Postoperative C-reactive protein-to-albumin ratio predicts poor prognosis in patients with bladder cancer undergoing radial cystectomy

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Abstract. The purpose of the present study was to investigate the prognostic value of the postoperative C-reactive protein/albumin ratio (CAR) in patients with bladder cancer undergoing radial cystectomy. The present study retrospectively reviewed 102 patients who underwent radical cystectomy and were followed for ≥6 months postoperatively at our institution, and evaluated clinicopathological factors and laboratory parameters for cancer-specific survival (CSS) and extraurothelial recurrence-free survival (ERFS). Multivariate analysis using the Cox proportional hazards model revealed that only postoperative CAR ≥0.27 [hazard ratio (HR), 3.368; 95% confidence interval (CI), 1.674-6.731; P<0.001] was an independent factor for poor CSS rate. Higher postoperative CAR was also the only significant factor for shortened ERFS time (HR, 2.401; 95% CI, 1.196-4.684; P=0.015). No significant association was identified between postoperative CAR ≥0.27 and any pathological factors or postoperative laboratory markers besides postoperative neutrophil-to-lymphocyte ratio. Furthermore, postoperative CAR (≥0.27) was an independent factor for poor CSS and ERFS rates in 48 patients with advanced pT stage (≥pT3) in the multivariate analysis (P=0.026 and P=0.036, respectively). A higher postoperative CAR value can provide additional information about the possibility of poor CSS and ERFS rates in patients with bladder cancer undergoing radical cystectomy.

Introduction

Bladder cancer is the tenth most common cancer in the world, with approximately 550,000 new cases and 200,000 deaths in 2018 (1). Approximately 25% of bladder cancer patients present with muscle-invasive bladder cancer at the time of diagnosis. This indicates a high possibility of metastasis and of affecting survival (2).

Radical cystectomy is an aggressive, conventional and standard therapeutic option for patients with muscle-invasive or bacillus Calmette-Guérin (BCG)-refractory non-muscle-invasive bladder cancer. Postoperative survival time has a high association with the pathological status at the time of radical cystectomy. In patients with stage II or III bladder carcinoma, the 5-year survival rates range from 50 to 80% (3-5). However, clinicopathological data alone has been insufficient for deciding the optimal treatment option (6). Based on poor surgical outcomes after radical cystectomy, the optimal postoperative monitoring option for high-risk bladder carcinoma is required.

There has been accumulating evidence supporting the rationale for the association of systemic inflammatory response (SIR) with tumor development and progression (7). Proinflammatory cytokines and growth factors are released into the systemic circulation as factors for SIR. In addition, it has been speculated that tumor growth factors expedite the release of cytokines from tissues. SIR may be activated secondary to local tissue damage caused by mutual responses between tumor necrosis factors and original cancer cells (8). These SIR markers include C-reactive protein (CRP), the Glasgow Prognostic Score (GPS), neutrophil-to-lymphocyte ratio (NLR), and platelet to lymphocyte ratio (PLR) (9-12). In addition, nutritional status, such as lower levels of serum albumin (Alb) and low body mass index, is associated with worse clinical outcomes postoperatively in patients with carcinoma, and CRP to Alb ratio (CAR), in combination with the systemic status of inflammation and nutrition, has been reported as an independent prognosticator in some types of carcinoma (13-16).

SIR markers have been measured preoperatively (13-16), but nutritional or inflammatory status needs to be stable before surgery or other invasive treatment. However, reports suggest postoperative SIR markers have potential prognostic significance, especially in patients with urothelial carcinoma. To the best of our knowledge, only a few studies have investigated the association of postoperative NLR and poor prognosis in patients with upper urinary tract and bladder urothelial carcinoma (17-19). Therefore, we sought to examine postoperative, as well as preoperative SIR markers, including CAR, to determine independent factors of poor prognosis in locally advanced bladder cancer.

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In the present study, we retrospectively investigated the clinicopathological and laboratory data of patients with bladder carcinoma who underwent radical cystectomy at National Defense Medical College (single center) to clarify whether postoperative CAR could be an independent prognostic factor for shorter time to cancer-specific death and/or extraurothelial recurrence.

Patients and methods

Patients. The medical records of 102 patients who underwent radical cystectomy between January 2007 and January 2020 and who were pathologically diagnosed with urothelial carcinoma before or at the time of cystectomy were retrospectively reviewed. They were followed for at least 6 months postoperatively at our institution. The study protocol (ID 2734) was accepted on June 14, 2017, by National Defense Medical College Ethics Committee, and an opt-out approach on the web page of the National Defense Medical College was used instead of collecting written informed consent from all participants.

A total of 80 males and 22 females with a median age of 71 years (range, 49-83 years) were included in the present study. The median follow-up period after surgery was 38.9 months (range, 6.1-162.2 months). Table I shows additional clinicopathological and laboratory data. The absence of tumor from the histopathological examination of the cystectomy specimen is interpreted as pT0, which translated to 22 pT0 patients.

Extraurothelial recurrence after radical cystectomy indicates tumor recurrence outside the bladder or distant metastasis. In the present study, we defined recurrence-free survival as extraurothelial recurrence-free survival (ERFS).

The method of lymphadenectomy was the same as that described in earlier studies (20,21). All patients received regional lymphadenectomy, and 21 showed positive lymph node metastasis. Neoadjuvant chemotherapy was administered to 47 patients, 22 of whom developed postoperative recurrence or distant metastasis.

As part of postoperative chemotherapy, adjuvant chemotherapy was administered to 11 patients with histologically confirmed lymphovascular invasion (LVI) or pathologically determined pT3 or pT4 cancer, and salvage chemotherapy was administered to 26 patients who developed recurrence and/or distant metastasis after surgery. Both adjuvant and salvage chemotherapy were administered to 5 patients. The dose of cisplatin was adjusted according to the renal function of the patient.

All surgical specimens were processed according to standard pathological procedures and were histologically confirmed to be urothelial carcinoma with or without other tumor cell types. The pathological staging of the primary tumor (pT) was determined according to the American Joint Committee on Cancer TNM Classification (22), whereas tumor grading was determined according to the 2004 WHO classification of urothelial tumors (23). Tumor specimens were evaluated by two pathologists, and the patients were divided into two groups on the basis of the 2004 WHO classification system for tumor grading.

Each patient was monitored for local recurrence or distant metastasis every 3-6 months for the first 5 years after cystectomy and 6-12 months thereafter.

Estimated glomerular filtration rate and inflammatory indices. Preoperative laboratory tests were performed within 1 week before cystectomy, and postoperative laboratory tests was measured 1 to 2 months after surgery. In cases requiring postoperative chemotherapy, the postoperative blood examination was performed prior to postoperative chemotherapy. None of the patients enrolled in the present study had inflammatory diseases or hematological disorders at the time of blood tests.

The estimated glomerular filtration rate (eGFR) was calculated by computation using the following formula:

eGFR (ml/min/1.73 m^2)=194x(serum creatinine)$^{-1.094}$ x Age$^{-0.287}$ x(0.739, for women).

This formula is the isotope dilution mass spectrometry (IDMS)-traceable 4-variable Modification of Diet in Renal Disease (MDRD) Study equation, a modified equation from the IDMS MDRD Study with a coefficient derived from data by the Japanese Society of Nephrology-Chronic Kidney Disease Initiatives (JSN-CKDI). This formula has been reported to be more accurate for hospitalized Japanese patients with an eGFR of <60 ml/min/1.73 m^2 than the original IDMS MDRD Study Equation (24).

Inflammatory indices were calculated as follows. CAR was calculated by dividing the CRP value (mg/dl) by the Alb value (g/dl) (10,14,15). The NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count (9,19). The platelet to lymphocyte ratio (PLR) was calculated by dividing the absolute platelet count by the absolute lymphocyte count (11).

Statistical analysis. Univariate and multivariate analyses were performed using a Cox proportional hazards model to identify independent factors for shorter cancer-specific survival (CSS) and ERFS time. In addition, receiver operator characteristic (ROC) analysis was performed to determine the cut-off values of eGFR, CAR, NLR and PLR according to the method shown in earlier studies (9,19,25). We also applied the cut-off values determined on the basis of CSS rate, according to previous reports (9,19,25). Fisher's exact probability test was performed to examine the relationship between postoperative CAR ≥0.27 and any other pathological factors or postoperative laboratory markers. Survival curves were constructed using the Kaplan-Meier method, and the statistical differences among them were evaluated using the log-rank test. Statistical analyses were performed with JMP Pro 14 (SAS Institute). A P-value <0.05 was considered statistically significant.

Results

Independent factors for shortened CSS and ERFS time in all patients. ROC analysis revealed that patients with preoperative eGFR ≤46.88, postoperative eGFR ≤48.02, preoperative CAR ≥0.17, postoperative CAR ≥0.27, preoperative NLR ≥2.46, postoperative NLR ≥2.19, preoperative PLR ≥94.80 and postoperative PLR ≥105.23 had a higher association with cancer-specific death than patients without these conditions. As to eGFR, we considered 45 ml/min/1.73 m^2 was a practical threshold in the present study. The ROC curves for postoperative CAR for cancer-specific death and extraurothelial recurrence are shown in Fig. 1A and B. The postoperative CAR threshold was 0.27 for both CSS and ERFS.

Table I. Clinicopathological and laboratory parameters.

Parameters	Patients, n
Clinicopathologic	
Sex	
Men	80
Women	22
Urine cytology	
Positive	26
Negative	47
Unknown	29
Smoking history	
Present	71
Absent	31
History of UTUC	
Present	11
Absent	91
Recurrent or primary tumor	
Recurrent	36
Primary	66
Reason for cystectomy	
Muscle-invasive	87
BCG-refractory	15
Histology	
UC alone	57
UC and other subtypes	23
No tumor	22
Pathological T stage	
≥T3	48
≤T2	54
Tumor grade	
High	75
PUNLMP/low	27
Lymph node metastasis	
Positive	21
Negative	81
Ureteral involvement	
Positive	6
Negative	96
Surgical margins	
Positive	8
Negative	94
Lymphovascular invasion	
Positive	50
Negative	52
CIS	
Positive	10
Negative	92
Laboratory	
Preoperative eGFR, ml/min/1.73 m^2	
<45	27
≥45	75
Postoperative eGFR, ml/min/1.73 m^2	
<45	29
≥45	73
Preoperative CAR	
≥0.17	32
<0.17	70
Postoperative CAR	
≥0.27	25
<0.27	77
Preoperative NLR	
≥2.46	45
<2.46	57
Postoperative NLR	
≥2.19	55
<2.19	47
Preoperative PLR	
≥94.80	83
<94.80	19
Postoperative PLR	
≥105.23	85
<105.23	17

UTUC, upper urinary tract urothelial carcinoma; BCG, bacille Calmette-Guérin; PUNLMP, papillary urothelial neoplasm of low malignant potential; CIS, carcinoma *in situ*; eGFR, estimated glomerular filtration rate; CAR, C-reactive protein (mg/dl) to albumin (g/dl) ratio; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio.

A Cox proportional hazards model was performed to prove CAR was a more useful marker than CRP alone or Alb alone. On a univariate analysis, significantly shorter cancer-specific survival was associated with postoperative CRP ≥0.6 [hazard ratio (HR), 3.249; 95% confidence interval (CI), 1.713-6.204; P<0.001], postoperative Alb ≤3.4 [HR, 3.624; 95% CI, 1.822-6.938; P<0.001], and postoperative CAR ≥0.27 [HR, 4.209; 95% CI, 2.201-7.992; P<0.001]. Therefore, post-operative CAR was used according to HR. Additionally, preoperative CAR was also used.

Another Cox proportional hazards model was constructed to detect the independent clinicopathological factors and laboratory parameters for shortened CSS time. Among these factors, in a univariate analysis, pT stage, tumor grade, LVI, preoperative eGFR, preoperative CAR, and postoperative CAR were found to be independent factors for shortened CSS time (P<0.001, P=0.014, P<0.001, P=0.013, P=0.017, P<0.001, respectively). Among these independent factors in univariate analysis, only postoperative CAR (≥0.27) was an indepen-dent factor for worse CSS rate in the multivariate analysis [HR, 3.368; 95% CI, 1.674-6.731; P<0.001] (Table II).

In another univariate analysis, ERFS time was found to be shorter in patients with higher pT stage, high tumor grade, lymph node metastasis, LVI, preoperative eGFR <45,

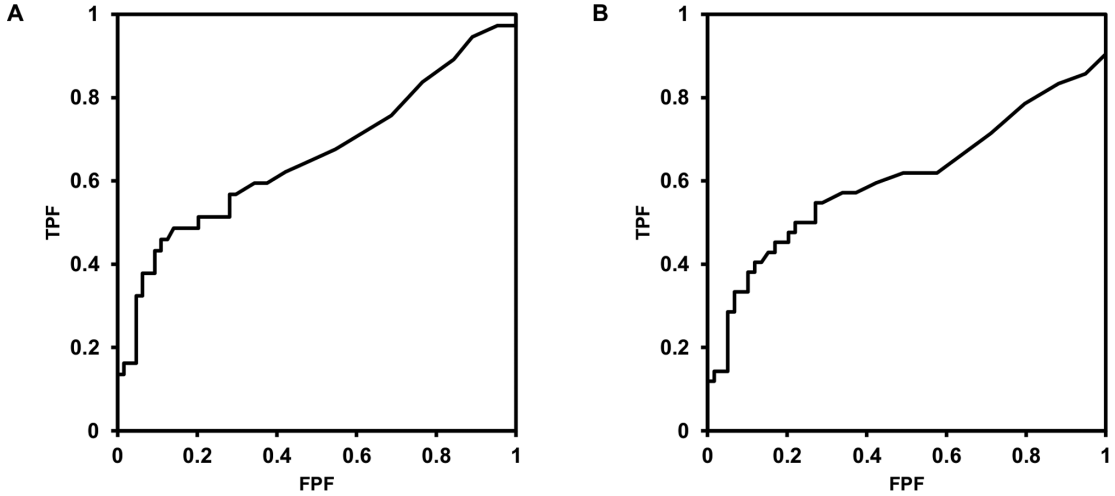

Figure 1. Receiver operating characteristic curves for postoperative C-reactive protein/albumin ratio for (A) cancer-specific mortality and (B) extraurothelial recurrence. The areas under the curves were (A) 0.667 and (B) 0.612. TPF, true positive fraction; FPF, false positive fraction.

preoperative CAR ≥0.17, postoperative CAR ≥0.27, and preoperative PLR ≥94.80 (P=0.002, P=0.011, P=0.039, P=0.007, P=0.015, P=0.032, P<0.001, P=0.037, respectively). Among these independent factors in univariate analysis, only postoperative CAR ≥0.27 was found to act as an independent factor for worse ERFS rate in the multivariate analysis (HR, 2.401; 95% CI, 1.196-4.684; P=0.015) (Table III). Age, sex, body mass index, urine cytology, smoking history, history of upper urinary tract urothelial carcinoma, recurrent or primary tumor, reason for radical cystectomy, and the presence of histological subtypes were not independent predictors of worse CSS or ERFS rates in univariate analysis (data not shown).

Postoperative CAR ≥0.27 was observed in 25 (24.5%) patients. A statistically significant association was observed between postoperative CAR ≥0.27 and postoperative NLR ≥2.19 (P=0.012), but there was not any significant association between postoperative CAR ≥0.27 and any other pathological factors or postoperative laboratory markers (Table IV).

The Kaplan-Meier curves and the results of the log-rank test revealed a significant difference in the CSS and ERFS rates between all patients with and without postoperative CAR ≥0.27 (both P<0.001) (Fig. 2A and B).

Independent factors for shortened CSS and ERFS time in patients with advanced pT stage. Next, we sought to establish the independent factors of shorter CSS rates in patients with higher pT stage (≥T3). A Cox proportional hazards model was generated to determine the independent factors of shortened CSS rates among clinicopathological factors and laboratory parameters in 48 advanced pT stage (≥pT3) patients. In a univariate analysis, postoperative CAR and preoperative PLR were found to be independent factors for shortened CSS time (P=0.006, P=0.038, respectively). Among these independent factors in univariate analysis, only postoperative CAR (≥0.27) was an independent factor for worse CSS rate in the multivariate analysis (HR, 2.600; 95% CI, 1.126-5.833; P=0.026) (Table V).

Another univariate analysis of Cox proportional hazards model revealed that ERFS time was found to be shorter in patients with postoperative CAR ≥0.27 and preoperative PLR ≥94.80 (P=0.012, P=0.038, respectively). Among these independent factors in univariate analysis, only postoperative CAR ≥0.27 was found to act as an independent factor for worse ERFS rate in the multivariate analysis (HR, 2.399; 95% CI, 1.062-5.297; P=0.036) (Table VI).

The Kaplan-Meier curves and the results of the log-rank test revealed significant differences in the CSS and ERFS rates between ≥pT3 patients with and without postoperative CAR ≥0.27 (P=0.003, P=0.006, respectively) (Fig. 3A and B).

In total, 28 (58.3%) patients with advanced pT stage (≥T3) received postoperative chemotherapy. Adjuvant chemotherapy was administered to 7 patients, and salvage chemotherapy was administered to 16 patients. Both adjuvant and salvage chemotherapy were administered to 5 patients. A total of 24 patients (85.7%) received cisplatin plus gemcitabine, 2 (7.1%) received docetaxel plus gemcitabine, and 2 (7.1%) received carboplatin plus gemcitabine. The median number of chemotherapy cycles was three. Compared with those who underwent surgical treatment alone, patients with advanced pT stage (≥T3) who received postoperative chemotherapy showed significantly worse CSS or ERFS rates (P=0.044, P=0.005, respectively) (Fig. 4A and B).

Discussion

In the present study, only postoperative CAR ≥0.27 was an independent predictor of worse CSS as well as ERFS rates. Other laboratory parameters, such as eGFR, NLR, and PLR were found to be independent factors for shortened CSS time in univariate analyses but not independent factors in multivariate analyses. Although we added clinicopathological factors such as pathological T stage, tumor grade, lymph node metastasis, and LVI, postoperative CAR ≥0.27 was designated as an only prognostic factor for worse CSS and ERFS rates in multivariate analysis of Cox proportional hazards model. Postoperative CAR ≥0.27 did not have any significant association with pathological factors or postoperative laboratory parameters besides preoperative NLR, which means postoperative CAR is independent of pathological factors. We also performed multivariate analysis in patients with advanced pT stage (≥T3) and

Table II. Univariate and multivariate analyses of independent factors for cancer-specific survival.

	Univariate			Multivariate		
Parameters	Hazard ratio	95% CI	P-value	Hazard ratio	95% CI	P-value
Clinicopathological						
Pathological T stage (≥T3 or ≤T2)	3.943	1.996-8.344	<0.001	2.149	0.974-5.070	0.058
Tumor grade (high or PUNLMP/low)	2.839	1.211-8.305	0.014	2.363	0.930-7.277	0.072
Lymph node metastasis (positive or negative)	2.069	0.979-4.079	0.056			
Ureter involvement (positive or negative)	1.501	0.361-4.170	0.524			
Surgical margin (positive or negative)	1.405	0.419-3.530	0.539			
Lymphovascular invasion (positive or negative)	3.655	1.844-7.992	<0.001	1.615	0.712-3.942	0.258
Carcinoma *in situ* (positive or negative)	0.442	0.072-1.448	0.203			
Laboratory						
Preoperative eGFR (< or ≥45 ml/min/1.73 m^2)	2.364	1.205-4.501	0.013	1.972	0.949-3.982	0.068
Postoperative eGFR (< or ≥45 ml/min/1.73 m^2)	1.767	0.874-3.407	0.110			
Preoperative CAR (≥ or <0.17)	2.240	1.163-4.254	0.017	1.320	0.635-2.680	0.451
Postoperative CAR (≥ or <0.27)	4.209	2.201-7.992	<0.001	3.368	1.674-6.731	<0.001
Preoperative NLR (≥ or <2.46)	1.863	0.977-3.606	0.059			
Postoperative NLR (≥ or <2.19)	1.667	0.872-3.309	0.123			
Preoperative PLR (≥ or <94.80)	2.091	0.994-4.112	0.052			
Postoperative PLR (≥ or <105.23)	1.419	0.606-2.950	0.396			

UTUC, upper urinary tract urothelial carcinoma; RC, radical cystectomy; BCG, bacillus Calmette-Guérin; PUNLMP, papillary urothelial neoplasm of low malignant potential; eGFR, estimated glomerular filtration rate (ml/min/1.73 m^2); CAR, C-reactive protein (mg/dl) to albumin (g/dl) ratio; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio.

Table III. Univariate and multivariate analyses of independent factors for extraurothelial recurrence-free survival.

	Univariate			Multivariate		
Parameters	Hazard ratio	95% CI	P-value	Hazard ratio	95% CI	P-value
Clinicopathological						
Pathological T stage (≥T3 or ≤T2)	2.602	1.412-4.954	0.002	1.746	0.819-3.883	0.151
Tumor grade (high or PUNLMP/low)	2.724	1.238-7.187	0.011	1.867	0.800-5.107	0.156
Lymph node metastasis (positive or negative)	2.114	1.041-4.021	0.039	1.664	0.764-3.466	0.194
Ureter involvement (positive or negative)	1.858	0.557-4.622	0.278			
Surgical margin (positive or negative)	1.239	0.372-3.079	0.692			
Lymphovascular invasion (positive or negative)	2.323	1.256-4.469	0.007	1.050	0.486-2.346	0.902
Carcinoma *in situ* (positive or negative)	0.844	0.253-2.099	0.741			
Laboratory parameters						
Preoperative eGFR (< or ≥45 ml/min/1.73 m^2)	2.209	1.173-4.055	0.015	1.699	0.858-3.276	0.126
Postoperative eGFR (< or ≥45 ml/min/1.73 m^2)	1.586	0.824-2.933	0.162			
Preoperative CAR (≥ or <0.17)	1.987	1.065-3.637	0.032	1.327	0.651-2.623	0.427
Postoperative CAR (≥ or <0.27)	3.147	1.684-5.766	<0.001	2.401	1.196-4.684	0.015
Preoperative NLR (≥ or <2.46)	1.504	0.823-2.756	0.183			
Postoperative NLR (≥ or <2.19)	1.597	0.870-3.030	0.132			
Preoperative PLR (≥ or <94.80)	2.133	1.049-4.060	0.037	1.888	0.868-3.886	0.106
Postoperative PLR (≥ or <105.23)	1.407	0.633-2.814	0.379			

UTUC, upper urinary tract urothelial carcinoma; RC, radical cystectomy; BCG, bacillus Calmette-Guérin; PUNLMP, papillary urothelial neoplasm of low malignant potential; eGFR, estimated glomerular filtration rate (ml/min/1.73 m^2); CAR, C-reactive protein (mg/dl) to albumin (g/dl) ratio; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio.

Table IV. Association between postoperative CAR and clinicopathological parameters.

Parameters	Total (%) (n=102)	Postoperative CAR		P-value
		≥0.27, n (%)	<0.27, n (%)	
Pathological T stage				
≥T3	48 (47.1)	14 (29.2)	34 (70.8)	0.360
≤T2	54 (52.9)	11 (20.4)	43 (79.6)	
Tumor grade				
High	75 (73.5)	19 (25.3)	56 (74.7)	>0.999
PUNLMP/Low	27 (26.5)	6 (22.2)	21 (77.8)	
Lymph node metastasis				
Positive	21 (20.6)	7 (33.3)	14 (66.7)	0.393
Negative	81 (79.4)	18 (22.2)	63 (77.8)	
Lymphovascular invasion				
Positive	50 (49.0)	15 (30.0)	35 (70.0)	0.253
Negative	52 (51.0)	10 (19.2)	42 (80.8)	
Postoperative eGFR, ml/min/1.73 m^2				
<45	29 (28.4)	9 (31.0)	20 (69.0)	0.444
≥45	73 (71.6)	16 (21.9)	57 (78.1)	
Postoperative NLR				
≥2.19	55 (53.9)	19 (34.5)	36 (65.5)	0.012
<2.19	47 (46.1)	6 (12.8)	41 (87.2)	
Postoperative PLR				
≥105.23	85 (83.3)	20 (23.5)	65 (76.5)	0.758
<105.23	17 (16.7)	5 (29.4)	12 (70.6)	

CAR, C-reactive protein (mg/dl) to albumin (g/dl) ratio; PUNLMP, papillary urothelial neoplasm of low malignant potential; eGFR, estimated glomerular filtration rate (ml/min/1.73 m^2); NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio.

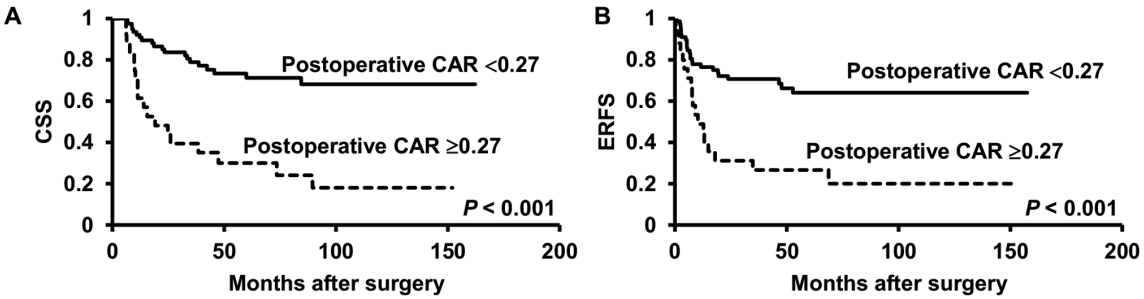

Figure 2. Survival analysis based on postoperative CAR values. There was a significant difference in time to (A) cancer-specific mortality and (B) extraurothelial recurrence between patients with and without postoperative CAR ≥0.27. CSS, cancer-specific survival; ERFS, extraurothelial recurrence-free survival; CAR, C-reactive protein/albumin ratio.

found that higher postoperative CAR was the only independent predictor of poor CSS (HR, 2.600; 95% CI, 1.126-5.833; P=0.026) and ERFS rates (HR, 2.399; 95% CI, 1.062-5.297; P=0.036). We also found that postoperative chemotherapy did not improve prognosis in patients with advanced pT stage. This may be because 21 out of 28 patients (75%) received salvage chemotherapy, and a higher postoperative CAR could facilitate monitoring of patients with ≥pT3 after radical cystectomy.

CIS at radical cystectomy is known to increase the risk of recurrence, especially in organ-confined patients (26-28). However, out of 10 patients with CIS, two had advanced pT stage (≥T3), one showed LVI, and other two had higher postoperative CAR (≥0.27) in the present study. This may explain why patients with CIS did not show worse survival in this study.

Numerous studies have demonstrated an association between preoperative NLR and survival (9,29,30). Conversely, some studies investigated whether postoperative SIR markers could be an effective prognostic marker for patients with clinically localized upper urinary tract urothelial carcinoma undergoing radical nephroureterectomy (19,31). Subsequently, postoperative NLR has been suggested as a beneficial prognostic marker not only in urothelial carcinoma (17,18), but also

Table V. Univariate and multivariate analyses of independent factors for cancer-specific survival in 48 patients with advanced pT stage (≥T3).

	Univariate			Multivariate		
Parameters	Hazard ratio	95% CI	P-value	Hazard ratio	95% CI	P-value
Clinicopathological						
Tumor grade (high or PUNLMP/low)	1.527	0.447-9.570	0.546			
Lymph node metastasis (positive or negative)	1.204	0.529-2.599	0.647			
Ureter involvement (positive or negative)	1.164	0.346-7.239	0.833			
Surgical margin (positive or negative)	1.069	0.410-3.653	0.902			
Lymphovascular invasion (positive or negative)	1.822	0.636-7.675	0.291			
Carcinoma *in situ* (positive or negative)	0.729	0.041-3.467	0.745			
Laboratory						
Preoperative eGFR (< or ≥45 ml/min/1.73 m^2)	1.848	0.846-3.951	0.121			
Postoperative eGFR (< or ≥45 ml/min/1.73 m^2)	1.434	0.631-3.087	0.376			
Preoperative CAR (≥ or <0.17)	1.843	0.854-3.952	0.118			
Postoperative CAR (≥ or <0.27)	3.067	1.398-6.588	0.006	2.600	1.126-5.833	0.026
Preoperative NLR (≥ or <2.46)	1.270	0.592-2.826	0.541			
Postoperative NLR (≥ or <2.19)	1.521	0.706-3.456	0.287			
Preoperative PLR (≥ or <94.80)	2.586	1.059-5.761	0.038	1.841	0.231-1.381	0.190
Postoperative PLR (≥ or <105.23)	1.489	0.545-3.485	0.409			

UTUC, upper urinary tract urothelial carcinoma; RC, radical cystectomy; BCG, bacillus Calmette-Guérin; PUNLMP, papillary urothelial neoplasm of low malignant potential; eGFR, estimated glomerular filtration rate (ml/min/1.73 m^2); CAR, C-reactive protein (mg/dl) to albumin (g/dl) ratio; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio.

Table VI. Univariate and multivariate analyses of independent factors for extraurothelial recurrence-free survival in 48 patients with advanced pT stage (≥T3).

	Univariate			Multivariate		
Parameters	Hazard ratio	95% CI	P-value	Hazard ratio	95% CI	P-value
Clinicopathological						
Tumor grade (high or PUNLMP/low)	2.560	0.542-45.733	0.284			
Lymph node metastasis (positive or negative)	1.560	0.702-3.342	0.266			
Ureter involvement (positive or negative)	1.051	0.313-6.536	0.945			
Surgical margin (positive or negative)	1.050	0.403-3.582	0.928			
Lymphovascular invasion (positive or negative)	1.770	0.616-7.465	0.317			
Carcinoma *in situ* (positive or negative)	1.121	0.063-5.302	0.913			
Laboratory						
Preoperative eGFR (< or ≥45 ml/min/1.73 m^2)	1.736	0.793-3.727	0.164			
Postoperative eGFR (< or ≥45 ml/min/1.73 m^2)	1.315	0.579-2.830	0.499			
Preoperative CAR (≥ or <0.17)	1.329	0.599-2.841	0.473			
Postoperative CAR (≥ or <0.27)	2.777	1.265-5.971	0.012	2.399	1.062-5.297	0.036
Preoperative NLR (≥ or <2.46)	1.004	0.469-2.165	0.992			
Postoperative NLR (≥ or <2.19)	1.711	0.786-4.003	0.179			
Preoperative PLR (≥ or <94.80)	2.613	1.061-5.902	0.038	2.058	0.208-1.230	0.122
Postoperative PLR (≥ or <105.23)	1.416	0.518-3.316	0.469			

UTUC, upper urinary tract urothelial carcinoma; RC, radical cystectomy; BCG, bacillus Calmette-Guérin; PUNLMP, papillary urothelial neoplasm of low malignant potential; eGFR, estimated glomerular filtration rate (ml/min/1.73 m^2); CAR, C-reactive protein (mg/dl) to albumin (g/dl) ratio; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio.

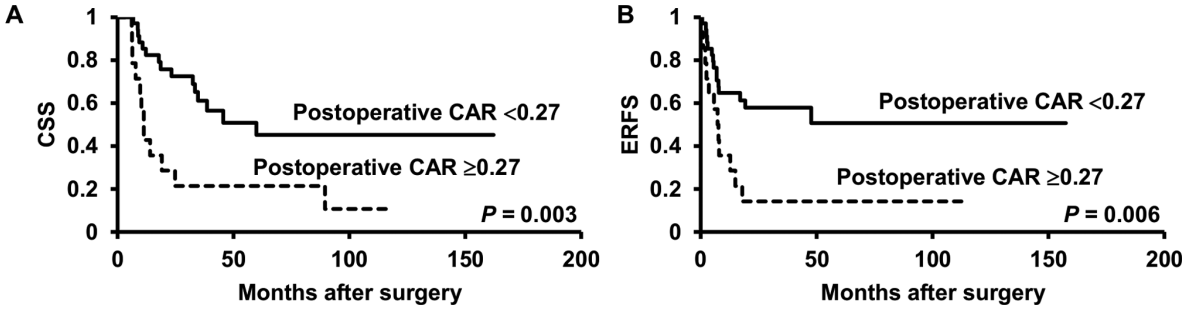

Figure 3. Survival analysis based on postoperative CAR of 48 patients with advanced pT stage (≥T3). There was a significant difference in time to (A) cancer-specific mortality and (B) extraurothelial recurrence between patients with and without postoperative CAR ≥0.27. CSS, cancer-specific survival; ERFS, extraurothelial recurrence-free survival; CAR, C-reactive protein/albumin ratio.

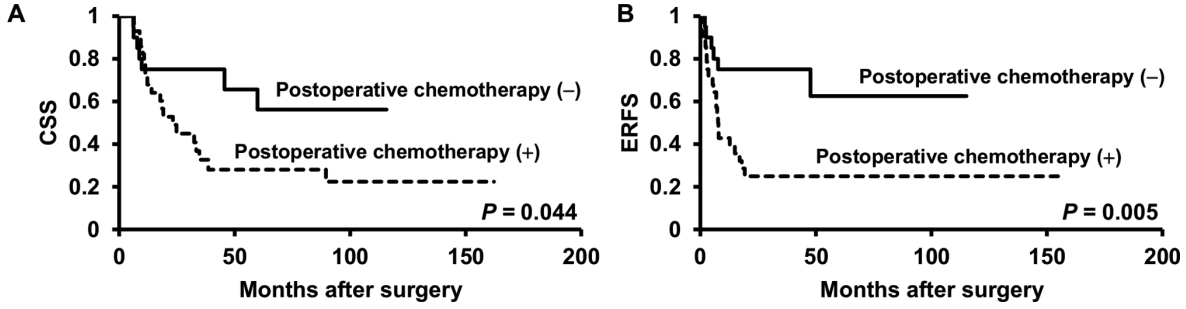

Figure 4. Survival curves of 48 patients with advanced pT stage (≥T3) who received postoperative chemotherapy. There was a significant difference in time to (A) cancer-specific mortality and (B) extraurothelial recurrence between patients with and without postoperative chemotherapy. CSS, cancer-specific survival; ERFS, extraurothelial recurrence-free survival.

in other carcinomas (32,33). Preoperative NLR only reflects the balance host protumor inflammatory status and antitumor immune status before surgery, whereas postoperative NLR indicates the balance between tumor inflammatory response and host immune response after surgical removal of the tumor, which should provide a more precise indication of treatment response (33).

On a similar note to papers reporting on the prognostic value of NLR, several studies have investigated presurgical or pretreatment CAR as a predictor of poor prognosis in patients with several types of tumors (14-16). The prognostic value of postoperative CAR has remained unclear in patients with bladder cancer undergoing radical cystectomy, although several reports have implied clinical significance of postoperative CRP (31,34). The present study demonstrated that high postoperative CAR levels were significantly associated with poor prognosis in patients with locally advanced bladder cancer. Patients with higher postoperative CAR also exhibited a significantly worse prognosis compared with those with lower postoperative CAR, even among those with advanced pT stage (≥T3). Based on this finding and in relation to earlier suggestions (19,33), this may be because higher postoperative CAR possibly indicates potential residual cancer, including micrometastases, whereas preoperative CAR values indicate the presence of the primary tumor and potential micrometastatic lesions. This is the reason why higher preoperative CAR is an independent factor only in univariate analysis, whereas higher postoperative CAR is an independent predictor of worse CSS and ERFS rates in multivariate analysis. Thus, if postoperative CAR reflects micrometastases, it is potentially a significant prognostic marker in patients with locally advanced bladder cancer undergoing surgical treatment.

Approximately 20% of all cancer-related deaths are attributable to malnutrition (35). In addition, malnutrition is present in 40-80% of all patients with cancer at some stage during the clinical course of their disease (35). Malnutrition and inflammation suppress the synthesis of serum Alb, which is an indicator of the nutritional status of patients, as well as the severity, progression, and prognosis of the disease (36). Serum Alb is an independent predictor of clinical outcomes in various cancers (37,38). Moreover, many studies have combined CRP and Alb to create new SIR markers, such as GPS and CAR. In fact, both GPS and CAR are independent indicators of poor survival in various types of cancer (12,14-16). In the present study, CAR was applied as a variable because CAR is a continuous value compared with GPS, which is a dichotomous variable, although it was required to determine the cut-off values for cancer-specific death and/or extraurothelial recurrence.

This study has some potential limitations. First, our sample size was relatively small, although the CSS and ERFS rates were evaluated as our clinical endpoint. With a longer follow-up and a larger sample population, the statistical strength of our study can be reinforced, leading to more precise prognosis. Second, we could not clarify the background between postoperative CAR and worse survival rates in patients with advanced bladder cancer, although the possible implications for patients with a higher postoperative CAR value are suggested. Third, several other factors that may have influenced the inflammatory status, such as diabetes mellitus and/or hyperlipidemia, were not included in the present study. However, we deemed

these conditions had only minimal influence on the values of inflammatory indices because body mass index did not have any significant association with prognosis (data not shown). Notwithstanding these limitations, our data indicate that a higher postoperative CAR can be an independent prognostic factor for worse survival rates.

In summary, a higher postoperative CAR value can provide additional information about the possibility of worse CSS and ERFS rates.

In conclusion, among the patients with bladder cancer undergoing radical cystectomy, survival rates are worse in those with higher postoperative CAR values than in those with lower postoperative CAR values. Therefore, patients with higher postoperative CAR should undergo additional treatment or at least careful follow-up.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

KK, ST, AH and KI were involved in the conception and design of the study. KK, ST, AH and KI collected the data, and KK analyzed the data. KK drafted the manuscript. KK and KI reviewed and edited the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All procedures performed in the studies were in accordance with the ethical standards of the National Defense Medical College (Saitama, Japan; ID 2734). The study protocol was accepted on June 14, 2017, by the National Defense Medical College Ethics Committee, and an opt-out approach on the web page of the National Defense Medical College was used instead of collecting written informed consent from all participants.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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