Original Article

Development of nomograms related to inflammatory biomarkers to estimate the prognosis of bladder cancer after radical cystectomy

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Background: Bladder cancer is one of the most common carcinomas and it brings about huge social economic burden. There is not a reliable way to predict the prognosis of bladder patients. We develop the nomogram to predict the prognosis of bladder cancer patients.

Methods: A total of 127 bladder cancer patients after radical cystectomy were studied retrospectively. Their clinicopathological data were collected for statistical analysis.

Results: The level of albumin/globulin ratio (AGR), C-reactive protein/albumin ratio (CAR), neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) associated with pathological and hematological parameters like T stage and hemoglobin. Furthermore, the AGR was associated with overall survival (OS) and CAR, NLR, and PLR were associated with both OS and progression-free survival (PFS) ($P<0.05$). The multivariate analysis revealed that tobacco smoking, tumor T stage, M stage, NLR, CAR, and AGR were all independent predictors for OS of patients and tobacco smoking, tumor T stage, NLR, CAR, and AGR were independent predictors for PFS of patients. In addition, AGR, CAR, and NLR, as well as, the clinicopathological parameters in the development of nomograms with a C index of 0.901 (95% CI: 0.505–1.269) for OS, and 0.807 (95% CI: 0.755–0.858) for PFS. The nomograms were able to provide a prognosis of the OS with the area under the curve (AUC) =0.86. Further, tests assessed the PFS with the AUC =0.84.

Conclusions: This study demonstrates that the nomograms of the inflammatory biomarkers were able to predict prognosis of bladder cancer patients after radical cystectomy.

Keywords: Nomogram; bladder cancer; inflammatory biomarkers; prognosis

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Introduction

Bladder cancer is a significant global health problem, with 429,800 newly diagnosed cases and 165,100 cancer-related deaths worldwide in 2012 (1). In China, 80,000 new cases and 32,000 cancer-related deaths were reported in 2015. To date, approximately 75% of the diagnosed bladder cancer cases are non-muscle invasive bladder cancer (NMIBC), whereas the remaining 25% of patients have muscle-invasive bladder cancer (MIBC). Unfortunately, patients diagnosed with MIBC often have a poorer prognosis than patients with NMIBC.

Patients who have undergone radical cystectomy have shown better prognosis than patients without surgery (2). However, there are no reliable biomarkers for the prediction of bladder cancer and post-cystectomy treatment response. Therefore, the identification and evaluation of biomarkers is essential for the risk stratification of patients, assessment of treatment decisions, and prediction of bladder cancer prognosis. Previous studies reported that bladder cancer development and progression were closely related to the host inflammatory and immune responses. The progression and metastasis of tumor cells occur through various mechanisms such as the inflammatory response (3). During the inflammatory response, a number of neutrophils and platelets, as well as acute phase proteins such as C-reactive protein and albumin, are altered. Many of these inflammatory indicators show potential as markers for the clinical assessment of cancer prognosis. For example, the albumin/globulin ratio (AGR), C-reactive protein/albumin ratio (CAR), neutrophil to lymphocyte ratio (NLR), and platelet to lymphocyte ratio (PLR) have been used to predict the prognosis of bladder cancer patients (4,5). However, conflicting reports on the effectiveness of these measured parameters requires further investigation to determine their predictive potential. Therefore, we developed nomograms to assess the usefulness of these parameters for predicting bladder cancer prognosis.

We present the following article in accordance with the TRIPOD reporting checklist (available at https://dx.doi.org/10.21037/atm-21-4097).

Methods

Patients and data collection

In this study, we retrospectively included 150 bladder cancer patients who received medical care between January 2005 and December 2017 at Shanghai Tenth People's Hospital (Shanghai, China). Patients were selected based on the following criteria: (I) histopathological diagnosis of bladder cancer including MIBC and recurrence of high-grade T1 (T1HG) bladder cancer; (II) laboratory tests were collected 3 days before surgery, including serum levels of albumin, C-reactive protein, and neutrophil count, among others; and (III) complete clinical and follow-up data was collected. Patients with a history of cardiovascular and cerebrovascular disease and type 2 diabetes were also included in the study. Patients who received neoadjuvant/adjuvant chemotherapy or suffered from other inflammatory conditions were excluded from the study. Therefore, a total of 127 patients could be used to construct the nomograms.

The following clinicopathological data were collected from patient medical records: age, gender, smoking status, tumor size, cancer history, laboratory tests (urinary cytology, cystoscopy, serum creatinine, ultrasonography, and computed tomography or magnetic resonance imaging), and pathological findings (tumor histology, staging, grading, and lymph nodes). Tumor histology was classified as urothelial carcinoma or squamous cell carcinoma. Pathologists assessed the pathological grade and stage of the tumor according to the 2004 WHO classification system and the tumor, lymph node, metastasis (TNM) staging system. The AGR was calculated as albumin divided by globulin, and the CAR was calculated as C-reactive protein divided by albumin. The NLR and PLR were calculated as platelets, and the absolute count of neutrophils was divided by the absolute count of lymphocytes.

Patients were followed up by 2 experienced non-surgical physicians. Cystoscopy and urine cytology were performed every 3 months within 2 years after surgery, every 6 months for the next 3 years, and then annually. Abdominal CT examinations were performed every 6 months after surgery for 2 years, and once a year thereafter. All results were obtained through outpatient visits or telephone interviews. All patients were followed up regularly until March 2018. The overall survival (OS) was defined as the duration between the first tumor diagnosis and death, while the progression-free survival (PFS) was defined as the time between the first tumor diagnosis and disease progression after treatment.

The study was approved by the Ethics Committee of the Shanghai Tenth People's Hospital (SHSY-IEC-4.1/19-120/01), and all participants provided written informed consent before registration. The study is also in

line with the Helsinki Declaration (as revised in 2013).

Statistical analysis

SPSS v24.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. The median and interquartile range (IQR) were used to evaluate continuous variables, while frequency and scale were used to classify variables. Receiver operating characteristic (ROC) curves were used to determine the best cut-off values for the AGR, CAR, NLR, and PLR. Kaplan-Meier curves and the log rank test were used to predict OS and PFS after stratified sampling of the AGR, CAR, NLR, and PLR. Univariate and multivariate Cox regression analyses were performed to calculate the corresponding hazard ratio (HR) and 95% confidence interval (CI). Nomograms and time-dependent ROCs were established using R (http://www.R-project.org) and EmpowerStats software (www.empowerstats.com, The X&Y solutions, Inc., Boston MA). A P value <0.05 was considered statistically significant.

Results

Characteristics of patients

We retrospectively analyzed a cohort of 127 bladder cancer patients after radical cystectomy. The clinicopathological data showed that there were 110 males and 17 females with a median age of 66 years old (ranging between 29 and 87 years). Based on clinical records, 61 patients had smoked tobacco and 66 never smoked tobacco. Of all bladder cancer patients, 17 patients had low-grade bladder cancer while 110 had high-grade bladder cancer. Of the high-grade bladder cancer cases, 48 cases (37.8%) were stage T1, 26 (20.5%) were stage T2, 29 (22.8%) were stage T3, and 24 (18.9%) were stage T4. The mean body mass index (BMI) of these patients was 23.47. The pathology reports of 108 patients showed urothelial carcinoma, whereas the other 19 patients had squamous cell carcinoma.

Identification of the inflammatory biomarkers and their cut-off values

In order to more accurately determine the cut-off values for the assessed biomarkers, we plotted data using ROC curves to identify the pre-surgery values for the AGR, CAR, NLR, and PLR. It was ascertained that AGR =1.55, CAR =0.165, NLR =3.73, and PLR =124.4 were the cut-off values for each parameter and were identified as the best prognostic predictors for patients after radical cystectomy (*Figure 1*). Specifically, the area under the curve (AUC) of the AGR was 0.81 (95% CI: 0.74–0.88), with a sensitivity of 0.84 and a specificity of 0.66 (P<0.001). The AUC of the CAR was 0.76 (95% CI: 0.68–0.85), with a sensitivity of 0.67 and a specificity of 0.83 (P<0.001). The AUC of the NLR was 0.62 (95% CI: 0.53–0.72), with a sensitivity of 0.47 and a specificity of 0.81 (P<0.012). The AUC of the PLR was 0.62 (95% CI: 0.52–0.72), with a sensitivity of 0.72 and a specificity of 0.45 (P<0.015). Based on these cut-off values, we were able to separate these 127 patients into the following groups: low AGR group with 73 (57.5%; <1.55), high AGR group with 54 (42.5%; ≥1.55); low CAR group with 75 (59.1%; <0.16), high CAR group with 52 (40.9%; ≥0.16); low NLR group with 76 (59.8%; <3.73), high NLR group with 51 (40.2%; ≥3.73); low PLR group with 45 (35.4%; <106), high PLR group with 82 (64.6%; ≥106).

Association of these inflammatory biomarkers with the clinicopathological features of patients

The identified inflammatory biomarkers were then linked with patient clinicopathological features. We found that a high AGR level was associated with tobacco smoking, tumor size, T stage, tumor-infiltrating neutrophils, and levels of serum albumin and hemoglobin (P<0.05). The CAR biomarker correlated with tobacco smoking, T stage, N stage, tumor-infiltrating neutrophils, and serum levels of albumin and hemoglobin (P<0.05). NLR levels were linked with tobacco smoking, tumor size, T stage, N stage, and levels of serum albumin, neutrophils, and hemoglobin (P<0.05). Moreover, a high PLR level corresponded with high BMI, tobacco smoking, and serum levels of hemoglobin (P<0.05; *Table 1*).

Furthermore, we plotted the Kaplan-Meier curves for OS and PFS stratified by these parameters and discovered that AGR levels predicted the OS of these patients, while levels of the CAR, NLR, and PLR forecasted both OS and PFS (P<0.05; *Figure 1*).

Univariate and multivariate analyses of OS and PFS

Univariate and multivariate analyses were employed to predict independent factors of OS and PFS. Our univariate analysis indicated that tobacco smoking, tumor size, T stage, N stage, M stage, NLR, PLR, CAR, AGR, and albumin levels were all significantly linked to the OS of patients

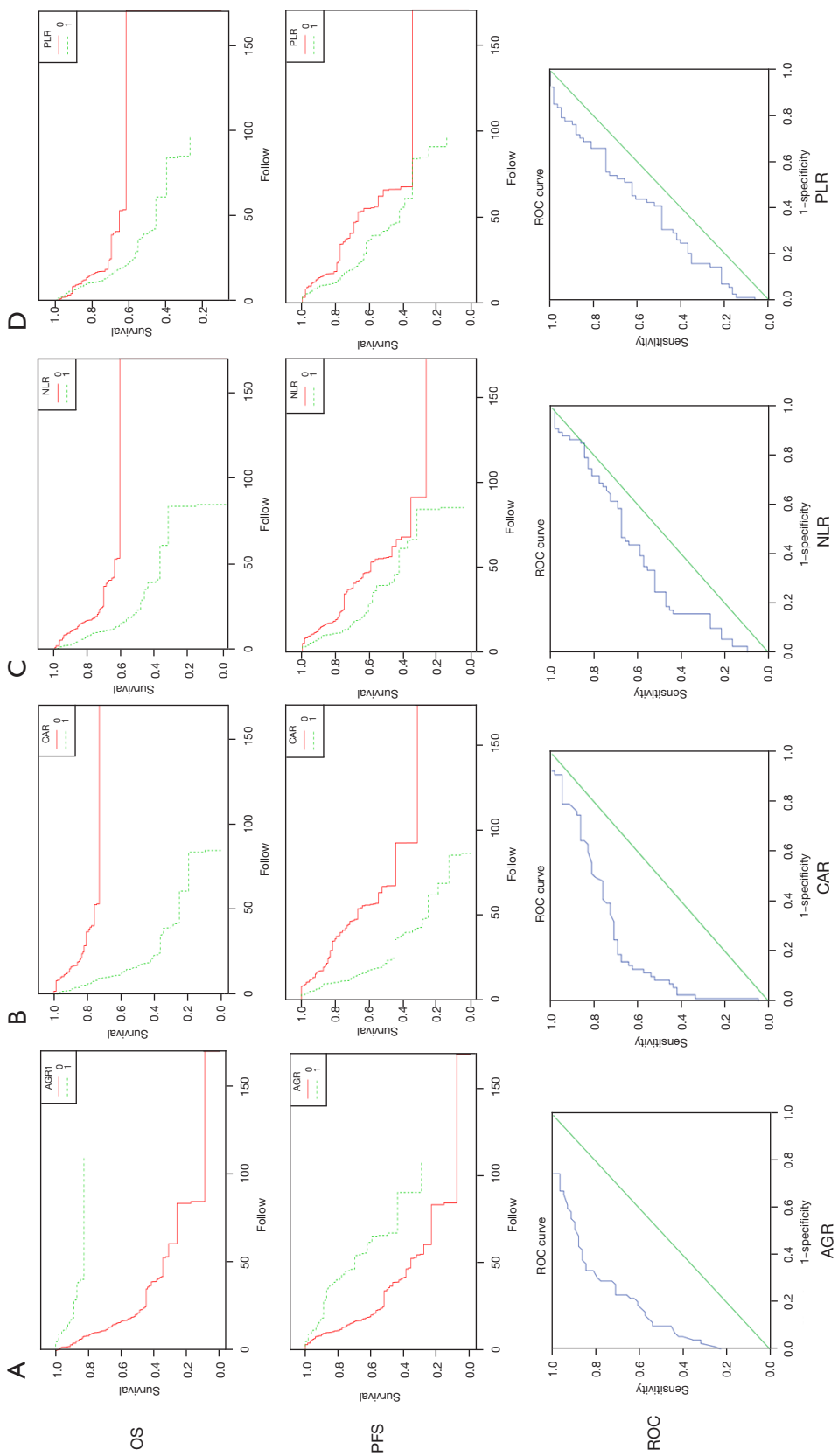

Figure 1 Kaplan-Meier survival curves of PFS and OS. All data presented represent biomarkers studied and stratified within a low to high range as follows: (A) AGR; (B) CAR; (C) NLR; (D) PLR. PFS, progression-free survival; OS, overall survival; AGR, albumin/globulin ratio; CAR, C-reactive protein/albumin ratio; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio.

Table 1 Association of the AGR, CAR, NLR, and PLR with the clinicopathological characteristics of patients

Factors	Low AGR group	High AGR group	P value	Low CAR group	High CAR group	P value	Low NLR group	High NLR group	P value	Low PLR group	High PLR group	P value
Age (years)	66.10±12.01	65.63±10.60	0.273	64.19±9.99	68.37±12.85	0.052	64.62±10.58	67.80±12.37	0.504	64.28±11.26	66.78±11.43	0.200
BMI (kg/m^2)	23.47±3.14	23.48±2.71	0.831	23.42±2.56	23.54±3.48	0.824	25.83±2.96	22.94±2.9	0.096	24.15±2.78	23.1±3.00	0.050
Smoking status			<0.001			0.030			0.007			0.010
Yes	45	16		50	21		29	32		12	49	
No	28	38		30	36		47	19		33	33	
Grade			0.350			0.299			0.660			0.900
Low	8	9		12	5		11	6		6	11	
High	75	45		63	47		65	45		39	71	
Tumor histological types			0.139			0.875			0.325			0.844
Urothelial	60	48		64	44		66	42		38	70	
Squamous	13	6		11	8		10	9		7	12	
Cardiopulmonary disease			0.111			0.07			0.140			0.190
Yes	14	17		14	17		15	16		8	23	
No	59	37		51	35		61	35		37	59	
Diabetes mellitus			0.569			0.226			0.290			0.680
Yes	12	11		11	12		16	7		9	14	
No	61	43		64	40		60	44		36	68	
T stage			0.001			0.015			0.020			0.110
Non-muscle invasive	17	36		41	12		38	15		23	30	
Muscle invasive	56	18		34	40		38	36		22	52	
N stage			0.160			0.014			0.050			0.330
N0	63	50		71	42		71	42		44	69	
N1	10	4		4	10		5	9		4	10	

Table 1 (*continued*)

Table 1 (*continued*)

Factors	Low AGR group	High AGR group	P value	Low CAR group	High CAR group	P value	Low NLR group	High NLR group	P value	Low PLR group	High PLR group	P value
M stage			0.091			0.189			0.240			0.509
M0	70	51		73	48		74	47		57	64	
M1	3	3		2	4		2	4		3	3	
Tumor size			0.045			0.106			0.070			0.442
<4 cm	40	39		51	28		51	28		30	49	
≥4 cm	33	15		24	24		24	24		15	33	
Albumin	36.66±6.70	41.61±4.64	0.045	40.13±5.63	35.48±6.78	0.001	39.75±5.55	35.96±7.22	0.001	38.75±5.5	37.94±7.03	0.502
Neutrophil	5.36±2.89	4.66±2.30	0.042	4.20±2.12	6.28±2.90	0.001	3.78±1.5	6.98±2.89	0.001	4.47±2.28	5.38±2.82	0.680
Hemoglobin	115.37±18.95	136.37±11.98	0.002	131.77±13.46	113.5±21.47	0.001	130.65±15.55	114.82±20.68	0.001	130.48±16.94	120.89±19.84	0.007

AGR, albumin/globulin ratio; CAR, C-reactive protein/albumin ratio; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio.

(P<0.05; *Table 2*). Fewer clinicopathological features, such as tobacco smoking, tumor diameter, T stage, N stage, NLR, AGR, CAR, and levels of albumin and hemoglobin, were associated with PFS (P<0.05; *Table 3*). Our multivariate analysis revealed that tobacco smoking, T stage, M stage, NLR, CAR, and AGR were independent predictors for the OS of patients, while tobacco smoking, T stage, NLR, CAR, and AGR were independent predictors for the PFS of patients (P<0.05; *Table 2* and *Table 3*).

Development of the nomogram models of these inflammatory biomarkers for bladder cancer

Based on the significant independent factors of PFS and OS and from the data collected on the NLR, PLR, CAR, and AGR, we developed OS and PFS predictive nomogram models for bladder cancer patients using multivariate Cox regression analysis. We determined these scores based on the intersection of the vertical line and the point axis associated with each variable, while the total risk scores were summations of each variable score. Thus, these total scores established predictive measures of OS and PFS for each patient. Moreover, we revealed that the Harrell's C-index of the nomogram was 0.901 (95% CI: 0.50–1.26) for OS and 0.81 (95% CI: 0.75–0.85) for PFS (*Figure 2*). In addition, we analyzed the performance of the nomogram by time-dependent ROC curves compared with the TNM staging system, and for OS, we observed an AUC of 0.86, sensitivity of 0.96, and specificity of 0.63, while for PFS, the AUC was 0.84, the sensitivity was 0.83, and the specificity was 0.67 (*Figure 3*).

Discussion

Previous studies have assessed different inflammatory biomarkers including the AGR, CAR, NLR, and PLR to predict bladder cancer progression and prognosis. However, the data reported are inconsistent. Variations in laboratory test results and differences in the optimal cut-off values are likely to affect the data analysis and reported data accuracy. In the current study, we determined the optimal cut-off values of the AGR, CAR, NLR, and PLR in the prediction of bladder cancer prognosis using ROC curves. Our multivariate Cox analysis identified the AGR, CAR, and NLR as independent prognostic predictors. Through analyzing pre-surgery clinicopathological features and inflammatory biomarkers (AGR, CAR, and NLR), we have successfully developed 2 useful nomograms to

Table 2 Prognostic factors for OS in bladder cancer patients after radical cystectomy

Factors	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Sex	0.67	0.28–1.56	0.35			
Age	1.91	1.10–3.34	0.21			
BMI	0.89	0.53–1.49	0.67			
Smoking	4.85	2.67–8.83	0.01	2.49	1.30–4.78	0.006
Cardiopulmonary disease	1.17	0.65–2.07	0.59			
Diabetes mellitus	1.36	0.73–2.53	0.32			
Tumor size	1.84	1.10–3.09	0.02	1.54	0.90–2.64	0.11
T stage	7.04	3.32–14.94	0	3.72	1.66–8.32	0.001
N stage	2.50	1.28–4.87	0.007	1.33	0.64–2.77	0.43
M stage	2.98	1.18–7.50	0.02	2.80	1.01–7.77	0.048
Tumor histological types	1.35	0.83–2.19	0.223			
Grade	1.58	0.68–3.68	0.28			
AGR	0.15	0.075–0.31	0	0.25	0.11–0.55	0.001
NLR	2.79	1.65–4.69	0.001	2.11	1.05–4.24	0.019
PLR	2.04	1.12–3.73	0.019			
CAR	4.94	2.85–8.57	0	2.31	1.14–4.71	0.02
Albumin	0.59	0.34–1.02	0.06			
Hemoglobin	0.31	0.17–0.55	0	0.78	0.40–1.51	0.46
Neutrophil	1.56	0.93–2.60	0.089			

AGR, albumin/globulin ratio; CAR, C-reactive protein/albumin ratio; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio.

predict the OS and PFS of bladder cancer patients after radical cystectomy. Most importantly, we were able to use these nomograms to predict OS and PFS in each individual patient, contributing to the potential for personalized therapy.

Recently, nomograms have been used to predict the probability of clinical outcomes in a variety of cancer patients. Several studies have investigated clinical and pathological variables in the prognostic prediction of bladder cancer after radical surgery. Bochner *et al.* developed a nomogram including age, gender, operative time, pathological tumor stage, grading, and regional lymph node status to predict recurrence after radical surgery for bladder cancer (6). Yamada *et al.* used the data of tumor number, shape, grade, and intravesical instillation to construct a nomogram and used it to predict recurrence-free survival (7). In these studies, only the clinical and pathological data of the patients were included. In our study, we included patients' inflammation index, immune status, and clinicopathological data to make the results more convincing. We also noticed that Riester *et al.* included certain novel genes (such as FN1, NNMT, POSTN, and SMAD6) in their nomogram, which may make the predictions more accurate (8). However, such genetic testing has a higher financial burden. In China, measuring inflammation indicators such as the CAR and NLR may be less expensive and more affordable. Using these clinically readily available indicators to initially predict the prognosis of patients with bladder cancer may promote the individualized treatment of patients by doctors.

In recent years, the use of inflammation-related markers as predictive measures for determining the prognosis of cancer patients has received increasing attention (9,10). For bladder cancer in particular, several previous studies have confirmed the association of inflammation-related markers with the prognosis of patients. For example,

Table 3 Prognostic factors for PFS in bladder cancer patients after radical cystectomy

Factors	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Sex	0.53	0.22–1.23	0.14			
Age	1.51	0.91–2.53	0.11			
BMI	1.20	0.73–1.97	0.45			
Smoking	5.38	3.57–8.12	0.001	4.06	2.59–6.36	0.001
Cardiopulmonary disease	1.11	0.64–1.94	0.702			
Diabetes mellitus	1.50	0.82–2.72	0.18			
Tumor size	1.73	1.03–2.89	0.036	1.35	0.79–2.31	0.26
T stage	3.94	2.21–7.01	<0.001	4.36	1.93–9.85	0.001
N stage	2.47	1.24–4.89	0.01	1.54	0.73–3.24	0.24
M stage	1.86	0.67–5.15	0.22			
Tumor histological types	1.43	0.89–2.32	0.14			
Grade	1.87	0.80–4.33	0.14			
AGR	0.42	0.24–0.71	0.001	0.27	0.12–0.62	0.002
CAR	3.16	1.92–5.22	0.001	2.30	1.19–4.42	0.013
NLR	1.70	1.20–2.42	0.003	1.00	0.66–1.52	0.01
PLR	1.51	1.03–2.20	0.031	0.84	0.44–1.63	0.62
Albumin	0.52	0.31–0.89	0.019	0.91	0.44–1.89	0.81
Hemoglobin	0.41	0.24–0.69	0.001	0.77	0.37–1.57	0.47
Neutrophil	0.833	0.50–1.36	0.47			

AGR, albumin/globulin ratio; CAR, C-reactive protein/albumin ratio; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio.

Rajwa *et al.* evaluated the prognostic efficacy of the PLR, NLR, derived neutrophil-lymphocyte ratio (dNLR), and lymphocyte-monocyte ratio (LMR) in bladder cancer patients (11). Cheah *et al.* established that high CD14 expression in bladder cancer cells increased recruitment of more inflammatory factors, polarizing monocytes and macrophages to alter their immunosuppressive characteristics and promoting tumor cell growth (12). In this regard, the inflammation responses in bladder cancer demonstrate the systemic host immune status and reveal the complexity of the damage to immune surveillance caused by these cancer cells (13). Here, we assessed the values of these inflammation factors to evaluate and predict the prognosis of bladder cancer patients after radical cystectomy.

Furthermore, the value of the AGR is equal to the ratio of albumin/globulin, whereby serum albumin is primarily produced by the liver (14). Studies showed that a decrease in the levels of blood albumin led to an increase in systemic malnutrition and inflammation (15), while there was a close interaction between the blood albumin level and tumorigenesis (16). Conversely, globulin is a pro-inflammatory protein with complex components, including C-reactive protein (CRP), complement components, and immunoglobulin (17). Globulin's involvement in chronic inflammation was observed via elevated levels associated with inflammatory responses and immunosuppression (18). High serum levels of Globulin (GLB) resulted in the poor prognosis of several cancers (19,20). An increase in CRP has been reported in many cancer cases, which reflects the inflammatory and immune response against tumor cells of the human body (21). In the current study, we first revealed the association of the CAR with bladder cancer as an independent prognostic predictor.

Additionally, previous studies have demonstrated that

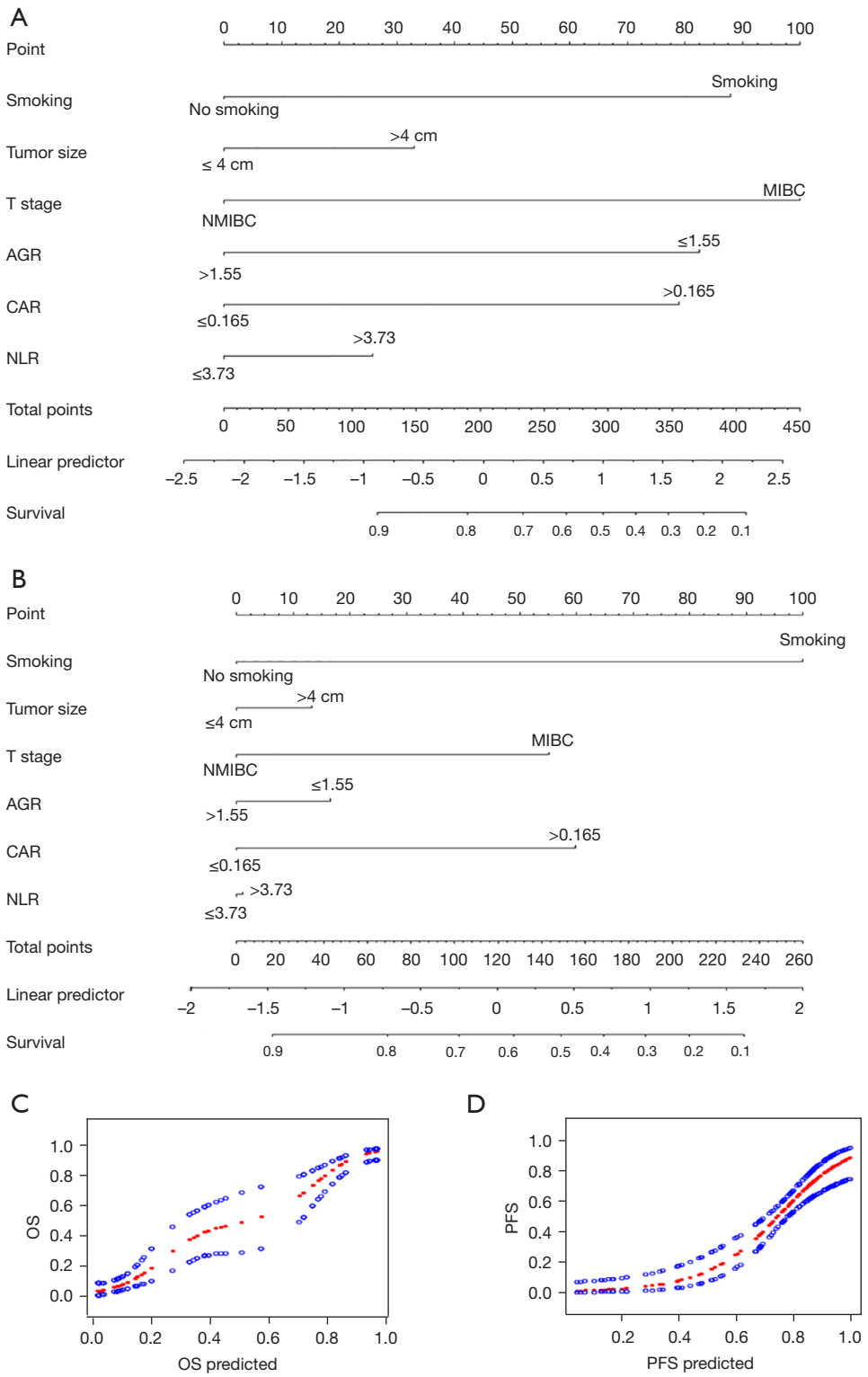

Figure 2 Nomogram models of inflammatory biomarkers. Nomograms convey prognostic models stratified by the clinicopathological characteristics and pretreatment inflammatory biomarkers for (A) OS prediction; (B) PFS prediction; (C) the Harrell's C-index to predict OS; (D) the Harrell's C-index to predict PFS. OS, overall survival; PFS, progression-free survival.

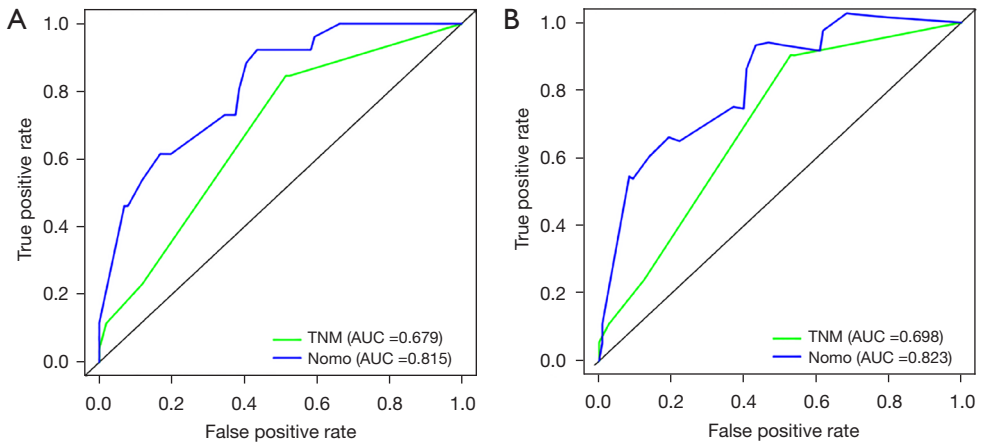

Figure 3 ROC curves compared with the TNM staging system. Time-dependent ROC curves by nomogram and TNM staging system for (A) OS prediction; and (B) PFS prediction. ROC, receiver operating characteristic; OS, overall survival; PFS, progression-free survival.

the NLR and PLR are indicators of bladder cancer (22,23). The level of NLR reflects the human body's immune response affiliated with cancer immunosurveillance, immunoediting, and immunosubversion (24). The upregulation of NLR indicated the relative increase in neutrophils and decrease in lymphocytes, leading to the promotion of tumor inflammation and an increase in the risk of cancer metastasis and recurrence (25). Meanwhile, neutrophils secrete IL-6, vascular endothelial growth factor (VEGF), and transforming growth factor beta (TGF-β) in the tumor microenvironment, resulting in the induction of lymphocyte apoptosis and immunosuppression (26). Albisinni *et al.* also suggest NLR and HPR seem closely related to the RFS, CSS and OS in bladder cancer (27). Platelets also play an important role in the recruitment and regulation of monocytes and granulocytes into tumor lesions (13), suggesting that platelet functionality may be critical for the production of tumor-associated macrophages and tumor-associated neutrophils (28). However, the PLR as an independent predictor of prognosis remains controversial, and many reports have shown that PLR does not have a significant ability to predict prognosis. Giakoustidis *et al.* (29) investigated the role of the NLR and PLR in the prognosis of 127 patients undergoing pancreatic ductal adenocarcinoma resection. They demonstrated the disadvantage of PLR as a prognostic factor (30). In our study, we also found that the PLR was not significantly associated with prognosis. However, further research is still needed to assess PLR as a prognostic factor in bladder cancer.

Smoking is known as one of the most significant risk factors for bladder cancer (31,32). Studies have also shown that smoking affects the prognosis of patients with bladder cancer (33,34). In this study, all inflammatory biomarkers were associated with smoking in patients. Smoking can induce systemic inflammation by increasing oxidative stress. Smoking also enhances the activation of redox-sensitive transcription factors such as nuclear factor-kappa B (NF-κB) and activator protein-1 (AP-1), which induce IL-8, IL-6, and tumor necrosis factor-α (TNF-α), leading to systemic inflammation (30,35). Therefore, smoking affects the body's immune regulation through these factors. Thus, compared with non-smoking patients, smoking can promote the development of tumors.

Most of the pathological diagnosis of bladder cancer is urothelial carcinoma, and a few are squamous cell carcinoma or other pathological types. For squamous cell carcinoma, in Egypt and other countries, the incidence of bladder cancer is closely related to schistosomiasis infection, and inflammation plays an important role in it (36). In our cohort, no significant differences in inflammatory markers between squamous cell carcinoma and urothelial carcinoma were observed. Severin Rodler *et al.* showed that changes in platelets and hemoglobin were not observed as independent risk factors in the bladder squamous cell carcinoma cohort (37). This may require more pathological data of squamous cell carcinoma for further research.

However, our current study does have some limitations. For example, our study is a single-center retrospective cohort study. Thus, we are not convinced of the efficacy of this predictive model, particularly when evaluating different ethnic groups. In order to enhance the model, further

research is required through larger multicenter prospective cohort studies. Moreover, the data of this group of patients may not represent other bladder cancer patients who have refused surgical intervention for various reasons.

Conclusions

In summary, our current data suggest that preoperative inflammatory biomarkers (AGR, NLR, and CAR) are independent prognostic predictors for the PFS and OS of bladder cancer patients after radical cystectomy. The nomograms based on these inflammatory biomarkers more accurately and practically predicted the OS and PFS of bladder cancer patients after radical cystectomy.

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Footnote

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