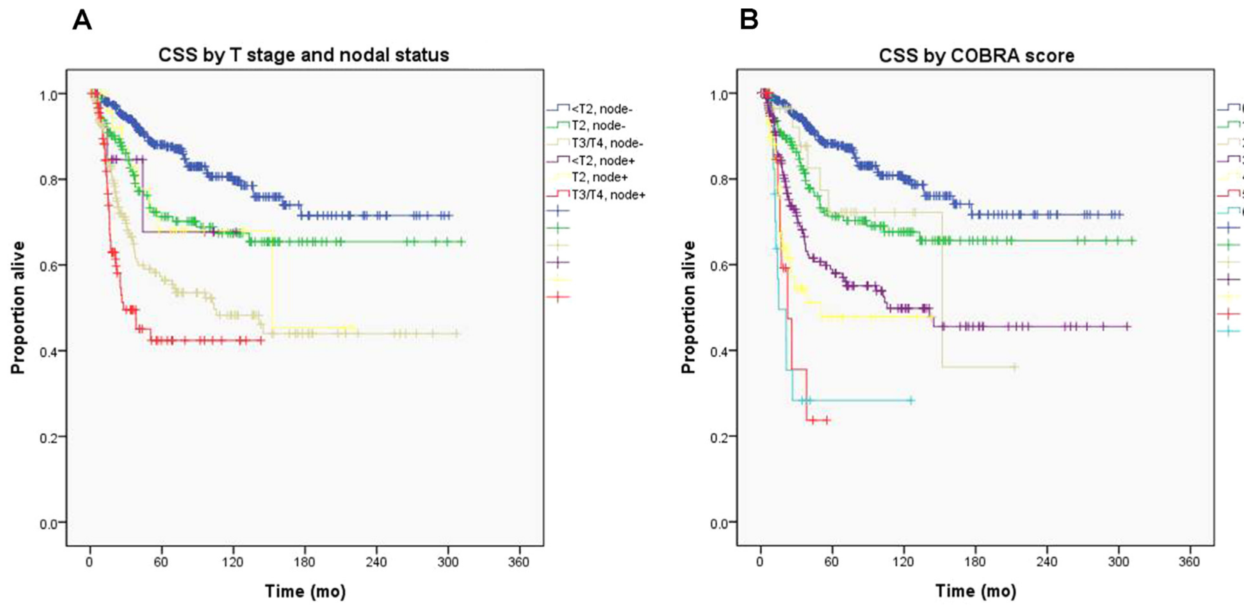

Fig. 1. Kaplan−Meier curves for estimated cancer-specific survival (CSS). (A) By a combination of tumor stage and lymph node status. (B) By the Cancer of the Bladder Risk Assessment (COBRA) score.

tumor (Fig. 1A). Additionally, we stratified patients by adopting the COBRA score and conducted survival analysis. As a result of Kaplan−Meier analysis, significant difference in CSS was only observed between 0 score group and other score groups. However, no significant difference in CSS was observed among score groups (scores of 1−6) (Fig. 1B). These associations were also similarly identified in Cox-proportional hazard models for evaluating the impact of the COBRA score on CSS (Table 2). The COBRA score as a continuous variable was a significant predictor of worse CSS (hazard ratio [HR]: 1.50, 95% confidence interval [CI]: 1.39−1.62). A maximum COBRA score of 6 was significantly correlated with an 11-fold increased risk of cancer-specific death over the COBRA score of 0 (HR: 11.20, 95% CI: 5.79−21.64). Contrary to results in the existing COBRA development cohort, there was no significant difference in the risk of cancer-specific death related to each COBRA score level compared to the prior level except that there was significant risk difference in cancer-specific death between COBRA scores of 0 and 1 (Table 2).

Additionally, we performed the same survival analyses for the AJCC staging system. When the patients were divided according to the AJCC stage, the Kaplan−Meier plots revealed CSS significantly differed in each AJCC stage group except between stage III and IV (Supplemental Fig. 1). A similar trend was also observed in the results of the Cox proportional hazards model for the AJCC staging system (Supplemental Table 2). Each stage (II, III, and IV) was the significant predictor of cancer-specific death compared to stage I disease. There was also significant difference in the risk of cancer-specific death between each stage, except between stage III and IV (HR: 1.13, 95% CI: 0.78−1.62).

Table 2
Risk of cancer-specific death by cancer of the bladder risk assessment (COBRA) score level based on Cox- proportional-hazards modeling using the COBRA score as a continuous variable, as a categorical variable compared with a score 0, as a categorical variable compared with 1 COBRA level lower

		Compared with COBRA = 0			Compared with prior COBRA level		
COBRA score	No.	HR	95% CI	*P* value	HR	95% CI	*P* value
Continuous	855	1.50	1.39−1.62	<0.01			
0	370	Ref	−	−			
1	161	1.92	1.28−2.90	<0.01	1.93	1.28−2.91	<0.01
2	29	1.88	0.85−4.13	0.12	0.93	0.42−2.08	0.87
3	191	3.52	2.45−5.06	<0.01	1.91	0.88−4.16	0.10
4	70	5.60	3.51−8.92	<0.01	1.46	0.94−2.28	0.10
5	17	9.54	4.49−20.27	<0.01	1.46	0.67−3.22	0.34
6	17	11.20	5.79−21.64	<0.01	1.27	0.51−3.18	0.61

Abbreviations: CI = confidence interval; HR = hazard ratio; Ref = reference category.

Table 3
Discrimination estimates for prediction of 2-and 5-year cancer-specific survival

Characteristic	Discrimination estimates (95% confidence interval)	
	2-year cancer-specific survival	5-year cancer-specific survival
AJCC staging system	73.1 (70.7−78.2)	68.3 (65.0−71.6)
COBRA score	77.3 (73.6−81.4)	70.6 (67.2−74.0)

Abbreviations: AJCC = American Joint Commission on Cancer; COBRA = Cancer of the Bladder Risk Assessment.

3.3. External validation of the COBRA score compared with the AJCC staging system

Table 3 summarizes the results of discrimination estimates for 2 and 5-year CSS in the COBRA score and AJCC staging system. Discrimination accuracies of the CORBA score for CSS at 2 and 5 years after RC were 77.3% (95% CI: 73.6−81.4) and 70.6% (95% CI: 67.2−74.0), respectively. At the same time, points discrimination accuracies for CSS using the AJCC staging system were 73.1% (95% CI: 70.7−78.2) and 68.3% (95% CI: 65.0−71.6), respectively. Calibration plots revealed that the COBRA score showed adequate correspondence between predicted CSS and actual CSS at 2 years and 5 years after RC, indicating that the use of the COBRA score in our cohort functioned better for predicting CSS than the AJCC staging system (Fig. 2). Results of DCA suggested that application of the COBRA score within this cohort was associated with higher clinical net benefits over the AJCC staging system across a wide range of threshold probabilities (Fig. 3).

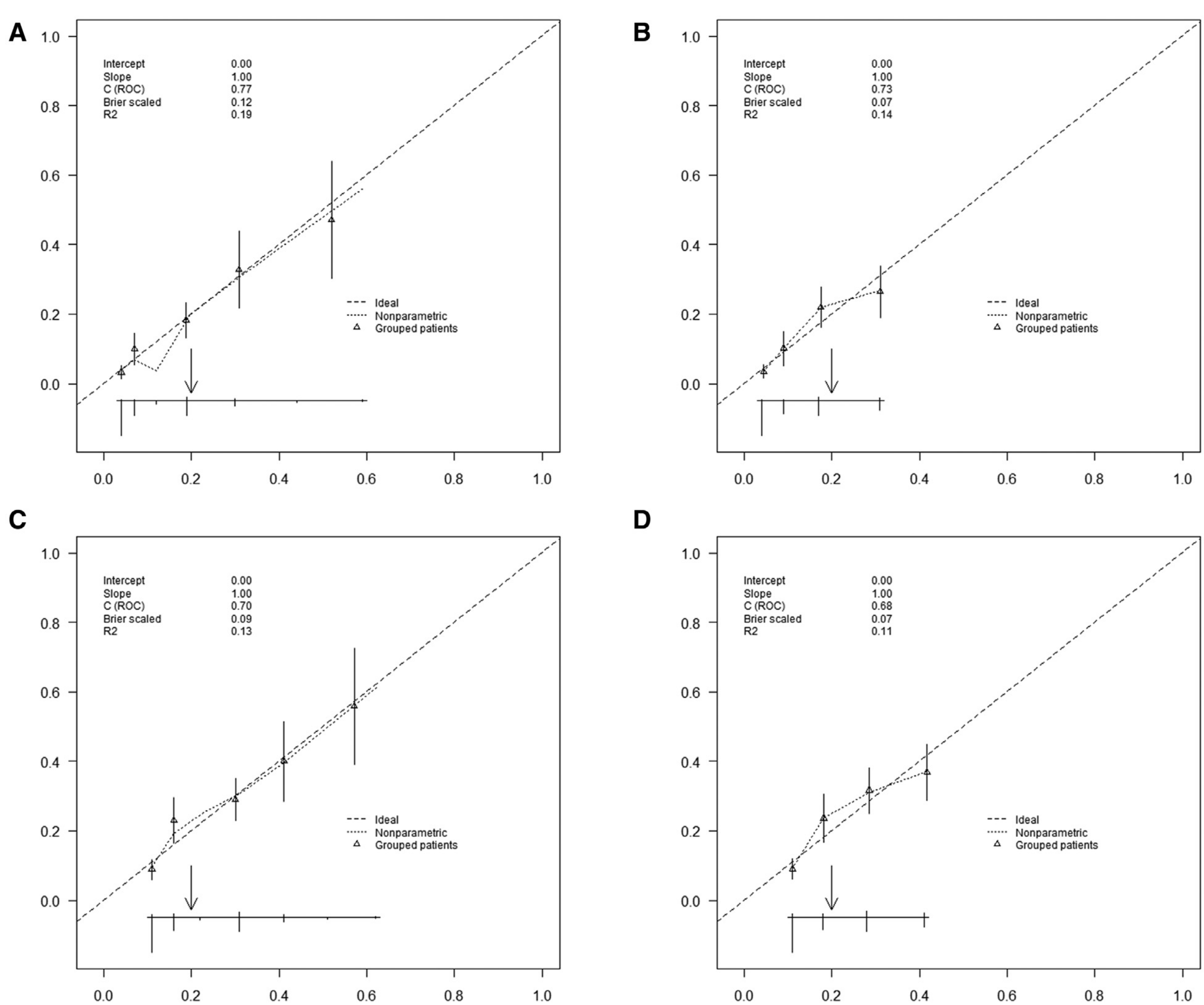

Fig. 2. Calibration plots depicting correlation between predicted cancer-specific survival (CSS) and actual CSS. (A) The COBRA score at 2 years. (B) The AJCC staing system at 2 years. (C) The COBRA score at 5 years. (D) The AJCC staging system at 5 years.

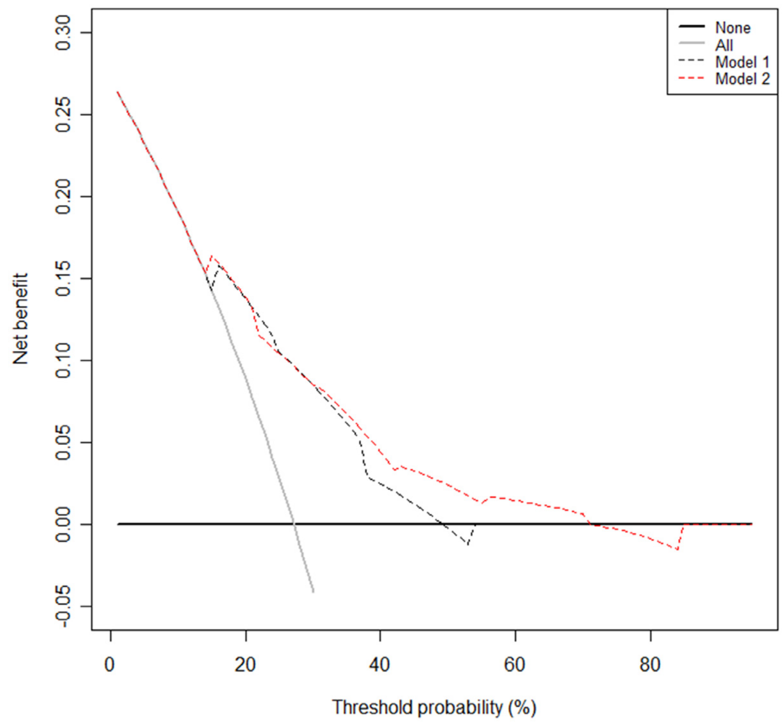

Fig. 3. Decision curve analysis for 5 years of cancer-specific survival. The y-axis measures net benefit calculated by summing benefits (true-positive findings) and subtracting harms (false-positive findings). *Straight line* has assumption that all patients will die. *Horizontal line* has assumption that no patient will die. *Dotted line* indicates net benefit using the new model. Model 1 = the AJCC staging system; Model 2 = the COBRA score.

4. Discussion

Although RC with PLND has been primarily used as the gold standard of care for nonmetastatic muscle invasive and high-risk nonmuscle invasive UCB, UCB generally presents diverse clinical behaviors in terms of postsurgical outcomes, including recurrence, metastases, and survival depending on various prognostic factors and the presence of occult micrometastasis at initial diagnosis [3,4,23,24]. Considering these diverse behavioral features of UCB, appropriate prediction on postsurgical outcomes may aid in postoperative patient counseling and clinical decision-making regarding the need of additional treatments, including neoadjuvant and/or adjuvant chemotherapy and radiotherapy [5−7].

The AJCC staging system is based on pathological tumor (pT) and LN (pN) stages. It is currently used as the gold standard predictive tool to estimate the risk of recurrence and survival after RC for UCB [8,9]. Although both pT and pN stages are established predictors of post-RC outcomes [2], classification of LN status (pN1, N2, N3) in the AJCC staging system does not accurately reflect different outcomes after RC in patients with LN-positive UCB, indicating limited prognostic significance of AJCC pN stages [10]. Therefore, combinations with other clinical (i.e., age, gender, the use of perioperative chemotherapy, and adjuvant radiotherapy) and pathological (i.e., tumor grade, tumor histology, carcinoma in situ, lymphovascular invasion (LVI), positive surgical margin, and LN density) factors as well as pT and pN stages might improve its predictive accuracy of prognosis [3,23−25]. To date, several nomograms that incorporate multivariable prognostic factors have been developed to predict individualized risk of recurrence or survival outcomes after RC, demonstrating improved predictive accuracy over the AJCC staging system [11−14]. Besides, external validation studies for these nomograms have documented adequate discrimination and calibration with better predication accuracy than the AJCC staging system [15−17]. However, the application of these nomograms in real clinical practice is limited owing to differences in the number and type of variables and end-points included in each nomogram. Therefore, more simplified model predicting survival after RC for UCB is needed.

The COBRA score was developed based on a total of 14,828 UCB patients who underwent RC with PLND identified with 18 Surveillance, Epidemiology, and End Results registries. Scores ranging from 0 to 7 were created by combining each point assigned to final variables including age, tumor stage, and LN density (Supplemental Table 1). The developed COBRA score was also internally validated using 19,362 patients from National Cancer Data Base. In summary, the COBRA score offers a straightforward, simplified risk stratification that can accurately predict the risk of cancer-specific death after RC for UCB [18]. Old age (≥80 years) included in this model was emphasized as an independent predictor of worse survival outcomes after RC in a previous study [26]. The prognostic value of LN density on post-RC survival outcomes has already been confirmed in prior studies [27,28]. Besides, in a recent study, LN density showed better prognostic value over the AJCC staging system in patients with LN-positive UCB [29].

To the best of our knowledge, our study is the first external validation of the COBRA score in a contemporary single institutional cohort of UCB patients. Unlike survival analysis results in the original development cohort, risk group stratification by the COBRA score in our cohort showed no clear difference in CSS among groups (Fig. 1B). This conflicting result can occur because of the insufficient number of patients assigned to each COBRA score group as followings; 29, 17, and 17 patients in the COBRA score 2, 5 and 6 group, respectively. These small groups could be a major contributor to weak statistical power, and as a result, there was no significant difference in CSS according to each COBRA score. Besides, there are several reasons for the COBRA score to underperform in an external cohort. First, the performance of predictive model generally tends to be lower when external validation is conducted due to exclusion of other relevant prognostic factors such as tumor grade, LVI, and positive surgical margin which may contribute to accurate risk assessment by improving results of analyses if they are included in the model [3,11,12,23]. Second, the level of model complexity should be taken into account. The COBRA score as a simplified model incorporating only 3 variables is easier to use in clinical practices. However, it might offer suboptimal accurate information. Lastly, external application of the predictive model may be hampered by the influence of an uneven distribution of unknown prognostic factors (i.e., the use of chemotherapy or radiotherapy) and differences in ethnic or genetic backgrounds, treatment strategies, and follow-up protocols between the development cohort and validation cohort. Although the COBRA score did not provide completely accurate risk stratification for CSS in the current cohort, the COBRA score showed a modest level of discrimination (Table 3), better calibration (Fig. 2), and meaningful clinical net benefits (Fig. 3) in terms of CSS prediction than the AJCC staging system. Therefore, our results may provide an additional evidence for the use of the COBRA score as a potential simplified prediction tool in other UCB patient cohort.

The present study is limited by several factors. First, data were collected and managed for all analyses with retrospective manner. This might lead to inherent bias as the main drawback of our study. Second, although limited variables (age, tumor stage, and LN density) were only selected for external validation of the COBRA score, further improvements of the predictive model could have been achieved by incorporating other significant clinico-pathological variables that were not exactly identified in the current data, such as surgical margin status, LVI, histologic variant of UC, and perioperative additional treatment (neoadjuvant and/or adjuvant chemotherapy). Next, given that the current validation cohort consisted of RC and PLND patients performed by several surgeons in a single institution during more than 2 decades, there might have been potential differences in RC skills or extent and quality of PLND among surgeons and clinical decision-making related to the performance of additional treatments such as neoadjuvant and/or adjuvant chemotherapy and radiotherapy. Because these differences could not be adjusted in a retrospective setting, these factors might affect the performance of the COBRA score for predicting CSS in our cohort. Finally, a DCA was used to assess and compare the clinical usefulness of each prediction model. A limitation of DCA is that the concept of net benefit is difficult to be clinically applied since it is a mathematically derived definition and may not aid in selecting an acceptable probability threshold [22]. Therefore, our results do not always imply that the COBRA score may be a better predictive tool over the AJCC staging system for the prediction of CSS after RC when applying in real clinical practice.

5. Conclusions

We conducted the first external validation of the COBRA score in an Asian patient cohort. In the present analysis, the COBRA score did not provide completely accurate risk stratification for CSS. However, the COBRA score showed a modest level of discrimination, adequate calibration, and better clinical benefits than the AJCC staging system in terms of CSS prediction. Therefore, our results suggest the COBRA score may serve as another potential predictive tool for predicting CSS after RC in Asian UCB patients. Future studies should focus on prospective comparative trials to investigate whether the COBRA score can improve patient care and treatment outcomes when it is applied in real clinical practice.

Author contributions

Conception and design: Hyung Suk kim, Ja Hyeon Ku, Cheol Kwak, Hyeon Hoe Kim; Data acquisition: Hyung Suk Kim, Ja Hyeon Ku; Data analysis and interpretation: Ja Hyen Ku, Hyung Suk Kim; Manuscript drafting: Hyung Suk Kim, Ja Hyeon Ku; Critical revision of the manuscript for scientific and factual content: Ja Hyeon Ku, Hyung Suk Kim; Statistical analysis: Hyung Suk Kim, Ja Hyeon Ku; Supervision: Hyung Suk Kim, Ja Hyeon Ku, Cheol Kwak, Hyeon Hoe Kim.

Conflict of interest

The authors declare no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2019.03.006.

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