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ORIGINAL ARTICLE

Immune-inflammatory-nutritional status predicts oncologic outcomes after radical cystectomy for urothelial carcinoma of bladder

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KEYWORDS
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Abstract
Objective: To perform the first investigation of the role of immune-inflammatory-nutritional status (INS) on oncological outcomes in patients undergoing open radical cystectomy (ORC) for urothelial carcinoma (UC).
Materials and Methods: The records of consecutive patients who underwent ORC for non-metastatic bladder cancer between 2009 and 2020 were retrospectively analyzed. Neoadjuvant chemotherapy, non-urothelial tumor biology, and absence of oncological follow-up were exclusion criteria. Systemic immune-inflammatory index (SII) and Prognostic Nutritional Index (PNI) values were calculated and optimal cut-off values for these were used to designate four subgroups: ''high SII-high PNI'', ''low SII-high PNI'', ''low SII-low PNI'', and ''high SII-low PNI''. The Low SII-high PNI INS group had best overall survival (OS) rate while the remainder were included in non-favorable INS group. Survival curves were constructed, and a multivariate Cox regression model was used for OS and recurrence-free survival (RFS).
Results: After exclusions, the final cohort size was 173 patients. The mean age was 64.31 ± 8.35 and median follow-up was 21 (IQR: 9-58) months. Optimal cut-off values for SII and PNI were 1216 and 47, respectively. The favorable INS group (low SII-high PNI, n = 89) had the best OS rate (62.9%). Multivariate Cox regression analysis indicated that non-favorable INS (n = 84) was a worse independent prognostic factor for OS (HR: 1.509, 95%CI: 1.104–3.145, p = 0.001) and RFS (HR: 1.285; 95%CI: 1.009–1.636, p = 0.042).
Conclusion: Preoperative assessment of INS may be a useful prognostic panel for OS and RFS in patients who had ORC for UC.
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PALABRAS CLAVE
Cáncer de vejiga;
Cistectomía radical;
IIS;
IPN;
Inmunidad inflamación;
Nutrición

El estado inmunológico-inflamatorio-nutricional predice los resultados oncológicos tras la cistectomía radical por carcinoma urotelial de vejiga

Resumen

Objetivo: Evaluar por primera vez el papel del estado inmunológico-inflamatorio-nutricional (EIIN) en los resultados oncológicos de pacientes sometidos a cistectomía radical abierta (CRA) por carcinoma urotelial (CU).

Materiales y métodos: Se analizaron retrospectivamente los registros de pacientes consecutivos sometidos a CRA por cáncer de vejiga no metastásico entre 2009 y 2020. La quimioterapia neoadyuvante, el tumor no urotelial y la ausencia de seguimiento oncológico fueron criterios de exclusión. Se calcularon los valores del índice de inmunidad-inflamación sistémica (IIS) y del índice pronóstico nutricional (IPN) y se utilizaron los valores de corte óptimos para estos, con el fin de designar cuatro subgrupos: ÏIS alto – IPN alto ; ÏIS bajo – IPN alto ; ÏIS bajo – IPN bajo ÿ ÏIS alto – IPN bajo . El grupo de EIIN con IIS bajo-IPN alto tuvo la mejor tasa de supervivencia global (SG), mientras que el resto se incluyó en el grupo de EIIN desfavorable. Se elaboraron curvas de supervivencia y se utilizó un modelo de regresión de Cox multivariante para la SG y la supervivencia libre de recidiva (SLR).

Resultados: Tras aplicar los criterios de exclusión, el tamaño final de la cohorte fue de 173 pacientes. La edad media fue de 64,31 ± 8,35 y la mediana de seguimiento fue de 21 (RIQ: 9-58) meses. Los valores de corte óptimos para IIS y IPN fueron 1216 y 47, respectivamente. El grupo de EIIN favorable (IIS bajo-IPN alto, n = 89) tuvo la mejor tasa de SG (62,9%). El análisis multivariante de regresión de Cox indicó que el EIIN desfavorable (n = 84) era un factor independiente de pronóstico para una SG peor (HR: 1,509; IC 95%: 1,104—3,145; p = 0,001) y la SLR (HR: 1,285; IC 95%: 1,009—1,636; p = 0,042).

Conclusión: La evaluación preoperatoria del EIIN puede constituir un panel útil para el pronóstico de la SG y la SLR en pacientes sometidos a CRA por CU.

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Introduction

In the United States, bladder cancer is the fourth most commonly diagnosed cancer in men,[1] and approximately 75% are non-muscle-invasive bladder cancer (NMIBC), including Ta, T1, and carcinoma in situ (CIS). Radical cystectomy with lymph node dissection is the standard treatment and is recommended to patients with bacillus Calmette-Guérin unresponsive high-risk NMIBC, to those who have very high-risk NMIBC, and to those with non-metastatic muscle-invasive bladder cancer (MIBC).[2] Although radical cystectomy provides a curative treatment modality, recurrence and disease-specific survival rates may vary depending on prognostic factors and markers.[3] Recent studies have shown a close link between oncologic outcomes after radical cystectomy and preoperative systemic immune-inflammatory and nutritional status.[4,5]

There is a complex counter-balance between tumor microenvironment and antitumor immunity. That is, although immune-based mechanisms are able to control cancer (tumor cytotoxic CD8 + T lymphocytes, etc.),[6] some inflammatory elements, such as neutrophil- and platelet-derived pro-inflammatory cytokines and chemokines, including transforming growth factor-β, may promote a shift of the balance favoring carcinogenesis.[7,8] Regarding immune-inflammation, an increased ratio of neutrophils to lymphocytes, usually involving a decreased lymphocyte count, is found to be correlated with increase of IL-6 and IL-8 in serum and upregulation of FoxP3 on tumor-infiltrating lymphocytes, and consequently result in inflammation-mediated tumoral progression in MIBC.[9] A meta-analysis reported that worse oncologic outcomes were associated with an increased ratio of platelet to lymphocytes in bladder cancer.[10] A definition of immune-inflammation is based on a formula utilizing platelet, neutrophil, and lymphocyte counts, and is known as the ''Systemic immune-inflammatory index (SII)''. A high SII has been associated with poor prognosis in patients undergoing surgery for NMIBC, MIBC, and upper tract urothelial carcinomas.[4,11–14] Therefore, it is generally considered that host immune-inflammatory status influences the bladder tumor microenvironment.

It is also known that poor nutritional status, also termed malnutrition, is likely to decrease host immune function and therefore, if present, may lead to worse oncological outcomes after radical cystectomy.[15,16] Proinflammatory cytokines may also cause cancer-related cachexia and hypoalbuminemia.[17] Another study reported a close association between poor oncologic outcome in urothelial cancer and hypoalbuminemia.[18] Several studies have shown that the Prognostic Nutritional Index (PNI), which is generally accepted to reflect the nutritional status of the patient, and is derived from albumin concentrations and lymphocyte counts, is directly associated with oncological survival and predicts cystectomy related complications.[5,19,20]

Taken together, a combination of SII and PNI may provide prognostic prediction for patients treated with radical cystectomy. To date, there have been no reports about the impact of the combination of both immune-inflammatory and nutritional status on oncological outcomes in patients undergoing open radical cystectomy (ORC) for urothelial carcinoma (UC). We therefore used and sought this approach, which we refer to as ''immune-inflammatory-nutritional status (INS)'', which used a combination of SII and PNI, for the first time in the prediction of oncological outcomes in patients who underwent ORC for UC.

Materials and methods

Patients

We retrospectively reviewed the data of 206 consecutive patients who did not receive neoadjuvant chemotherapy and underwent radical cystectomy at a tertiary academic referral center between 2009 and 2020. Exclusion criteria for this study were as follows: presence of non-urothelial tumor biology; and the absence of oncological follow-up (less than 1 month). The demographic characteristics, histopathological findings on radical cystectomy specimens, laboratory data, and oncologic outcomes were obtained from the hospital records and analyzed. The demographic and clinical variables reviewed were age, gender, smoking history, elapsed time from transurethral resection (TUR) to cystectomy, clinical tumor stage (cT), and non-age adjusted Charlson Comorbidity Index (CCI). Pathological data included concomitant CIS, pT, lymph node (pN) involvement, surgical margin status, variant histology of UC, and the number of nodes removed. The localization of the positive surgical margin was noted as urethra, ureter, or soft-tissue.[21] Surgical data items included concomitant nephroureterectomy, concomitant urethrectomy, and urinary diversion type. Concomitant urethrectomy was performed in patients with positive urethral frozen section assessment or high-risk for urethral recurrence (multifocality, prostatic urethral involvement, bladder neck involvement, carcinoma in situ). After radical cystectomy, adjuvant chemotherapy was recommended to the patients with pT3-4 and/or pN + disease. SII and PNI were calculated as index data and the timing and occurrence of recurrence and death during follow-up were extracted as oncological data. The status of disease recurrence and death were accessed using hospital records and direct contact. The eligibility criteria for SII and PNI were that their analysis should be made within 30 days preoperatively. SII was calculated using the following formula: neutrophil count (10^9/L) x platelet count (10^9/L) / lymphocyte count (10^9/L).[22] PNI was calculated with the following formula described by Onodera et al.: (10 $\times$ albumin [g/dL]) + (0.005 x total lymphocyte counts [per mm^3]).[23]

- The study was approved by the local ethics committee (Approval number: KÜGOKAEK-2022/03.20). The informed and signed consent has been obtained from all patients prior to surgery.

Cut-off determination, patient stratification, and statistical analysis

To determine the optimal cut-off levels for SII and PNI, X tile® software (version 3.6.1., Yale University) was used.[24] All of the patients were individually evaluated as having low or high SII and PNI with reference to the determined cut-off values. The patients were then categorized into the following INS groups: (1) high SII-high PNI, (2) low SII-high PNI, (3) low SII-low PNI, and (4) high SII-low PNI. Among these four INS groups, the one with the best overall survival (OS) by Kaplan–Meier analysis was designated as the ''favorable'' INS group. The other three groupings were combined into a single ''non-favorable'' group.

Kolmogorov-Smirnov test was used to determine the normality of the numeric data. Mean and median values are reported with standard deviation (SD) and interquartile range (IQR), respectively. The Spearman correlation test was used for correlation between SII and PNI. The demographic, pathological, surgical, index, and oncological data were compared between favorable and non-favorable INS groups using the Student's t-test, Mann–Whitney U test, and Chi-square test, appropriately. For OS calculation, time from surgery to the date of any cause of death (in months) was used, while the time from surgery to the date of any disease recurrence (in months) was used for the calculation of recurrence-free survival (RFS). The region of disease recurrence was described as follows: cystectomy bed and pelvic lymph nodes as locoregional recurrence; non-regional lymph nodes, bones, and visceral organs as distant recurrence; urethra and upper urinary tract as urinary tract recurrence; and more than one region as multi-site recurrence. Additionally, INS-based survival analysis and significance calculation for OS and RFS was performed by the Kaplan–Meier method and log-rank test. When the Kaplan–Meier method was performed for more than two groups, Bonferroni correction was used to adjust for multiple comparisons (low SII-low PNI vs. low SII-high PNI vs. high-SII low-PNI vs. high-SII high-PNI) and for example, the Bonferroni-corrected significance between these four groups was accepted as less than 0.5/4 = 0.0125. Then, using univariable COX regression analysis, age ($\geq$65 vs. <65), non-adjusted CCI (>2 vs. $\leq$2), gender (female vs. male), smoking history (yes vs. no), the time from TUR to cystectomy (>3months vs. $\leq$3 months), pT stage (pT_{3-4} vs. pT_{0-2}), pN involvement (positive vs. negative), concomitant CIS (presence vs. absence), variant histology (presence vs. absence), and INS (non-favorable vs. favorable) were investigated as possible prognostic factors for OS and RFS. For OS and RFS, multivariate COX regression analysis was performed by using the significant variables of the univariate analysis for the determination of the independent prognostic factors. To minimize the risk of bias, it was paid attention that the multivariable models did not exceed the role of ''10 events per variable'' in the OS and RFS setting. The discrimination ability of the COX regression model was assessed with Harrell's Concordance Index (C-index). In pairwise comparisons and Cox regression analysis, all *p*-values less than 0.05 were considered as statistically significant. G*power software Version 3.1.9.6 was used to evaluate the statistical power of our study. Post-hoc power analysis was found as 84.4%.

Subgroup analysis

To assess the impact of INS on OS and RFS in a more homogenous population, finally, the pT and pN factors that were identified as independent prognostic factors for both OS and RFS, and also whether to be received the adjuvant chemotherapy were distinguished for subgroup analysis. These factors were categorically allocated (pN- vs. pN+; pT0-2 vs. pT3-4; not receiving adjuvant chemotherapy vs. receiving adjuvant chemotherapy) and subgroup analyses were subsequently performed according to INS by Kaplan–Meier methods.

Results

The final number of patients included in the study was 173 and 85.5% of them were male. The mean age was 64.31 $\pm$ 8.35 years. Pathological T3 and higher stage patients (54.9%) constituted the majority of the patients in this study. Eleven (6.3%) patients had pT0 disease. The mean number of lymph nodes removed was 21.3 $\pm$ 10.0. Variant histology of urothelial cancer was present in 37 (21.4%) patients (27 squamous, 5 sarcomatoid, 3 micropapillary, 1 nested, and 1 plasmacytoid). The presence of a positive surgical margin was noted in 8 (4.6%) patients' pathology reports (two patients at the level of ureter, one patient at the level of urethra, and five patients at the level of soft-tissue). In some patients concomitant radical nephroureterectomy (n = 16) or urethrectomy (n = 14) was performed. The majority of the patients (n = 162, 93.6%) had undergone ileal loop urinary diversion, while a continent urinary diversion was performed in 9 (5.2%). Of the patients, 64 (37.0%) received adjuvant chemotherapy. In a median follow-up of 21 months (9–58), the death and recurrence rates were 48.0% (83/173) and 40.5% (70/173), respectively. The recurrence sites were locoregional-only in 10 patients, distant-only in 40 patients, multi-site in 17 patients, and urinary tract-only in 3 patients.

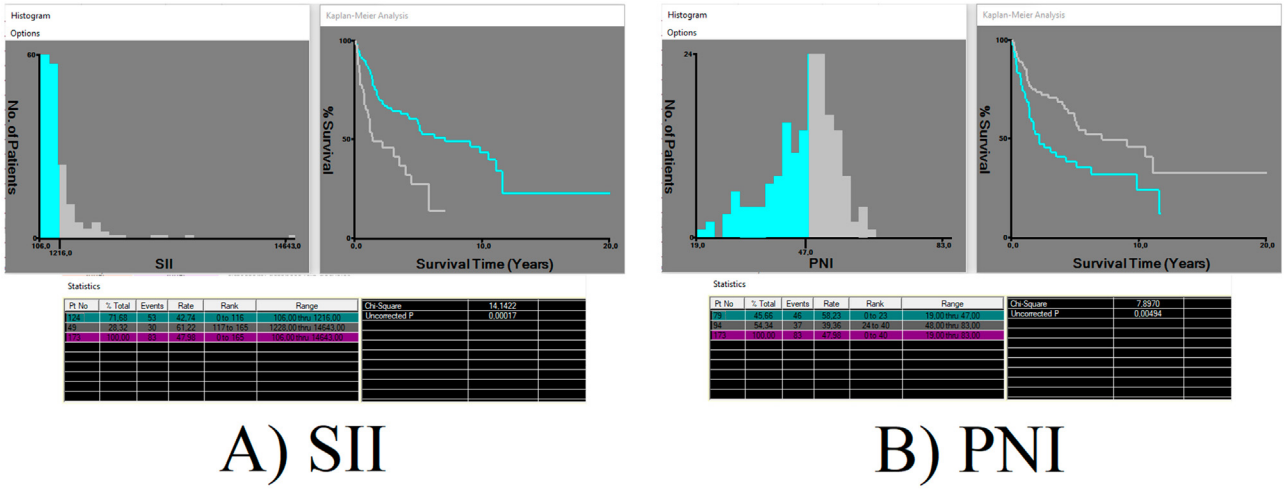


Figure 1 (A) The optimal cut-off levels of SII and (B) PNI were determined using **X tile**® software

Median SII and mean PNI levels were 795 (469–1373) and 46.93 ± 9.12, respectively. Spearman correlation analysis showed that there was a significant inverse relationship between SII and PNI (p < 0.001, r= -0.568). Optimal cut-off levels were determined as 1,216 for SII (low ≤1,216 vs. high >1,216) and 47 for PNI (low ≤47 vs. high >47). Of the whole cohort, the 124 patients with low SII and 94 patients with high PNI had statistically significantly better OS (Fig. 1). The OS rates of the patients with, low SII-high PNI (n = 89), high SII-low PNI (n = 38), low SII-low PNI (n = 34), and high SII-high PNI (n = 12) were, 62.9%, 44.7%, 41.2%, and 25%, respectively. In pairwise comparison, low SII-high PNI had significantly better OS compared with high SII-low PNI (log-rank p = 0.001) and the high SII-high PNI (log-rank p = 0.007) INS groups. However, despite poorer OS rates in low SII-low PNI compared with low SII-high PNI patients, this difference did not reach the level of significance (log-rank p = 0.095, Fig. 2).

As described in the methods section, we chose the low SII-high PNI as favorable INS group (n = 89) because this group had the best OS rate, and the remainder were categorized into one non-favorable INS group (n = 84). There was no statistically significant difference in terms of the demographic, pathological, and surgical data between favorable and non-favorable INS groups. Regarding the follow-up oncological data, the overall death rate in the non-favorable (59.5%) INS group was higher than the favorable (37.1%) INS group (p < 0.05). The recurrence of disease was observed in 34.8% (31/89) of the favorable and in 46.4% (39/84) of the non-favorable INS groups, whereas the recurrence rates and sites were not statistically different. The detailed patient characteristics are presented in Table 1.

According to Kaplan–Meier curve estimations, favorable and non-favorable INS groups had 77.5% and 55.9% 2-year, and 75.3% and 50.0% 3-year OS rates (p = 0.001), and similarly favorable and non-favorable INS groups had 77.5% and 59.6% 2-year, and 74.2% and 58.3% 3-year RFS rates (p = 0.010), respectively. Thus, as demonstrated in Fig. 3, the favorable INS group had significantly better OS and RFS rates than the non-favorable INS group.

Age, interval time between TUR and cystectomy, variant histology, pT stage, pN status, and INS were statistically significantly associated with OS in univariate Cox regression analyses (all p < 0.05). Furthermore, univariate Cox regression analyses showed that age, variant histology, pT stage, pN status, concomitant CIS, and INS were statistically significant variables for RFS (all p < 0.05, Table 2).

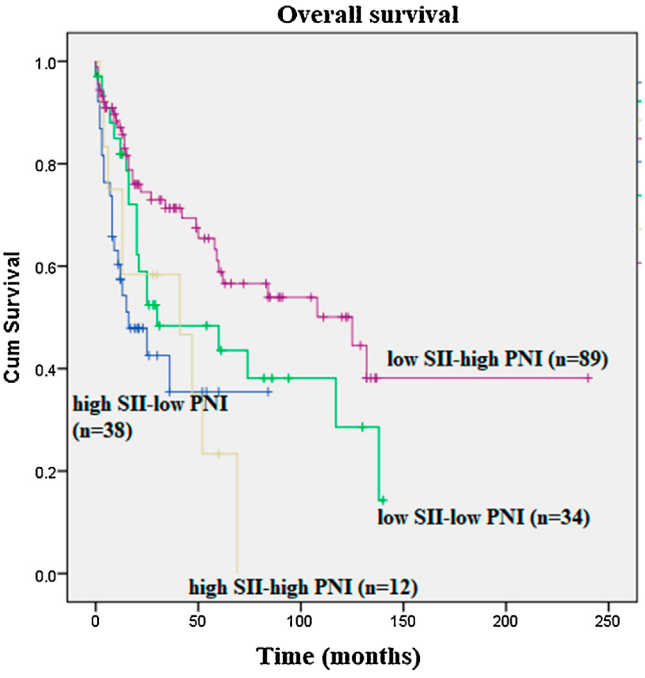


Figure 2 Kaplan–Meier curves for overall survival regarding high SII-high PNI patients (n = 12), low SII-high PNI patients (n = 89), low SII-low PNI patients (n = 34), and high SII-low PNI patients (n = 38).

Multivariate Cox regression analysis indicated that interval time between TUR and cystectomy more than three months (HR: 2.751; 95%CI: 1.670–4.533), presence of variant histology (HR: 1.914; 95%CI: 1.107–3.309), pathologic T3 and higher stage (HR: 2.427; 95%CI: 1.405–4.191), pathological lymph node metastasis (HR: 1.931; 95%CI: 1.138–3.276), and belonging to the non-favorable INS group (HR: 1.968; 95%CI: 1.203–3.221) were independent poor prognostic factors for OS (all p < 0.05). Moreover, the presence of variant histology (HR: 1.864; 95%CI: 1.104–3.145), pathologic T3 and higher stage (HR: 2.332; 95%CI: 1.331–4.083), pathological lymph node

Table 1 Patients' characteristics according to preoperative INS groups.

	All (*N* = 173)	Non-favorable INS* (*n* = 84)	Favorable INS* (*n* = 89)	*P* value
Demographics and clinical data				
Gender, *n* (%)				0.709†
Male	148 (85.5)	71 (84.5)	77 (86.5)	
Female	25 (14.5)	13 (15.5)	12 (13.5)	
Age, *n* (%)				0.263†
≥65 y	81 (46.8)	43 (51.2)	38 (42.7)	
<65 y	92 (53.2)	41 (48.8)	51 (57.3)	
Smoking history, *n* (%)				0.479†
Yes	138 (79.8)	68 (81.0)	70 (78.7)	
No	33 (19.1)	14 (16.7)	19 (21.3)	
Missing	2 (1.2)	2 (2.4)	0 (0)	
Time from TUR to RC, months, *n* (%)				0.962†
>3	40 (23.1)	20 (23.8)	20 (22.5)	
≤3	113 (65.3)	56 (66.7)	47 (64.0)	
Missing	20 (11.6)	8 (9.5)	12 (13.5)	
Clinical tumor stage				
<cT2	13	5 (5.9)	8 (9)	0.309†
cT2	80	39 (46.4)	41 (46.1)	
cT3	57	25 (29.8)	32 (35.9)	
cT4	23	15 (17.9)	8 (9)	
Non-age adjusted CCI, *n* (%)				0.230†
<3	59 (38.1)	24 (28.6)	35 (39.3)	
≥3	101 (58.4)	51 (60.2)	50 (56.2)	
Missing	13 (7.5)	9 (10.7)	4 (4.5)	
Pathologic				
Pathological tumor stage, *n* (%)				0.136†
≤pT2	78 (45.1)	33 (39.3)	45 (50.6)	
≥pT3	95 (54.9)	51 (60.7)	44 (49.4)	
Pathological node stage, *n* (%)				0.613†
N1	63 (36.4)	32 (38.1)	31 (34.8)	
N0	109 (63.0)	51 (60.7)	58 (65.2)	
Missing	1 (0.6)	1 (1.2)	0 (0)	
Positive surgical margins, *n* (%)				0.933†
Yes	8 (4.6)	4 (4.8)	4 (4.5)	
No	165 (95.4)	80 (95.2)	85 (95.5)	
Concomitant CIS, *n* (%)				0.355†
Yes	42 (24.3)	23(27.4)	19 (21.3)	
No	131 (75.7)	61(72.6)	70 (78.7)	
Variant histology, n (%)				
None	136 (78.6)	64	72	0.450†
Squamous	27 (15.6)	14	13	
Sarcomatoid	5 (2.9)	4	1	
Micropapillary	3 (1.7)	2	1	
Nested	1 (0.6)	0	1	
Plasmacytoid	1 (0.6)	0	1	
Surgical				
Number of nodes removed, mean ± SD	21.28 ± 10.02	20.51 ± 9.25	21.92 ± 10.62	0.451¶
Concomitant nephroureterectomy				
Presence	16 (9.2)	11(13.1)	5 (5.6)	0.090†
Absence	157 (90.8)	73 (86.9)	84 (94.4)	
Concomitant urethrectomy, n (%)				
Presence	14 (8.1)	7 (8.3)	7 (7.9)	0.910†
Absence	159 (91.9)	77 (91.7)	82 (92.1)	
Urinary diversion type, n (%)				
Ileal loop	162 (93.6)	80 (95.2)	82 (92.1)	0.097†

Table 1 (*Continued*)

	All (*N* = 173)	Non-favorable INS* (*n* = 84)	Favorable INS* (*n* = 89)	*P* value
Continent type	9 (5.2)	2 (2.4)	7 (7.9)	
Ureterocolostomy	2 (1.2)	2 (2.4)	0 (0)	
Indexes				
SII**, median (IQR)		1447 (847–2163)	563 (411–798)	<0.001‡
PNI**, mean ± SD		40.36 ± 7.78	53.14 ± 5.03	<0.001¶
Oncological				
Adjuvant chemotherapy, n (%)				
Presence	64 (37.0)	32 (38.1)	32 (36.0)	0.876†
Absence	107 (61.8)	52 (61.9)	55 (61.8)	
Missing	2 (1.2)	0	2 (2.2)	
Recurrence number and sites, n (%)				
None	102 (59.0)	45	57	0.603†
Locoregional-only	10 (5.8)	6	4	
Distant-only	40 (23.1)	21	19	
Urinary tract-only	3 (1.7)	2	1	
Multi-sites	17 (9.8)	10	7	
Unknown	1 (0.6)	–	–	
Death, *n* (%)	83 (48.0)	50 (59.5)	33 (37.1)	0.003†

CCI, Charlson Comorbidity Index; CIS, Carcinoma in situ; IQR, Interquartile range; INS, Immune-inflammatory-nutritional status; PNI, Prognostic Nutritional Index; RC, Radical Cystectomy; SII, Systemic Immune-inflammatory Index; SD, Standard Deviation; TUR, Transurethral Resection. *Non-favorable INS group constitutes from the 34 low SII low PNI, 12 high SII high PNI, 38 high SII low PNI patients, while favorable INS was the 89 low SII high PNI patients. **The cut-off levels of SII and PNI were determined by X Tile® software as 1,216 and 47, respectively. 124 of 173 patients with SII ≤ 1,216 was qualified low SII and 49 of 173 patients with >1,216 was high SII. 79 of 173 patients with ≤47 was qualified low PNI and the 94 of 173 patients with >47 was high PNI. †Chi-square test. ††Fisher's Exact test. ¶Student's t-test. ‡Mann–Whitney U test.

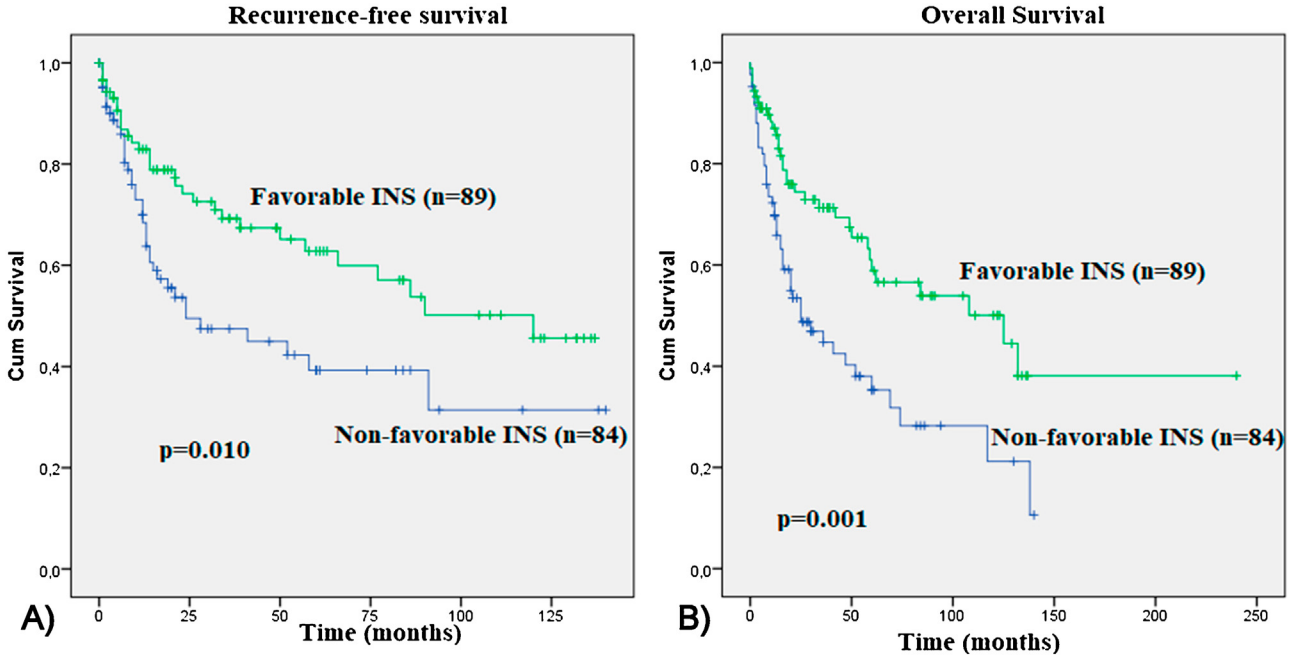


Figure 3 According to Favorable INS and Non-favorable INS, Kaplan–Meier curves in 173 patients treated with open radical cystectomy. (A) Overall survival. (B) Recurrence-free survival.

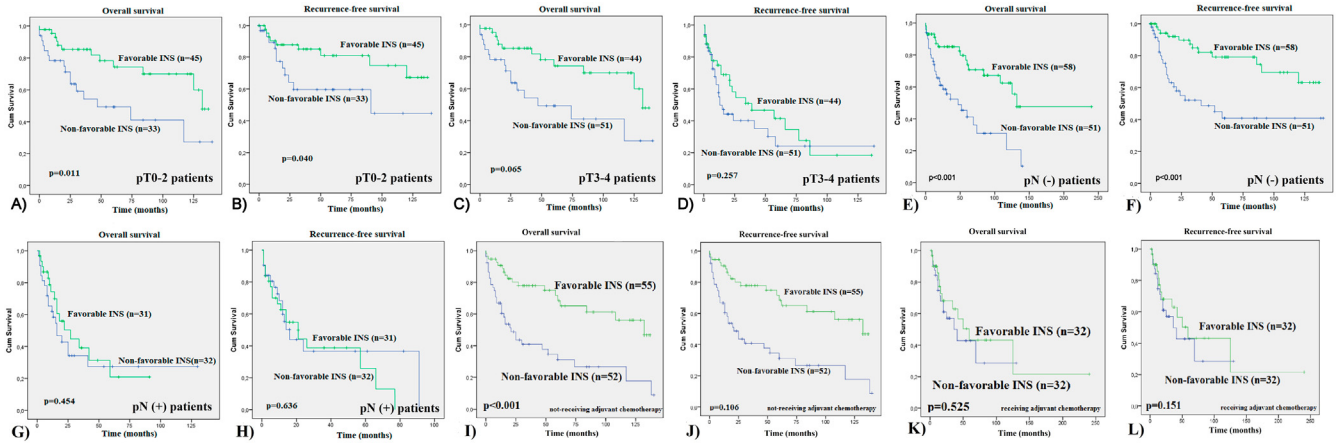


Figure 4 Kaplan–Meier curves for overall survival (A, C, E, G, I, K) and recurrence-free survival (B, D, F, H, J, L). Kaplan–Meier curves according to Favorable INS and Non-favorable INS in pT0-2 (n = 78, A, B) and pT3-4 (n = 95, C, D) patients. Kaplan–Meier curves according to Favorable INS and Non-favorable INS in pN- (n = 109, E, F) and pN+ (n = 63, G, H) patients. Kaplan–Meier curves according to Favorable INS and Non-favorable INS in those not-receiving adjuvant chemotherapy (n = 107, I, J) and in those receiving adjuvant chemotherapy (n = 64, K, L).

metastasis (HR: 1.902; 95%CI: 1.148–3.152), concomitant CIS (HR: 1.916; 95%CI: 1.151–3.190), and belonging to the non-favorable INS group (HR: 1.285; 95%CI: 1.009–1.636) were independent poor prognostic factors for RFS (all $p < 0.05$, Table 2). Furthermore, the C-index of the adjusted COX model without INS, for OS and RFS was 0.69 and 0.71, respectively. However, in the model with INS, a 2% of improvement for the C-index was observed in OS (0.71) and RFS (0.73).

For the subgroup analysis, when the pT0-2 (n = 78) and pT3-4 (n = 95) patients were separately analyzed with respect to INS, favorable INS had significantly better OS ($p = 0.011$) and RFS ($p = 0.040$) curves in the pT0-2 stage (Fig. 4A and B). However, in pT3-4 stage, OS and RFS curves were similar both in the favorable and non-favorable INS groups ($p > 0.05$, Fig. 4C and D). Additionally, when the pN- (n = 109) and pN+(n = 63) patients were also separately analyzed with respect to INS, favorable INS had significantly better OS ($p < 0.001$) and RFS ($p < 0.001$) curves in pN (-) patients (Fig. 4E and F). However, in pN + patients, OS and RFS curves were similar, both for the favorable and non-favorable INS groups ($p > 0.05$, Fig. 4G and H). Ultimately, favorable INS had significantly better OS ($p < 0.001$) but not RFS curves (p=0.106) in patients who did not receive adjuvant chemotherapy (n=107, Fig. 4I and J). Regarding patients who received adjuvant chemotherapy, there was no significant difference in favorable and non-favorable INS groups for OS and RFS (n = 64, $p > 0.05$, Fig. 4K and L).

Discussion

Considering the inflammatory nature of bladder cancer [25] and the significance of nutrition for radical cystectomy, which is a major surgical procedure, the investigation of a combination of SII and PNI seems reasonable in terms of a novel and informative prognostic indicator. For instance, reportedly high-risk NMIBC patients with low SII (467.76), or high PNI (≥50.17), were both associated with better cancer-specific survival (CSS) and OS.[22] In line with our hypothesis, and similar to our study, other authors have also shown that a combination of low SII-high PNI was related to better OS in patients with upper tract urothelial carcinoma[14] and medulloblastoma.[26] In our study, we defined these patients with low SII-high PNI as being the favorable INS group. To our knowledge, the prognostic effect of INS based on SII and PNI has not previously been assessed in patients who underwent ORC for UC. This study presents the association between INS and oncologic outcome in patients undergoing ORC for UC. With nearly two years of follow-up, patients in the favorable INS group, those with ≤ pT2 stage, absence of lymph node metastasis, absence of variant histology, and less than three months interval from TUR to radical cystectomy were independently associated with better OS. Additionally, favorable INS, absence of concomitant CIS, absence of variant histology, ≤pT2 stage, and absence of lymph node metastasis were independently associated with better RFS in our study. Regarding the OS- and RFS-related independent prognostic factors mentioned in this paper, many studies have previously shown that these factors are associated with oncologic outcomes in bladder cancer. For instance, age and pT stage had been integrated into a scoring system called the ''Cancer Of Bladder Risk Assessment – COBRA score'' that used the density of lymph node metastasis, and it was validated by multicentric collaborative studies as an important prognostic model.[27] Classically, delayed radical cystectomy (>3 months after TUR) and presence of variant histology have also been known to be poor prognostic factors that increase the risk of death from bladder cancer.[3,28] A systematic review and meta-analysis including 20,647 patients emphasized that concomitant CIS is a poor prognosticator for RFS and CSS.[29] Another study showed that factors including pT3 and pT4 stage, and lymph node invasion were associated with abdominopelvic, thoracic, and bone recurrence after radical cystectomy.[30] Notably, OS- and RFS-related prognostic factors that are significant in our study are parallel with these previous reports.

In a 3-year follow-up, the RAZOR trial showed that the OS rate for ORC is 68.5%.[31] Moreover, according to a systemic review and meta-analysis including 48 articles with 18 to 350 months follow-up, overall 5-year RFS rates ranged between 58% and 81%.[32] In another Canadian cohort study, at a median 29 months follow-up, a total of 33% of patients had recurrence.[33] In this study a worse pathologic stage distribution was present with more than half the patients being pT3-4 However, in our study which also contained more than half of patients with pT3 and higher stage, we had a 40.5% recurrence and 48% death rate at a median follow-up of 21 months. Patients in our favorable INS group had better 2- and 3-year RFS (77.5% and 74.2%) and OS (77.5% and 75.3%) rates compared with the earlier studies cited. Additionally, our subgroup analysis showed that pT0-2 or pN- patients with favorable INS had even better OS and RFS.

Enhanced recovery after surgery (ERAS) protocol, which includes early nutrition, has gained importance during the past two decades.

Table 2 Univariate and multivariate analysis of OS and RFS in 173 ORC patients who had urothelial carcinoma of bladder.

Variables	OS				RFS			
	Univariate		Multivariate		Univariate		Multivariate	
	P	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)
Age (years) ≥65 y vs <65	**0.027***	1.63 (1.06–2.52)	0.119	1.46 (0.9–2.36)	**0.034***	1.67 (1.04–2.67)	0.111	1.49 (0.91–2.42)
Non-age adjusted CCI >2 vs 0—2	0.571	1.16 (0.70–1.91)	–	–	0.315	1.32 (0.77–2.28)	–	–
Gender Female vs Male	0.920	1.03 (0.55–1.96)	–	–	0.793	1.09 (0.56–2.14)	–	–
Smoking history Yes vs No	0.062	1.65 (0.98–2.80)	–	–	0.479	1.25 (0.68–2.28)	–	–
Time from TUR to RC (months) >3 vs ≤3	**0.005***	1.99 (1.23–3.22)	**<0.001***	2.75 (1.67–4.53)	0.363	1.29 (0.75–2.22)	–	–
pT stage T3—4 vs T0—2	**<0.001***	2.45 (1.54–3.89)	**0.001***	2.43 (1.41–4.19)	**<0.001***	3.39 (1.99–5.76)	**0.003***	2.33 (1.33–4.08)
pN stage N + vs N0	**<0.001***	2.32 (1.47–3.66)	**0.015***	1.93 (1.14–3.28)	**<0.001***	3.00 (1.84–4.89)	**0.013***	1.90 (1.15–3.15)
Concomitant CIS Presence vs absence	0.319	1.30 (0.78–2.16)	–	–	**0.001***	2.35 (1.43–3.88)	**0.012***	1.92 (1.15–3.19)
Variant histology Presence vs absence	**0.014***	1.82 (1.13–2.93)	**0.020***	1.91 (1.11–3.31)	**0.005***	2.07 (1.25–3.43)	**0.020***	1.86 (1.10–3.15)
INS Non-favor vs Favor	**0.001***	1.45 (1.16–1.81)	**0.007***	1.97 (1.20–3.22)	**0.012***	1.36 (1.07–1.73)	**0.042***	1.29 (1.01–1.64)
C-index without INS			0.69				0.71	
C-index with INS			0.71				0.73	

CCI, Charlson comorbidity index; CIS, carcinoma in situ; INS, Immune-inflammatory-nutritional Status; ORC, Open radical cystectomy; OS, Overall survival; RFS, Recurrence-free survival; TUR, transurethral resection. *The bold p values indicate a $p < 0.05$, that is a statistically significant difference.

Even if this protocol diminishes the perioperative complications, patients treated with radical cystectomy within the ERAS protocol did not obtain any benefit regarding long-term oncologic outcomes. Nevertheless, the ERAS protocol may render the patients more suitable for adjuvant chemotherapy after cystectomy.[34,35] Thus, a positive contribution to oncologic outcomes of radical cystectomy may be provided. There were similar adjuvant chemotherapy rates in our favorable or non-favorable-INS groups and there were less recurrence and death in our favorable-INS group. This may be explained by the synergistic effect of better nutrition and immune-inflammation status. With respect, the association between survival and novel NAPLES prognostic scoring system, which includes immune and nutritional parameters such as total cholesterol, lymphocyte to monocyte ratio, neutrophil to lymphocyte ratio, and albumin, was shown elsewhere.[36–38] For a better understanding of this synergism, further research is needed in larger, prospective, and more heterogeneous cohorts.

In our study, optimal cut-off levels of SII and PNI were 1,216 and 47, respectively. These cut-off levels have varied in a host of other cancer studies. For example, Grossmann et al. found an SII

cut-off level of >610 for worse oncologic outcomes in patients treated with radical cystectomy,[4] while Tang et al. reported that cut-off higher than 1337,8 was associated with poor pathologic findings.[39] Onodera et al., who first described the PNI, found the PNI cut-off level to be 45, and emphasized that gastrointestinal resection and anastomosis may be performed safely in patients with PNI more than 45.[23] PNI cut-off levels in the bladder cancer literature ranged between 45 and 51.7.[5,20,39] Cut-off estimates for SII and PNI may be more reliable and consistent in future studies including higher number of subjects.

The single-center retrospective design, limited patient number, and relatively short follow-up are the main limitations of this study. Lack of detailed histopathologic findings (lymphovascular invasion, perineural invasion, and necrosis) is a further limitation. Despite the pT3-4 predominance of the cohort, the oncological outcomes may also have been negatively affected by a relatively low (37%) adjuvant chemotherapy administration in our patients. As a matter of fact that due to chemotherapy may alter the immune and nutrition parameters,[40,41] the exclusion of patients receiving neoadjuvant chemotherapy may acceptable limitation in the study, because neoadjuvant chemotherapy is a standard treatment for MIBC in the current guidelines. In the light of our results, whether radical cystectomy may be recommended to patients who have either favorable INS and willing to skip neoadjuvant chemotherapy in localized MIBC management should be investigated in further studies.

Conclusions

In conclusion, INS, which is a combination of SII and PNI, is an independent prognostic factor for RFS and OS in our patients who underwent ORC for UC. Since it is a low-cost and rapid laboratory analysis tool, INS may be a useful prognostic panel before radical cystectomy. Further multicentric and larger population studies are necessary for external validation and identification of the most accurate cut-off values.

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Ethical statement

The study was approved by the local ethics committee (Approval number: KÜ GOKAEK-2022/03.20). The informed and signed consent has been obtained from all patients prior to surgery.

Conflict of interest

All of the authors have no relevant financial or non-financial interests to disclose.

Author contributions

Conceptualization, K.T.; Methodology, K.T., I.E.A; Formal Analysis, K.T., H.Y., and O.K.; Investigation, K.T., N.B.C., I.E.A., and E.A.B.; Data Curation, K.T., I.E.A., E.B., and S.P.; Writing – Original Draft, K.T.; Writing – Review & Editing, O.D. and K.T.; Visualization, I.E.A., E.B., and S.P.; Supervision, O.D., K.T. All authors critically reviewed the manuscript and approved it. All authors take full responsibility for the integrity of the study and the data presented.

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References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. CA Cancer J Clin. 2021;71:7–33.
2. Babjuk M, Burger M, Capoun O, Cohen D, Comperat EM, Dominguez Escrig JL, et al. European association of urology guidelines on non-muscle-invasive bladder cancer (Ta, T1, and carcinoma in situ). Eur Urol. 2022;81:75–94.
3. Witjes JA, Bruins HM, Cathomas R, Comperat EM, Cowan NC, Gakis G, et al. European association of urology guidelines on muscle-invasive and metastatic bladder cancer: summary of the 2020 guidelines. Eur Urol. 2021;79:82–104.
4. Grossmann NC, Schuettfort VM, Pradere B, Rajwa P, Quhal F, Mostafaei H, et al. Impact of preoperative systemic immune-inflammation Index on oncologic outcomes in bladder cancer patients treated with radical cystectomy. Urol Oncol. 2022;40:106.e11–9.
5. Karsiyakali N, Karabay E, Yucetas U. Predictive value of prognostic nutritional index on tumor stage in patients with primary bladder cancer. Arch Esp Urol. 2020;73:132–9.
6. Teke K, Yaprak Bayrak B, Yuksekkaya M, Uslubas AK, Kosem ME, Yilmaz H, et al. Profile based on CD8+ and FoxP3+ T lymphocytes in the peritumoral and intratumoral subsites for renal cell carcinoma. Int Urol Nephrol. 2020;52:2289–99.
7. Masucci MT, Minopoli M, Carriero MV. Tumor associated neutrophils. Their role in tumorigenesis, metastasis, prognosis and therapy. Front Oncol. 2019;9:1146.

8. Palacios-Acedo AL, Mege D, Crescence L, Dignat-George F, Dubois C, Panicot-Dubois L. Platelets, thrombo-Inflammation, and cancer: collaborating with the enemy. Front Immunol. 2019;10:1805.
9. Morizawa Y, Miyake M, Shimada K, Hori S, Tatsumi Y, Nakai Y, et al. Correlation of immune cells and cytokines in the tumor microenvironment with elevated neutrophil-to-lymphocyte ratio in blood: an analysis of muscle-invasive bladder cancer. Cancer Invest. 2018;36:395–405.
10. Wang X, Ni X, Tang G. Prognostic role of platelet-to-lymphocyte ratio in patients with bladder cancer: a meta-analysis. Front Oncol. 2019;9:757.
11. Katayama S, Mori K, Pradere B, Laukhtina E, Schuettfort VM, Quhal F, et al. Prognostic value of the systemic immune-inflammation index in non-muscle invasive bladder cancer. World J Urol. 2021;39:4355–61.
12. Mori K, Resch I, Miura N, Laukhtina E, Schuettfort VM, Pradere B, et al. Prognostic role of the systemic immune-inflammation index in upper tract urothelial carcinoma treated with radical nephroureterectomy: results from a large multicenter international collaboration. Cancer Immunol Immunother. 2021;70:2641–50.
13. Kobayashi S, Ito M, Takemura K, Suzuki H, Yonese I, Koga F, et al. Preoperative models incorporating the systemic immune-inflammation index for predicting prognosis and muscle invasion in patients with non-metastatic upper tract urothelial carcinoma. Int J Clin Oncol. 2022;27:574–84.
14. Zheng Y, Yu D, Yu Z, Zhao D, Chen Y, Chen W, et al. Association of preoperative systemic immune-inflammation index and prognostic nutritional index with survival in patients with upper tract urothelial carcinoma. J Cancer. 2020;11:5665–77.
15. Alwarawrah Y, Kiernan K, MacIver NJ. Changes in nutritional status impact immune cell metabolism and function. Front Immunol. 2018;9:1055.
16. Gregg JR, Cookson MS, Phillips S, Salem S, Chang SS, Clark PE, et al. Effect of preoperative nutritional deficiency on mortality after radical cystectomy for bladder cancer. J Urol. 2011;185:90–6.
17. Yuk HD, Ku JH. Role of systemic inflammatory response markers in urothelial carcinoma. Front Oncol. 2020;10:1473.
18. Shen C, Zhou K, Wang W, Zhang Y, Liu X. The prognostic value of preoperative serum albumin in patients with bladder urothelial carcinoma undergoing transurethral resection of bladder tumor: a prospective cohort study. Medicine (Baltimore). 2021;100:e26548.
19. Peng D, Gong YQ, Hao H, He ZS, Li XS, Zhang CJ, et al. Preoperative prognostic nutritional index is a significant predictor of survival with bladder cancer after radical cystectomy: a retrospective study. BMC Cancer. 2017;17:391.
20. Yu J, Hong B, Park JY, Hwang JH, Kim YK. Impact of prognostic nutritional index on postoperative pulmonary complications in radical cystectomy: a propensity score-matched analysis. Ann Surg Oncol. 2021;28:1859–69.
21. Claps F, van de Kamp MW, Mayr R, Bostrom PJ, Boormans JL, Eckstein M, et al. Risk factors associated with positive surgical margins' location at radical cystectomy and their impact on bladder cancer survival. World J Urol. 2021;39:4363–71.
22. Bi H, Shang Z, Jia C, Wu J, Cui B, Wang Q, et al. Predictive values of preoperative prognostic nutritional index and systemic immune-inflammation index for long-term survival in high-risk non-muscle-invasive bladder cancer patients: a single-centre retrospective study. Cancer Manag Res. 2020;12:9471–83.
23. Onodera T, Goseki N, Kosaki G. [Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients]. Nihon Geka Gakkai Zasshi. 1984;85:1001–5.
24. Camp RL, Dolled-Filhart M, Rimm DL. X-tile: a new bio-informatics tool for biomarker assessment and outcome-based cut-point optimization. Clin Cancer Res. 2004;10:7252–9.
25. Sui X, Lei L, Chen L, Xie T, Li X. Inflammatory microenvironment in the initiation and progression of bladder cancer. Oncotarget. 2017;8:93279–94.
26. Sihan Zhu ZC, Yuanjun H, Chen Z, Ji Z, Ke C, Yang Q, et al. Prognostic value of the systemic immune-inflammation index and prognostic nutritional index in patients with medulloblastoma undergoing surgical resection. Front Nutr. 2021;8:754958.
27. Muilwijk T, Akand M, Soria F, Giordano A, Milenkovic U, Moris L, et al. The Cancer of the Bladder Risk Assessment (COBRA) score for estimating cancer-specific survival after radical cystectomy: external validation in a large bi-institutional cohort. BJU Int. 2020;126:704–14.
28. Lee CT, Madii R, Daignault S, Dunn RL, Zhang Y, Montie JE, et al. Cystectomy delay more than 3 months from initial bladder cancer diagnosis results in decreased disease specific and overall survival. J Urol. 2006;175:1262–7, discussion 67.
29. Kimura S, Mari A, Foerster B, Abufaraj M, Vartolomei MD, Stangl-Kremser J, et al. Prognostic value of concomitant carcinoma in situ in the radical cystectomy specimen: a systematic review and meta-analysis. J Urol. 2019;201:46–53.
30. Umbreit EC, Crispen PL, Shimko MS, Farmer SA, Blute, ML, Frank I. Multifactorial, site-specific recurrence model after radical cystectomy for urothelial carcinoma. Cancer. 2010;116:3399–407.
31. Venkatramani V, Reis IM, Castle EP, Gonzalgo ML, Woods ME, Svatek RS, et al. Predictors of recurrence, and progression-free and overall survival following open versus robotic radical cystectomy: analysis from the RAZOR trial with a 3-year followup. J Urol. 2020;203:522–9.
32. Mari A, Campi R, Tellini R, Gandaglia G, Albisinni S, Abufaraj M, et al. Patterns and predictors of recurrence after open radical cystectomy for bladder cancer: a comprehensive review of the literature. World J Urol. 2018;36:157–70.
33. Yafi FA, Aprikian AG, Chin JL, Fradet Y, Izawa J, Estey E, et al. Contemporary outcomes of 2287 patients with bladder cancer who were treated with radical cystectomy: a Canadian multicentre experience. BJU Int. 2011;108:539–45.
34. Ziegelmueller BK, Jokisch JF, Buchner A, Grimm T, Kretschmer A, Schulz GB, et al. Long-term follow-up and oncological outcome of patients undergoing radical cystectomy for bladder cancer following an enhanced recovery after surgery (ERAS) protocol: results of a large randomized, prospective, single-center study. Urol Int. 2020;104:55–61.
35. Pang Q, Duan L, Jiang Y, Liu H. Oncologic and long-term outcomes of enhanced recovery after surgery in cancer surgeries - a systematic review. World J Surg Oncol. 2021;19:191.
36. Nakagawa N, Yamada S, Sonohara F, Takami H, Hayashi M, Kanda M, et al. Clinical implications of Naples prognostic score in patients with resected pancreatic cancer. Ann Surg Oncol. 2020;27:887–95.
37. Feng J-F, Zhao J-M, Chen S, Chen Q-X. Naples prognostic score: a novel prognostic score in predicting cancer-specific survival in patients with resected esophageal squamous cell carcinoma. Front Oncol. 2021;11:652537.
38. Li Q, Cong R, Wang Y, Kong F, Ma J, Wu Q, et al. Naples prognostic score is an independent prognostic factor in patients with oper-

able endometrial cancer: results from a retrospective cohort study. Gynecol Oncol. 2021;160:91–8.
39. Tang X, Cao Y, Liu J, Wang S, Yang Y, Du P. Diagnostic value of inflammatory factors in pathology of bladder cancer patients. Front Mol Biosci. 2020;7:575483.
40. Cohen S, Gal J, Freifeld Y, Khoury S, Dekel Y, Hofman A, et al. Nutritional status impairment due to neoadjuvant chemotherapy predicts post-radical cystectomy complications. Nutrients. 2021;13:4471.
41. Leibowitz-Amit R, Israel A, Gal M, Atenafu E, Symon Z, Portnoy O, et al. Association between the absolute baseline lymphocyte count and response to neoadjuvant platinum-based chemotherapy in muscle-invasive bladder cancer. Clin Oncol. 2016;28:790–6.