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Original Article

The impact of chemotherapy-naïve open radical cystectomy delay and perioperative transfusion on the recurrence-free survival: A perioperative parameters-based nomogram

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Abstract *Objective:* To develop and internally validate a nomogram to predict recurrence-free survival (RFS) including the time to radical cystectomy (RC) and perioperative blood transfusion (PBT) as potential predictors.
Methods: Patients who underwent open RC and ileal conduit between January 1996 to December 2016 were split into developing (n=948) and validating (n=237) cohorts. The time to radical cystectomy (TTC) was defined as the interval between the onset of symptoms and RC. The regression coefficients of the independent predictors obtained by Cox regression were used to construct the nomogram. Discrimination, validation, and clinical usefulness in the validation cohort were assessed by the area under the curve, the calibration plot, and decision curve analysis.
Results: In the developing dataset, the 1-, 5-, and 10-year RFS were 83.0%, 47.2%, and 44.4%, respectively. On multivariate analysis, independent predictors were TTC (hazards ratio [HR] 1.07, 95% confidence interval [CI] 1.05–1.08, p<0.001), PBT (one unit: HR 1.40, 95% CI 1.03–1.90, p=0.03; two or more units: HR 1.72, 95% CI 1.29–2.29, p<0.001), bilateral hydronephrosis (HR 1.54, 95% CI 1.21–1.97, p<0.001), squamous cell carcinoma (HR 0.60, 95% CI 0.45–0.81, p=0.001), pT3-T4 (HR 1.77, 95% CI 1.41–2.22, p<0.001), lymph node status (HR 1.53, 95% CI 1.21–1.95, p<0.001), and lymphovascular invasion (HR 1.28, 95% CI 1.01–1.62, p=0.044). The areas under the curve in the validation dataset were 79.3%, 69.6%, and 76.2%, for 1-, 5-, and 10-year RFS, respectively. Calibration plots showed considerable correspondence between predicted and actual survival probabilities. The decision curve analysis revealed a better net benefit of the nomogram.

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Conclusion: A nomogram with good discrimination, validation, and clinical utility was constructed utilizing TTC and PBT in addition to standard pathological criteria.

1. Introduction

Radical cystectomy (RC) with urinary diversion is the standard treatment option for muscle-invasive and recurrent high-risk non-muscle-invasive bladder cancer. Various nomograms have been developed to calculate the probabilities of morbidity, mortality, and recurrence-free survival (RFS) after RC, which can be used pre- or post-operatively [1]. Various predictors included age, gender, marital status, comorbidities, thrombocytosis, hemoglobin, C-reactive protein level, pathological tumor stage (pT), lymph node (status, number, and density), concomitant carcinoma *in situ*, lymphovascular invasion (LVI), surgical margin, neoadjuvant chemotherapy (NAC), adjuvant chemotherapy, biomarkers (*e.g.*, p53 and pRB), gene expression and genetic markers, smoking, and the presence of hydronephrosis [1–5].

Nevertheless, an important factor has been recently identified to play a crucial role in cancer-related outcomes: the delay time to RC [6,7]. This delay varies depending on the gender, associated comorbidities, the reluctance to treatment, the nature of the health care system, the receipt of NAC, living in a high-poverty neighborhood or nonmetropolitan areas, and those of low income and education [8–11]. More importantly, the current state of the COVID-19 pandemic doubtlessly increased the burden on the medical service providers and potentially could lead to further delay [12].

Previous reports have described the impact of delay on cancer-specific outcomes [8,13–15]. Currently, the European Association of Urology guidelines have recommended a delay of no more than 12 weeks [12]. Nevertheless, a recent systematic review found heterogeneity among the studies regarding the start time of delay, the use of different cut-off values to define whether the patient is delayed or not, and the lack of describing the delay since having experienced the first symptom [11]. In addition, the review has suggested certain time points to be implemented to uniform the description of delay.

Additional clinical factors that were significantly associated with worse RC outcomes included thrombocytosis, hemoglobin level, and blood transfusion [16–19]. The combination of all potential non-pathological predictors has not been previously reported. Herein, we opted for developing a nomogram that involves the time factor and other clinical factors in a large cohort of patients who underwent RC.

2. Patients and methods

2.1. Design

From January 1996 to December 2016, patients who underwent chemotherapy-naïve open RC and ileal conduit for muscle-invasive bladder cancer were reviewed in the tertiary referral center (Urology and Nephrology Center, Mansoura University, Egypt). The protocol of the study was approved by the institutional review board and the local ethical committee (MS/16.04.64) with patient consents waived because of the retrospective nature of the study. Exclusion criteria included patients who underwent palliative cystectomy ($n=136$) and those with missed relevant data ($n=56$).

2.2. Measurements

Data on demographics, operative, and pathological details were recorded for each patient in an electronic database with a permission obtained to retrieve the data. Preoperative renal function was calculated by the modification of diet in renal disease equation, and the associated comorbidities by the Charlson Comorbidity Index. Anemia was defined based on the World Health Organization recommendations as to the baseline hemoglobin level of less than 13 g/dL and less than 12 g/dL for males and females, respectively. Perioperative blood transfusion (PBT) was recorded as the number of packed red blood cells given intra- or post-operatively. The platelet count was described as a continuous variable and a categorical variable with thrombocytosis was defined as more than 400×10^9/L. Pathological data included pT, lymph node status, and the presence of LVI. Histological cell types were described based on the three main categories: urothelial carcinoma, squamous cell carcinoma, and adenocarcinoma. Micropapillary, small cell carcinoma, lymphoepithelioma-like, and other rare histopathological subtypes were grouped because of the limited number of each.

2.3. Intervention

Included patients underwent open RC with bilateral pelvic lymphadenectomy to the level of common iliac arteries followed by urinary diversion. The early recovery protocol after surgery was not adopted in this cohort. Postoperative complications were graded according to the modified Clavien-Dindo grading system with Grades III-IV considered high-grade. Postoperatively, patients were scheduled for life-long follow-up in a dedicated clinic, every 3 months in the first year and then every 6 months thereafter. None of our patients received NAC during the study period.

2.4. Study outcome

The primary outcome of the study was to determine the impact of the time interval from the onset of symptoms to RC on RFS. The time to radical cystectomy (TTC) was defined as the duration between the time of the

development of the first symptom that drives medical consultation and the date of RC and was described in weeks. For patients with incidentally discovered tumors or those with previous transurethral resection of bladder tumor, the TTC was determined based on the date of cystoscopy during which an invasive disease was diagnosed. In addition, the impact of PBT, preoperative anemia, and platelet count was explored. RFS was defined based on the date the patient developed either local recurrence or distant metastasis obtained by computed tomography urography, magnetic resonance imaging, and/or bone scan.

2.5. Statistical analysis

The data were split into nomogram developing (80%) and validating (20%) datasets. Continuous variables are presented as mean with standard deviation (SD) or median with interquartile range (IQR) based on the parametric distribution and compared using the student *t*-test or Mann-Whitney *U* test, respectively. Categorical variables are presented as numbers and percentages and compared using the Chi-squared test. Survival was evaluated using Kaplan-Meier curves, and median values were compared using log-rank tests. Univariate Cox regression analysis was performed to identify significant predictors associated with RFS and then used to construct the multivariable Cox proportional regression model.

Coefficients of the independent predictors were used to construct a nomogram. Discrimination of the nomogram was examined using the area under the curve (AUC). Internal validation was performed using bootstrapped resampling with 100 iterations to calculate the AUC at 1-year, 5-year, and 10-year survival points. Calibration plots were drawn after bootstrapping in the developing dataset and after the application of the nomogram on the validating dataset at the same time points. Decision curve analysis (DCA) was performed to reveal the clinical utility of the nomogram whereas the net benefit refers to the difference between true and false positives divided by the sample size. DCA was performed for both the developing and validating datasets at 1-year, 5-year, and 10-year survival points. Statistical analysis was performed using SPSS statistics for Windows, version 25.0. (IBM Corp, Armonk, NY, USA) and R programming language environment version 3.6.3 (http://www.r-project.org) via the caret, rms, survival, and riskRegression packages. DCA was plotted using the stdca function for the Cox regression model (http://decisioncurveanalysis.org).

3. Results

3.1. Demographics and histopathological characteristics

A total of 948 patients were included in the developing cohort and 237 patients in the validation cohort. There was no significant difference between both groups regarding the demographics and clinicopathological criteria (Table 1). In total, the median TTC was 12 (IQR 4—12) weeks. Local recurrence and distant metastasis occurred in 314 (26.5%) and 262 (22.1%) patients over a median of 22 (IQR 9—36) months and 16 (IQR 7.7—28) months, respectively. The median follow-up was 31 (IQR 11—72) months.

3.2. Predictors of RFS

The 1-, 5-, and 10-year RFS were 83.0%, 47.2%, and 44.4% in the developing dataset, and 83.0%, 50.0%, and 47.0% in the validation cohort, respectively. On univariate Cox regression, older patient age, baseline anemia, longer TTC, PBT, the presence of bilateral hydronephrosis, squamous cell carcinoma histopathological type, pT (>pT2), lymph node positivity, and the presence of LVI were significantly associated with the RFS in the developing cohort. Thrombocytosis did not significantly associate with RFS on univariate analysis. On multivariate Cox regression, all apart from the presence of anemia and older age retained their independent significance. Table 2 demonstrates the results of univariate and multivariate COX regression. Kaplan-Meier survival curves are depicted for categorical variables (Fig. 1).

3.3. Nomogram development and validation

Standard pathological criteria (pT, lymph node positivity, histopathological cell type, and LVI) in addition to the TTC and the number of blood transfusions were utilized to construct a nomogram to predict 1-, 5-, and 10-year RFS in the developing cohort (Fig. 2). The probability of individual survival was calculated by adding the scores for each selected variable at a certain time point. The predictive ability of the nomogram to discriminate between patients with good and bad prognoses was investigated using the AUC. In the developing dataset, the 1-, 5- and 10-year AUCs were 76.6% (95% CI 72.7%—80.6%), 76.3% (95% CI 72.7%—79.9%), and 80.5% (95% CI 76.5%—84.5%), respectively. In addition, the AUCs in the validation dataset were 79.3% (95% CI 71.2%—87.4%), 69.6% (95% CI 61.4%—77.7%), and 76.2% (95% CI 67.1%—85.3%), respectively. Supplement Fig. 1 shows the AUC curve in the validation dataset for all time points.

Calibration plots were generated to validate the RFS predicted by the nomogram and the actual survival rate obtained using the Kaplan-Meier method. The predicted 1- and 5- and 10-year RFS closely corresponded with the actual survival in both the developing (supplementary Fig. 2) and validation datasets (Fig. 3). For investigating the clinical utility of the nomogram, the DCA shows that the nomogram had better net benefit than treating-all and treating-none for a range of threshold probabilities in both the developing (supplementary Fig. 2) and validating datasets (Fig. 3).

4. Discussion

In this study, a nomogram to estimate the probability of 1-, 5-, and 10-year RFS defined as radiological evidence of local recurrence and/or distant metastasis was developed and internally validated in a large cohort of patients who

Table 1 The differences between the developing and validating cohorts in patients who underwent radical cystectomy and ileal conduit.

Variable	Developing cohort (n=948)	Validating cohort (n=237)	Total (n=1185)	p-Value
Age, year	60.2±8.3	60.3±8.1	60.3±8.3	0.9
Albumin, g/dL	3.5±0.5	3.5±0.4	3.5±0.5	0.4
BMI, kg/m^2	27.6±4.8	27.9±5.2	27.6±4.9	0.4
Discharge eGFR, mL/min/1.73 m^2	65.2±24.9	65.5±24.3	65.3±24.8	0.8
Hb, g/dL	12.7±1.7	12.7±1.7	12.7±1.7	0.7
Platelet, x10^9/L	273.5±105.3	277.8±102.3	274.4±104.7	0.5
TTC, weeks	12 (4–12)	12 (4–12)	12 (4–12)	0.4
Anemia				0.6
No	441 (46.5)	115 (48.5)	556 (46.9)	
Yes	507 (53.5)	122 (51.5)	629 (53.1)	
PBT				0.4
No	182 (19.2)	42 (17.7)	224 (18.9)	
One	304 (32.1)	69 (29.1)	373 (31.5)	
Two or more	462 (48.7)	126 (53.2)	588 (49.6)	
Albumin				0.7
>3.5 g/dL	430 (45.4)	104 (43.9)	534 (45.1)	
≤3.5 g/dL	518 (54.6)	133 (56.1)	651 (54.9)	
BMI				0.7
<30 kg/m^2	658 (69.4)	161 (67.9)	819 (69.1)	
≥30 kg/m^2	290 (30.6)	76 (32.1)	366 (30.9)	
Diabetes mellitus				0.1
No	807 (85.1)	211 (89.0)	1018 (85.9)	
Yes	141 (14.9)	26 (11.0)	167 (14.1)	
Hypertension				0.4
No	759 (80.1)	184 (77.6)	943 (79.6)	
Yes	189 (19.9)	53 (22.4)	242 (20.4)	
CCI				0.1
I	767 (80.9)	184 (77.6)	951 (80.3)	
II	167 (17.6)	45 (19.0)	212 (17.9)	
III	14 (1.5)	8 (3.4)	22 (1.9)	
Gender				0.4
Male	758 (80.0)	195 (82.3)	953 (80.4)	
Female	190 (20.0)	42 (17.7)	232 (19.6)	
Smoking				0.2
Never	308 (32.5)	75 (31.6)	383 (32.3)	
Former	112 (11.8)	37 (15.6)	149 (12.6)	
Current	528 (55.7)	125 (52.7)	653 (55.1)	
Solitary kidney				0.8
No	756 (79.7)	191 (80.6)	947 (79.9)	
Yes	192 (20.3)	46 (19.4)	238 (20.1)	
Hydronephrosis				0.3
No	420 (44.3)	118 (49.8)	538 (45.4)	
Unilateral	312 (32.9)	72 (30.4)	384 (32.4)	
Bilateral	216 (22.8)	47 (19.8)	263 (22.2)	
History of NMIBC				0.04
No	842 (88.8)	198 (83.5)	1040 (87.8)	
Yes	106 (11.2)	39 (16.5)	145 (12.2)	
Cell type				0.4
UC	705 (74.4)	170 (71.7)	875 (73.8)	
SCC	175 (18.5)	53 (22.4)	228 (19.2)	
Adeno	33 (3.5)	8 (3.4)	41 (3.5)	
Others	35 (3.7)	6 (2.5)	41 (3.5)	
Positive lymph node				0.9
No	653 (68.9)	162 (68.4)	815 (68.8)	
Yes	295 (31.1)	75 (31.6)	370 (31.2)	

(*continued on next page*)

Table 1 (*continued*)

Variable	Developing cohort ($n=948$)	Validating cohort ($n=237$)	Total ($n=1185$)	p-Value
LVI				
No	640 (67.5)	165 (69.6)	805 (67.9)	0.5
Yes	308 (32.5)	72 (30.4)	380 (32.1)	
pT				
T1-T2	425 (44.8)	113 (47.7)	538 (45.4)	0.4
T3-T4	523 (55.2)	124 (52.3)	647 (54.6)	
High-grade POC				
No	874 (92.2)	214 (90.3)	1088 (91.8)	0.4
Yes	74 (7.8)	23 (9.7)	97 (8.2)	
Distant metastasis				
No	735 (77.5)	188 (79.3)	923 (77.9)	0.6
Yes	213 (22.5)	49 (20.7)	262 (22.1)	
Local recurrence				
No	690 (72.8)	181 (76.4)	871 (73.5)	0.3
Yes	258 (27.2)	56 (23.6)	314 (26.5)	
Follow-up, month	31.5 (11.0—72.2)	29 (11—72)	31 (11—72)	0.8

Adeno, adenocarcinoma; BMI, body mass index; CCI, Charlson Comorbidity Index; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; LVI, lymphovascular invasion; NMIBC, non-muscle-invasive bladder cancer; PBT, perioperative blood transfusion; POC, postoperative complication; SCC, squamous cell carcinoma; TTC, time to radical cystectomy; UC, urothelial carcinoma; pT, pathological tumor stage.
Note: values are presented as mean±standard deviation, median (interquartile range), and *n* (%).

underwent RC. Besides the standard pathological criteria, two important risk factors were added, the TTC and PBT.

In a recent meta-analysis, Russell et al. [11] examined 19 studies about the delay time to RC. The authors found great heterogeneity in the methodology used and consequently varying results. The definition of the start point was inconsistent and was the time of either the diagnosis, transurethral resection of bladder tumor, NAC, referral to the first treatment, or the date of the first clinic. Various causes might contribute to the delay before the diagnosis of bladder cancer. For instance, indirect referrals significantly contributed to the overall delay time. Santos et al. [20] have defined indirect referrals as patients having six or more visits with a general practitioner before their first urologist visit. In 1271 patients, the authors observed that 49% of women and 33% of men experienced indirect referral and were 1.29 times more likely to have poor survival. Likewise, patients from regions of lower income and education were more likely to experience a delay in a study including the National Cancer Database [9]. Furthermore, gender has been nominated as an important factor for the delay [9,10]. Therefore, the definition of delay starting from the time of diagnosis might underestimate the actual delay time, particularly when considering patients' denial and reluctance in seeking medical advice which is directly related to the level of education and socioeconomic status [8]. In addition, the use of the diagnosis time in this cohort was not feasible as many patients underwent cystoscopy and biopsy in nearby hospitals before referral, and the dates were not available because of the retrospective nature of our study.

In our healthcare system, most of our patients with hematuria are instantly referred to our institution for investigation. Hence, there is less likelihood of delay in treatment because of referrals or the nature of the healthcare system. On the other hand, the most important cause of delay is believed to be the delay in seeking medical advice since the onset of symptoms which is affected mainly by the level of education and income. Furthermore, our institutional policy is to perform transurethral resection of bladder tumor followed by RC in the same session which minimizes the impact of delay after the diagnosis on RC in our cohort. Therefore, we opted for defining the TTC as the duration from the onset of symptoms to RC in this cohort.

The European Association of Urology guidelines recommended no more than 12 weeks of delay between the time of diagnosis and RC [12]. We confirmed the same notion in our nomogram as, at this cut-off point, the score was approximately close to having pT4 disease and surpassed the positive lymph node status and the presence of LVI in the final histopathological specimens. Nevertheless, it is to be considered that the time of diagnosis was considered based on the approximate time the patient started symptomatizing as in our cohort the diagnosis was followed immediately by RC.

The relationship between PBT and the inferior cancer-related outcome is previously documented. Furrer et al. [16] have examined 885 patients who underwent RC, of which 23% received packed red blood cells and/or fresh frozen plasma after surgery. The authors found that PBT was an independent predictor of all-cause mortality and cancer-specific mortality. Likewise, in a retrospective review of 722 RC procedures, receiving either intraoperative or postoperative PBT was an independent predictor of RFS [18]. Moreover, the number of units was significantly associated with worse RFS as reported in the current nomogram. Additionally, PBT was linked to worse oncological outcomes in patients receiving NAC [21].

Various hypotheses have been postulated to clarify the association between PBT and worse RFS. PBT might exert immunosuppressive effects secondary to transfusion-related immune modulation [22]. This immune modulation results

Table 2 Univariate and multivariate Cox regression model for factors associated with independent predictors of cancer-specific survival in patients underwent radical cystectomy.

Variable	Univariate		Multivariate	
	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Age, 10 years[a]	1.18 (1.05–1.33)	0.005	–	–[b]
TTC, week	1.08 (1.06–1.09)	<0.001	1.07 (1.05–1.08)	<0.001
Anemia				
No	Reference	–	–	–
Yes	1.33 (1.10–1.62)	0.004	–	–[b]
PBT				0.001
No	Reference	–	–	
One	1.48 (1.09–2.00)	0.01	1.40 (1.03–1.90)	0.03
Two or more	1.82 (1.37–2.42)	<0.001	1.72 (1.29–2.29)	<0.001
Hydronephrosis				0.002
No	Reference	–	–	
Unilateral	1.30 (1.04–1.63)	0.02	1.20 (0.95–1.51)	0.1
Bilateral	1.73 (1.36–2.20)	<0.001	1.54 (1.21–1.97)	<0.001
Cell type				0.001
UC	Reference	–	–	
SCC	0.50 (0.38–0.66)	<0.001	0.60 (0.45–0.81)	0.001
Adeno	1.01 (0.60–1.69)	0.9	1.09 (0.64–1.84)	0.7
Others	1.17 (0.71–1.94)	0.5	1.58 (0.95–2.64)	0.07
Positive LN				
No	Reference	–	–	–
Yes	2.38 (1.95–2.91)	<0.001	1.53 (1.21–1.95)	<0.001
LVI				
No	Reference	–	–	–
Yes	2.21 (1.81–2.70)	<0.001	1.28 (1.01–1.62)	0.044
pT				
T1-T2	Reference	–	–	–
T3-T4	2.17 (1.78–2.66)	<0.001	1.77 (1.41–2.22)	<0.001

Adeno, adenocarcinoma; CI, confidence interval; HR, hazards ratio; LVI, lymphovascular invasion; LN, lymph node; PBT, perioperative blood transfusion number of packed red blood cells; SCC, squamous cell carcinoma; TTC, time to radical cystectomy; UC, urothelial carcinoma; pT, pathological tumor stage.

Note: univariate and multivariate analyses included only significant variables.

[a] HR was calculated per every 10-year increase of age.

[b] Stepwise approach excluded the non-significant variable from the final equation.

from the suppression of cytotoxic-T cells which couples with tumor manipulation to increase the likelihood of the release of circulating tumor cells and eventually distant metastasis. Furthermore, the impact of the locally advanced disease on the preoperative characteristics such as hemoglobin level and the presence of anemia might increase the likelihood of PBT and consequently is linked to worse RFS [23]. This is why it is recommended to control for preoperative anemia in the multivariate models assessing PBT [24]. In our nomogram, the presence of anemia, as defined by the World Health Organization recommendation, was significantly associated with worse RFS in the univariate but not in the multivariate analysis. Lastly, increased PBT rates might be linked to the excessive manipulation required during surgery to extirpate locally advanced tumors, consequently linking PBT to worse RFS [24].

It is not known yet whether the reduction of PBT would translate to better oncological outcomes with the increasing trend of the use of robotic-assisted RC (RARC) recently. A meta-analysis demonstrated that RARC was associated with a decreased blood loss and rate of blood transfusion (odds ratio: 0.31; $p<0.01$) when compared to open RC [25]. In a recent single center randomized clinical trial that was adjusted to detect the superiority of 50% transfusion rate reduction in RARC, the transfusion rate was 22% (RARC) versus 41% (open RC) ($p=0.04$) [26]. Nevertheless, the oncological outcomes have not been reported yet. In another recently published multicenter randomized clinical trial including 317 patients, there was no significant difference in cancer recurrence or overall mortality between both groups over a median of 18.4-month follow-up duration [27]. A potential explanation might be the unique nature of our center as it is mainly a tertiary referral and training center for RC. In our institution, trainee urologists are taking a large chance in performing the cases which might reflect on the increased percentage of blood transfusion despite being under direct supervision. In addition, we are receiving more advanced and complicated patients that denied surgery in nearby hospitals.

Our group has previously published a nomogram to predict 5-year RFS after RC [5]. Nevertheless, several differences need to be highlighted. Initially, the previous cohort

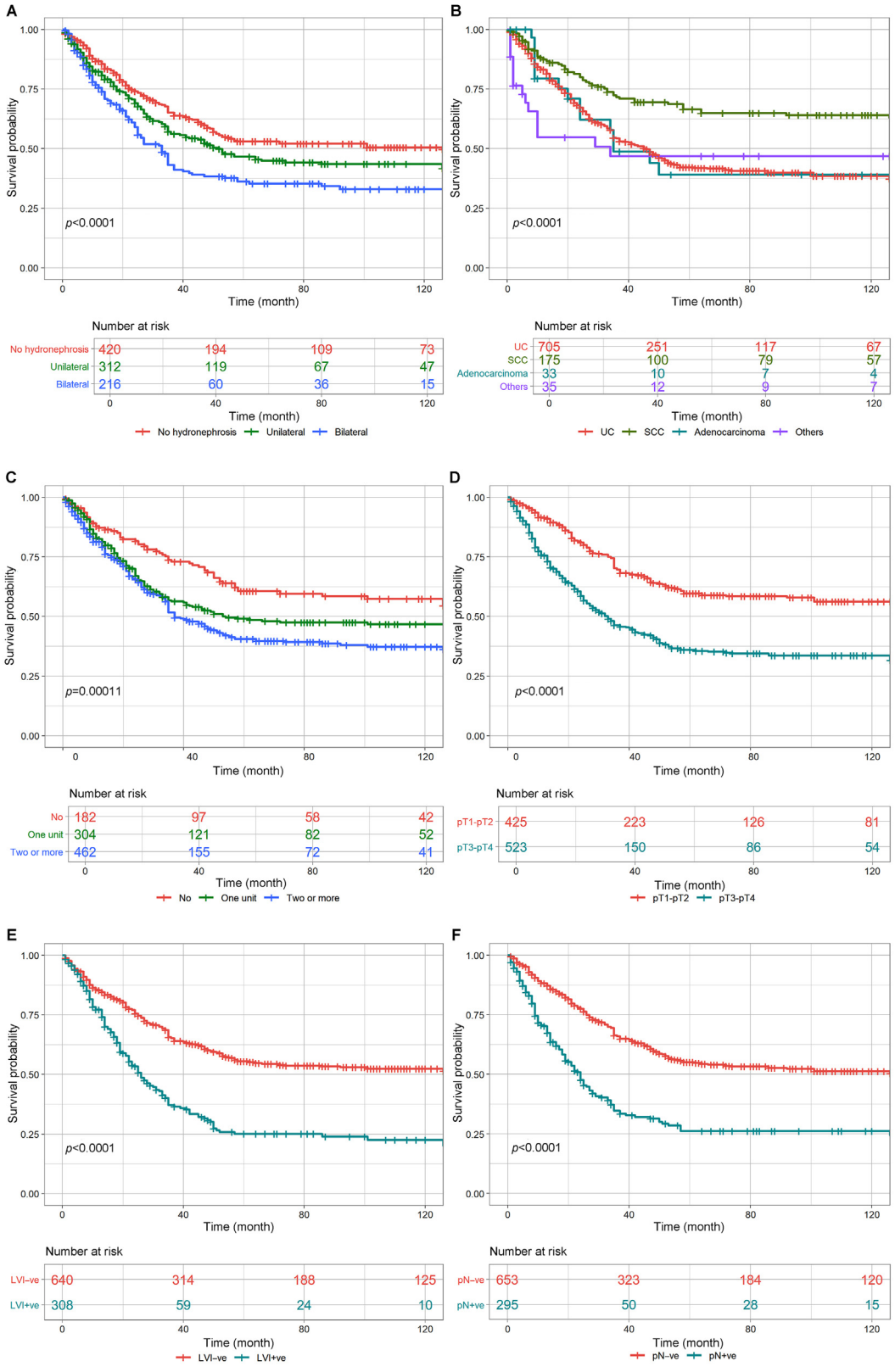

Figure 1 Kaplan-Meier survival curves for significant factors associated with recurrence-free survival in the developing set of patients who underwent radical cystectomy. (A) Hydronephrosis; (B) Histopathological diagnosis; (C) Perioperative blood transfusion (number of packed red blood cells transfused); (D) pT; (E) Lymphovascular invasion; (F) pN. *p*-Values were obtained by the log-rank test. UC, urothelial carcinoma; SCC, squamous cell carcinoma; pT, pathological tumor stage; pN, pathological lymph node; LVI−ve, negative lymphovascular invasion; LVI+ve, positive lymphovascular invasion; pN−ve, pathological negative lymph node; pN+ve, pathological positive lymph node.

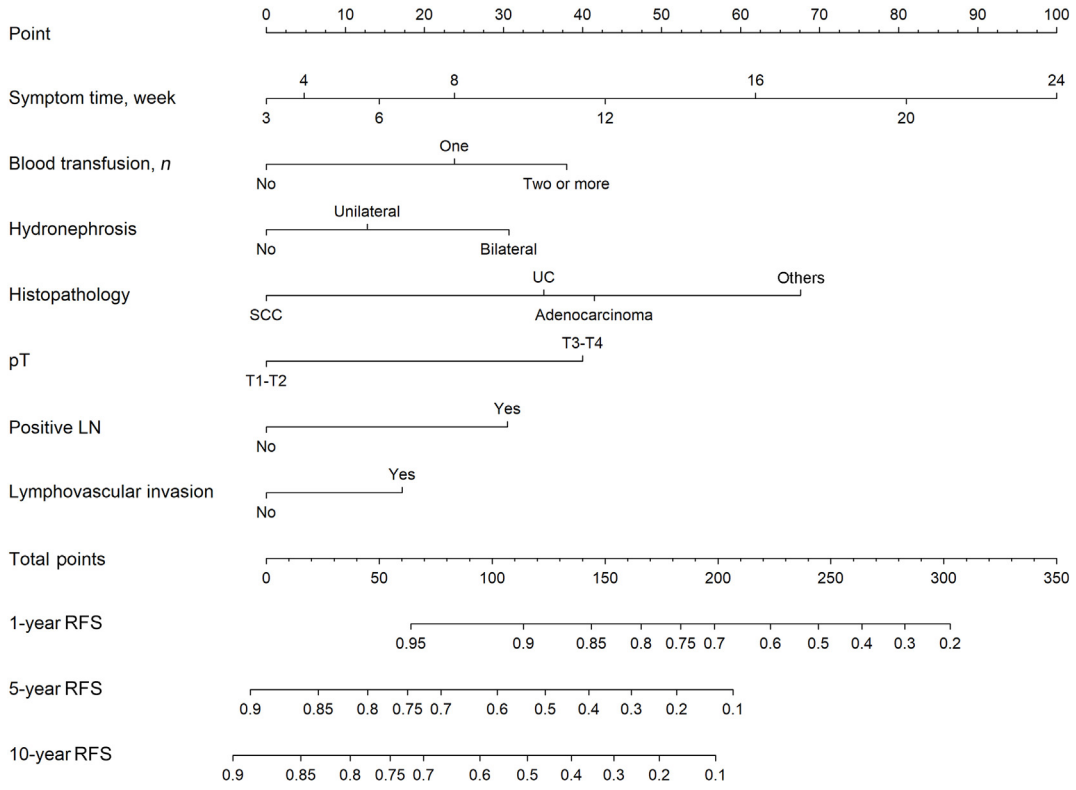

Figure 2 Nomogram to predict the probability of 1-, 5-, and 10-year RFS in patients who underwent radical cystectomy and ileal conduit. LN, lymph node; *n*, number of packed red blood cells; SCC, squamous cell carcinoma; pT, pathological tumor stage; RFS, recurrence-free survival.

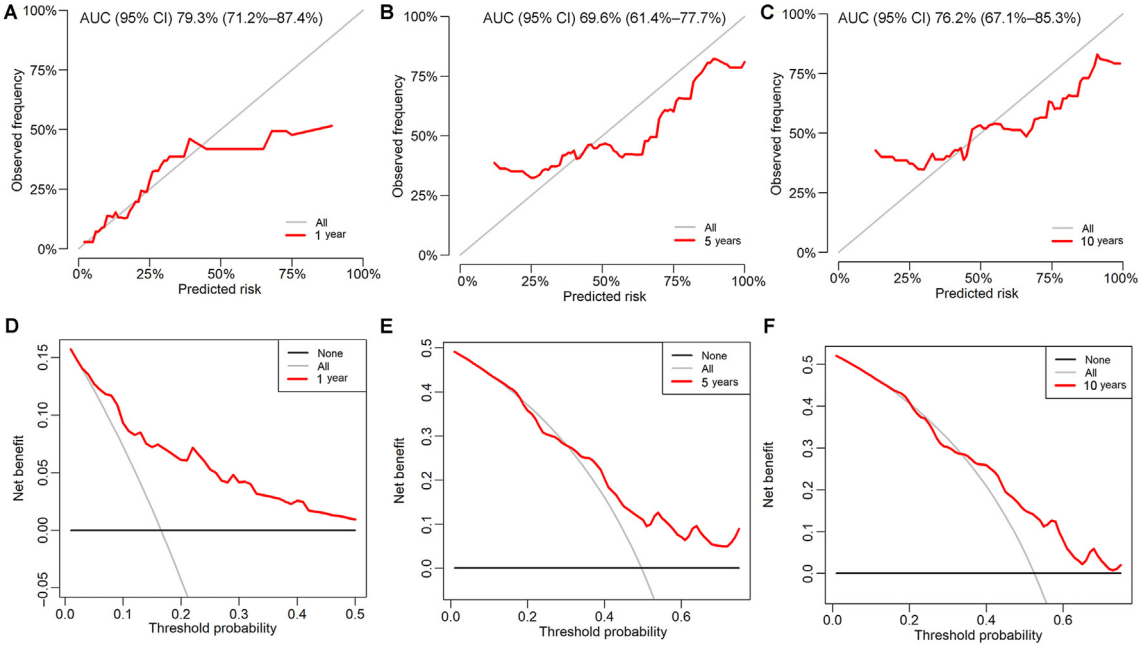

Figure 3 The validation dataset. (A–C) Calibration plot of the predicted probabilities of recurrence-free survival and the actual probabilities obtained by the Kaplan-Meier method: (A) 1 year; (B) 5 years; (C) 10 years. The closer the values to the diagonal line, the better the calibration. (D–F) Decision curve analysis depicting the net benefit against a range of threshold probabilities in comparison to treating-all or treating-none: (D) 1 year; (E) 5 years; (F) 10 years. AUC, area under the curve; CI, confidence interval.

included four types of urinary diversion compared to the current one which included only ileal conduit. Second, only histopathological criteria were included previously which is not similar to this study where we included TTC, PBT, and hydronephrosis. In the initial nomogram, histological cell types were not significantly associated with RFS on the univariate analysis compared to the current nomogram where it has become an independent predictor of the RFS. It is to be noted that there is a clinically significant time-dependent change in cancer etiology where squamous cell carcinoma/urothelial carcinoma ratio was 64%. In the current study, this ratio has decreased to 31% which might account for the difference in the impact of the histological cell type on the RFS.

We acknowledge that the addition of the TTC and PBT, which are potentially modifiable variables, might increase the stress on the surgeon and the health care system. The TTC is the sole property of the health care system and various non-modifiable factors might contribute to a longer waiting time such as multiple consultations and if the patient is to receive NAC. PBT largely depends on the local tumor stage, the subjective surgeon or anesthetist perception of the need for PBT depending on the patient hemodynamic status, and the patient surgical anatomy which is affected by the previous history of pelvic surgery or irradiation. In addition, there is no universal standardization of how to quantify the PBT or the optimal TTC cut-off value. Nevertheless, we believe that this piece of information should be clear to both the health care providers and the patients as a step to optimize the patient outcome.

Several limitations deserve to be mentioned in our study. Initially, no molecular or genetic biomarkers have been used in this nomogram which has been reported to improve the discrimination of the nomogram [1]. Nevertheless, biomarker data in our cohorts are not available for each patient and we aimed to use clinical parameters that are available for most of the patients. In addition, this is a single-center study that reflects our own patients' characteristics which are not identical to other patients of different demographics or ethnicity. Therefore, external validation is highly warranted for generalizability. We included only patients with ileal conduit in our cohort to control for the impact of urinary diversion on RFS. The choice of orthotopic neobladder depends mainly on the preoperative patients' characteristics which are evaluated in our predictive model. Consequently, we believe that the type of diversion would work as a confounding variable rather than a predictor. In a recent study comparing the type of urinary diversion on survival outcomes, the authors have found that a young man with early disease was likely to receive orthotopic neobladder and hence achieved a better survival [28]. However, validation in other types of urinary diversion will ensure the broader applicability of the model. Finally, the impact of chemotherapy on survival was not investigated. This is mainly because NAC has not been administered in our institution except in the last few years. In a recent study examining the trends in the treatment of muscle-invasive bladder cancer in Germany from 2006 to 2017, the combination therapy increased from 9% to 13% [29]. Another study from the USA showed that despite the increased use of NAC in their patients, there were worse survival outcomes in patients with extravesical and/or node-positive disease, which might be related to the use of NAC in pathologically advanced tumors [30]. This would certainly highlight the need to identify patients who might respond to NAC.

5. Conclusion

A nomogram including TTC and PBT in addition to standard pathological criteria is developed and internally validated to predict the probabilities of RFS after RC. This nomogram might aid in patient counseling and the planning of follow-up. Further studies are welcome to externally validate the nomogram.

Author contributions

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Conflicts of interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajur.2022.09.002.

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