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ORIGINAL RESEARCH

Prognostic Value of Preoperative Albumin-to-Alkaline Phosphatase Ratio in Patients with Muscle-Invasive Bladder Cancer After Radical Cystectomy

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Objective: This study investigated the prognostic value of the preoperative albumin alkaline phosphatase ratio (AAPR) in patients with muscle-invasive bladder cancer after radical cystectomy.

Materials and Methods: We performed a retrospective, single-center cohort study among patients with muscle-invasive bladder cancer who underwent radical cystectomy and urinary diversion at the Department of Urology Surgery of the Affiliated Hospital of Qingdao University from 2007 to 2015. Cox proportional hazards regression was used to evaluate the relationship between preoperative AAPR and outcomes which include OS and CSS and RFS. Survival analysis was conducted using the Kaplan–Meier method and the log rank test.

Results: In total, 174 patients were followed up for 1–125 months, with a median follow-up of 30 months, 93 survived and 81 patients died. The median serum AAPR level in all patients was 0.62 (range: 0.12–1.67). In multivariate analysis, the preoperative AAPR showed to be associated with overall survival (OS: HR 0.22,95% CI 0.06 to 0.82, P=0.024), cancer-specific survival (CSS: HR 0.12,95% CI 0.02 to 0.63, P=0.013) and recurrence-free survival (RFS: HR 0.15,95% CI 0.03 to 0.82, P=0.029) after adjustment for potential confounders. Kaplan–Meier analysis showed that patients with low AAPR tertiles had shorter OS, CSS and RFS than patients with high AAPR tertiles (OS: P<0.001, CSS: P<0.001, RFS: P<0.001). The relationship between AARP and OS, CSS and RFS was linear.

Conclusion: Preoperative AAPR may be a potentially valuable prognostic marker in patients who underwent radical cystectomy for muscle-invasive bladder cancer.

Keywords: albumin-to-alkaline phosphatase ratio, AAPR, muscle-invasive bladder cancer, radical cystectomy, prognosis

Introduction

Bladder cancer is the most common tumor of the urinary system, with a relatively high incidence in developing countries.[1] Approximately 75% of newly diagnosed bladder cancer patients suffer from non-muscle invasive bladder cancer (NMIBC), among which approximately 10% advance to muscle-invasive bladder cancers (MIBC) or metastatic bladder cancer.[2] Radical cystectomy (RC) remains the standard therapy for MIBC and high-risk NMIBC.[3] Despite advances in surgery, radiotherapy and chemotherapy, the prognosis of patients undergoing radical cystectomy for MIBC remains poor. Approximately 50%–~70% of patients who

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undergo radical cystectomy experience recurrence within 2 years, 50% of patients with high risk develop metastatic disease, and the 5-year overall survival rate is only 40% ~60% after surgery.[4] The evaluation of prognosis after radical cystectomy has been a major focus of urologists. In recent years, many preoperative markers have shown to be prognostic for bladder cancer, including albumin, CRP, NLR, PLR, MLR, etc.[5–9] The albumin-to-alkaline phosphatase ratio (AAPR), a novel blood biomarker, has been shown to be associated with the prognosis of liver cancer, nasopharyngeal cancer, small cell lung cancer, kidney cancer and other tumors.[10–13] However, data on the relationship between AAPR and bladder tumors are rare. The aim of this study was to investigate the relationship between preoperative AAPR and the overall survival of patients undergoing radical cystectomy of MIBC.

Materials and Methods

Participants

The Inclusion criteria were as fallows:1. All patients were diagnosed with nonmetastatic, muscle invasive bladder urothelial carcinoma before surgery. 2. Serum ALB and ALP were measured before surgery. 3. All patients underwent radical cystectomy and urinary diversion. 4. None of the patients received preoperative neoadjuvant chemotherapy. 5. None of the patients were diagnosed with other malignant tumors or had a history of cancer. 6. Complete data of clinicopathological features and follow-up information were available. Patients with cirrhosis, chronic hepatitis, nephrotic syndrome, active infections and bone fractures were excluded from the study. Finally, 174 patients were included in the study. This study was approved by the ethics committee of the Affiliated Hospital of Qingdao University. All patients participating in this retrospective study signed informed consent forms.

Clinical and Follow-Up Data

We collected the baseline and clinical characteristics information of the patients from the hospital medical system, including serum ALB and ALP, age, gender, BMI, tumor size, tumor number, pathological stage, tumor grade, lymph node status, hydronephrosis, adjuvant chemotherapy, ASA level, hypertension and diabetes, complication and number of lymph nodes dissected. Pathological staging was performed using the 7th edition of the AJCC TNM classification system. Tumor grading was performed using the 2004 WHO grading system. The endpoints of our study were overall survival (OS), cancer-specific survival (CSS) and recurrence-free survival (RFS). Patients follow-up were performed every 3 months for the first 2 years, followed by semiannual for an additional 2 years, and annual follow-up thereafter.

Statistical Analysis

The baseline characteristics of all patients were used to divide them into three groups based on AAPR tertiles. Continuous variables are expressed as the mean ± standard deviation and were analyzed by the Kruskal–Wallis test. Categorical variables are expressed as the frequency and proportion and were analyzed by Pearson's chi-square test or Fisher's exact test.

We set AAPR as a continuous variable as well as categorized-into tertiles to examine it relationship with outcomes. Cox proportional hazard and logistic regression models were used to evaluate the relationship with adjustment for confounding variables. We performed tests for linear trend by entering the median value of AAPR as a continuous variable in the models.

In the total sample, we conducted stratified and interaction analyses to explore the potential modifier and interaction effects on the 10-fold AAPR-outcomes association with adjusting for confounding variables. Kaplan-Meier survival curves and Log rank tests were used to determine differences in the survival outcomes.

All the analyses were performed using the statistical package R (http://www.R-project.org, The R Foundation) and Empower (R) (www.empowerstats.com; X&Y Solutions, Inc., Boston, MA). $P < 0.05$ was considered statistically significant.

Results

In total,174 patients were followed up for 1–125 months, with a median follow-up of 30 months, 93 survived and 81 patients died; Of those 81 died patients, 65 due to tumor recurrences or metastases, 16 due to other causes. The overall 3- and 5-year survival rates were 64% and 57%, the 3- and 5-year cancer-specific survival rates were 67% and 64%, The 3- and 5-year RFS rates were 72% and 62%, respectively. The median serum AAPR level in all patients was 0.62 (range: 0.12–1.67). In patients undergoing urinary diversion, there were 15 cases of orthotopic neobladder, 104 cases of ileal conduit and 55 cases of cutaneous ureterostomy. All patients underwent standard pelvic lymphadenectomy, the median number of dissected nodes was 6 [interquartile range (IQR)=3–10]. Surgical margins were

negative in all patients. During the follow-up, Complications in patients include that 25 cases of ileus, 33 cases of pyelonephritis, 35 cases of anastomotic stenosis, and 28 cases of hydronephrosis, 3 cases of urinary incontinence.

Table 1 compares the baseline clinical characteristics of the patients by tertiles of the AAPR.

In Table 2, the univariate Cox regression results showed the association between each variable and outcomes (OS, CSS and RFS). AAPR was one of the factors affecting OS (HR,0.06; 95% CI, 0.01 to 0.26; P<0.001), CSS (HR,0.05; 95% CI, 0.01 to 0.26; P<0.001) and RFS (HR,0.05; 95% CI, 0.01 to 0.25; P<0.001) when treated as a continuous variable. AAPR was also significant for OS (HR,0.33; 95% CI, 0.18 to 0.60; P<0.001), CSS (HR,0.26; 95% CI, 0.14 to 0.52; P<0.001) and RFS (HR,0.26; 95% CI, 0.13 to 0.52; P<0.001) when treated as a categorical variable.

The relationship between AAPR and outcomes (OS, CSS and RFS) was shown in Table 3. When we conducted analyses with the AAPR as a continuous variable, each 1 unit increase in AAPR was associated with a 78% decreased risk of all-cause mortality (HR,0.22; 95% CI, 0.06 to 0.82; P=0.024), a 88% decreased risk of bladder cancer-specific death (HR,0.12; 95% CI, 0.02 to 0.63; P=0.013) and a 85% decreased risk of tumor recurrence (HR,0.15; 95% CI, 0.03 to 0.82; P=0.029),The HR for high AAPR tertile was significantly lower than the HR for low AAPR tertile (OS: P=0.012,CSS: P=0.003,RFS: P=0.007). The P for trend (OS: P=0.014,CSS: P=0.002, RFS: P=0.006) in all of the models was significant and consistent with the P-value when AAPR was used as a continuous variable, suggesting the linear association between AAPR and OS,CSS and RFS.

We then investigated the association of AAPR with pT stage and pN stage on multivariate logistic regression analysis. The results in Table 4 showed that AAPR was not associated with pT stage (OR,0.24; 95% CI, 0.03 to 2.03; P=0.191) and pN stage (OR,0.15; 95% CI, 0.01 to 3.44; P=0.234) adjusted for all the factors (sex, age, bmi, tumor size, tumor number, pT stage, pN stage, pathological grade, hydronephrosis, ASA level, hypertension, diabetes, adjuvant chemotherapy). When AAPR was used as a categorical variable, the results still showed no correlation between AAPR and pathologic outcomes.

Table 5 shows the association between 10-fold AAPR and outcomes (OS, CSS and RFS) in the stratified and interaction analyses. Each stratification was adjusted for all the factors (sex, age, bmi, tumor size, tumor number, pT category, pN category, pathological grade, hydronephrosis, ASA level, hypertension, diabetes, adjuvant chemotherapy), except for the stratification factor itself. The association between AAPR and outcomes was consistent both in the stratified analysis and in the multivariable Cox regression analysis. This negative effect was evident in all subgroups considered and after careful adjustment. Stratified analysis failed in low grade and diabetes because of the small sample size. The interaction results showed no significant interaction.

Kaplan-Meier survival analysis was performed to analyze the difference in outcomes (OS, CSS, RFS) among the AAPR tertiles. The OS of the patients with an increased AAPR was significantly better than that of the patients with a low AAPR tertile (Figure 1A, P<0.001). The same trend was observed in the CSS (Figure 1B, P<0.001) and RFS (Figure 1C, P<0.001).

Discussion

The role of the inflammation in cancer development has received increasing attention in recent years. Inflammation is considered a dominant feature and a hallmark of cancer. Cancer-related inflammation is mainly associated with the local immune reaction found at the site of the tumor, which encompasses tumor-derived and host-derived cytokines, small inflammatory protein mediators, and infiltrating immune cells acting in the local tumor microenvironment. At the same time, these inflammatory mediators also lead to systemic inflammatory responses. The release of inflammatory factors plays an important role in tumorigenesis and tumor development.[14] Many inflammatory makers have been shown to be predictors of tumor prognosis. AAPR, an emerying biomarker of the inflammatory response, has been shown to be prognostic value in a variety of solid tumors. In our study, we first demonstrated the relationship between AAPR and MIBC patients undergoing radical cystectomy.

Albumin is the most abundant plasma protein synthesized by the liver. As a common marker, it has been shown to be associated with the prognosis of liver cancer, esophageal cancer, colon cancer and other tumors.[15–18] Albumin not only reflects nutritional status but also participates in the systemic inflammatory response and autoimmune regulation.[19] Albumin promotes DNA replication and increases cell survival it also plays an antioxidant role in tumorigenesis.[20] Malnutrition and tumor-related inflammatory reactions can inhibit albumin synthesis during

Table 1 Baseline Characteristics of participants (N=174)

Characteristics	AAPR Tertiles			p-value
	Low	Middle	High	
Number	58	58	58	
AAPR	0.42 ± 0.09	0.57 ± 0.04	0.86 ± 0.23	<0.001
SEX				0.628
Man	44 (75.86%)	47 (81.03%)	48 (82.76%)	
Woman	14 (24.14%)	11 (18.97%)	10 (17.24%)	
Age (year)				0.033
<60	10 (17.24%)	22 (37.93%)	20 (34.48%)	
≥0	48 (82.76%)	36 (62.07%)	38 (65.52%)	
BMI (kg/m^2)				0.006
<24	29 (50.00%)	39 (67.24%)	22 (37.93%)	
≥2	29 (50.00%)	19 (32.76%)	36 (62.07%)	
Tumor Size				<0.001
<3cm	7 (12.07%)	9 (15.52%)	23 (39.66%)	
≥3	51 (87.93%)	49 (84.48%)	35 (60.34%)	
Tumor Number				<0.001
Single	45 (77.59%)	33 (56.90%)	25 (43.10%)	
Multiple	13 (22.41%)	25 (43.10%)	33 (56.90%)	
pT Stage				0.115
2	30 (51.72%)	35 (60.34%)	42 (72.41%)	
3	25 (43.10%)	18 (31.03%)	15 (25.86%)	
4	3 (5.17%)	5 (8.62%)	1 (1.72%)	
pN Stage				0.460
0	49 (84.48%)	45 (77.59%)	53 (91.38%)	
1	6 (10.34%)	7 (12.07%)	3 (5.17%)	
2	3 (5.17%)	5 (8.62%)	2 (3.45%)	
3	0 (0.00%)	1 (1.72%)	0 (0.00%	
Pathological Grade				0.846
High Grade	54 (93.10%)	52 (89.66%)	52 (89.66%)	
Lower Grade	4 (6.90%)	6 (10.34%)	6 (10.34%)	
Hydronephrosis				0.025
NO	44 (75.86%)	42 (72.41%)	53 (91.38%)	
YES	14 (24.14%)	16 (27.59%)	5 (8.62%)	
ASA Level				0.057
1	3 (5.17%)	0 (0.00%)	0 (0.00%)	
2	17 (29.31%)	28 (48.28%)	30 (51.72%)	
3	35 (60.34%)	26 (44.83%)	25 (43.10%)	
4	3 (5.17%)	4 (6.90%)	3 (5.17%)	
Hypertension				0.674
NO	47 (81.03%)	50 (86.21%)	50 (86.21%)	
YES	11 (18.97%)	8 (13.79%)	8 (13.79%)	
Diabetes				0.733
No	54 (93.10%)	54 (93.10%)	52 (89.66%)	
YES	4 (6.90%)	4 (6.90%)	6 (10.34%)	
Adjuvant chemotherapy				0.014
NO	34 (58.62%)	29 (50.00%)	44 (75.86%)	
YES	24 (41.38%)	29 (50.00%)	14 (24.14%)	

Table 2 Univariate Cox Regression Analysis of AAPR for Outcomes (OS, CSS and RFS)

Variables	Statistics	OS		CSS		RFS	
		HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
AAPR	0.62 ± 0.23	0.06 (0.01, 0.26)	<0.001	0.05 (0.01, 0.26)	<0.001	0.05 (0.01, 0.25)	<0.001
AAPR Tertiles							
Low	58 (33.33%)	1.0		1.0		1.0	
Middle	58 (33.33%)	0.70 (0.43, 1.15)	0.163	0.58 (0.33, 1.01)	0.053	0.56 (0.32, 0.97)	0.0384
High	58 (33.33%)	0.33 (0.18, 0.60)	<0.001	0.26 (0.14, 0.52)	<0.001	0.26 (0.13, 0.52)	<0.0001
Sex							
Man	139 (79.89%)	1.0		1.0		1.0	
Woman	35 (20.11%)	0.68 (0.37, 1.23)	0.198	0.77 (0.41, 1.45)	0.425	0.79 (0.42, 1.47)	0.454
Age (year)							
<60	52 (29.89%)	1.0		1.0		1.0	
≥.0	122 (70.11%)	2.37 (1.34, 4.18)	0.003	2.06 (1.13, 3.75)	0.018	1.95 (1.08, 3.54)	0.027
BMI (kg/m2)							
<24	90 (51.72%)	1.0		1.0		1.0	
≥.0	84 (48.28%)	0.74 (0.47, 1.15)	0.182	0.66 (0.40, 1.08)	0.101	0.68 (0.41, 1.11)	0.124
Tumor Size (cm)							
<3	39 (22.41%)	1.0		1.0		1.0	
3≥	135 (77.59%)	1.80 (0.97, 3.32)	0.061	2.00 (0.99, 4.05)	0.054	2.07 (1.02, 4.19)	0.043
Number of tumors							
Single	103 (59.20%)	1.0		1.0		1.0	
Multiple	71 (40.80%)	0.72 (0.45, 1.16)	0.178	0.68 (0.40, 1.16)	0.154	0.63 (0.37, 1.07)	0.089
pT stage							
2	107 (61.49%)	1.0		1.0		1.0	
3	58 (33.33%)	4.94 (3.04, 8.04)	<0.001	5.14 (3.02, 8.75)	<0.001	5.46 (3.21, 9.31)	<0.001
4	9 (5.17%)	5.93 (2.67, 13.19)	<0.001	4.68 (1.76, 12.45)	0.002	4.83 (1.81, 12.88)	0.002
pN stage							
0	147 (84.48%)	1.0		1.0		1.0	
1	16 (9.20%)	2.73 (1.49, 4.99)	0.001	2.69 (1.36, 5.33)	0.005	2.74 (1.38, 5.43)	0.004
2	10 (5.75%)	1.48 (0.64, 3.43)	0.363	1.50 (0.60, 3.78)	0.390	1.63 (0.65, 4.11)	0.299
3	1 (0.57%)	15.09 (1.96, 115.90)	0.009	47.56 (5.29, 427.83)	0.001	39.13 (4.55, 336.95)	0.001
Pathological Grade							
High Grade	158 (90.80%)	1.0		1.0		1.0	
Lower Grade	16 (9.20%)	0.43 (0.16, 1.18)	0.101	0.39 (0.12, 1.23)	0.107	0.37 (0.11, 1.17)	0.089
Hydronephrosis							
NO	139 (79.89%)	1.0		1.0		1.0	
YES	35 (20.11%)	2.19 (1.35, 3.56)	0.002	1.83 (1.04, 3.22)	0.0037	1.87 (1.06, 3.30)	0.030
ASA Level							
1	3 (1.72%)	1.0		1.0		1.0	
2	75 (43.10%)	1.47 (0.20, 10.79)	0.703	1.27 (0.17, 9.34)	0.817	1.24 (0.17, 9.16)	0.831
3	86 (49.43%)	2.08 (0.28, 15.22)	0.472	1.78 (0.24, 13.14)	0.572	1.60 (0.22, 11.81)	0.643
4	10 (5.75%)	5.35 (0.65, 44.26)	0.120	4.92 (0.56, 43.19)	0.150	4.08 (0.47, 35.44)	0.203
Hypertension							
NO	147 (84.48%)	1.0		1.0		1.0	
YES	27 (15.52%)	0.96 (0.50, 1.81)	0.891	1.10 (0.58, 2.10)	0.773	1.26 (0.66, 2.43)	0.481

(*Continued*)

Table 2 (Continued).

Variables	Statistics	OS		CSS		RFS	
		HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Diabetes							
No	160 (91.95%)	1.0		1.0		1.0	
YES	14 (8.05%)	1.00 (0.43, 2.30)	0.100	0.92 (0.37, 2.29)	0.862	0.81 (0.30, 2.24)	0.690
Adjuvant chemotherapy							
NO	107 (61.49%)	1.0		1.0		1.0	
YES	67 (38.51%)	2.21 (1.42, 3.44)	0.001	2.59 (1.61, 4.16)	<0.001	3.24 (1.94, 5.43)	<0.001

Table 3 Multivariate Cox Regression Analysis of AAPR for Outcomes (OS, CSS and RFS)*

Variables	OS		CSS		RFS	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
AAPR	0.22 (0.06, 0.82)	0.024	0.12 (0.02, 0.63)	0.013	0.15 (0.03, 0.82)	0.029
AAPR Tertiles						
Low	Reference		Reference		Reference	
Middle	0.91 (0.51, 1.61)	0.741	0.63 (0.33, 1.20)	0.159	0.63 (0.34, 1.19)	0.156
High	0.41 (0.21, 0.82)	0.012	0.31 (0.14, 0.66)	0.003	0.35 (0.16, 0.75)	0.007
P for trend	0.014		0.002		0.006	

Notes: *Adjusted for all factors (sex, age, bmi, tumor size, tumor number, pT stage, pN stage, pathological grade, hydronephrosis, ASA level, hypertension, diabetes, adjuvant chemotherapy).

Table 4 Multivariate Logistic Regression Analysis of AAPR for pT Stage and pN Stage*

Variables	pT (T_2,T_{3-4})		pN (N_O,N_{1-3})	
	OR (95% CI)	P-value	OR (95% CI)	P-value
AAPR	0.24 (0.03, 2.03)	0.191	0.15 (0.01, 3.44)	0.234
AAPR Tertiles				
Low	Reference		Reference	
Middle	0.31 (0.08, 1.19)	0.088	1.09 (0.27, 4.36)	0.900
High	1.19 (0.28, 5.16)	0.812	0.50 (0.09, 2.66)	0.417

Notes: *Adjusted for all factors (sex, age, bmi, tumor size, tumor number, pT stage, pN stage, pathological grade, hydronephrosis, ASA level, hypertension, diabetes, adjuvant chemotherapy).

tumorigenesis and its progression, which will cause hypoalbuminemia.[21] The association between hypoalbuminemia and poor outcomes could be explained by a more aggressive biological behavior of the tumor, leading to poor humoral immune responses, cellular immunity,[22] subsequently, a poor anticancer response. Multivariate analysis showed that albumin was an important predictor of overall survival in patients who underwent radical cystectomy for bladder tumors.[23,24]

Alkaline phosphatase is an enzyme that is present in all tissues throughout the entire body, but is particularly concentrated in the liver, bone, intestine, kidney and placenta. It can be discharged through the liver and dephosphorylate various types of molecules to, ranging from nucleotides,

Table 5 Effect Size of 10-fold AAPR on Outcomes (OS, CSS and RFS) in Prespecified and Exploratory Subgroups in Each Subgroup

Characteristic	OS			CSS			RFS		
	HR (95% CI)	*P* value	*P* for Interaction	HR (95% CI)	*P* value	*P* for Interaction	HR (95% CI)	*P* value	*P* for Interaction
Age (year)			0.943			0.957			0.842
<60	0.80 (0.69, 0.94)	0.005		0.83 (0.71, 0.97)	0.019		0.81 (0.68, 0.97)	0.020	
≥.0	0.48 (0.29, 0.78)	0.003		0.41 (0.24, 0.71)	0.001		0.38 (0.22, 0.67)	0.001	
Sex			0.223			0.363			0.154
Male	0.91 (0.67, 1.25)	0.569		0.96 (0.70, 1.31)	0.784		0.94 (0.68, 1.30)	0.710	
Female	0.75 (0.65, 0.88)	<0.001		0.75 (0.64, 0.89)	0.001		0.70 (0.57, 0.85)	<0.001	
BMI (kg/m^2)			0.201			0.322			0.288
<24	0.80 (0.65, 0.98)	0.029		0.77 (0.62, 0.95)	0.016		0.72 (0.56, 0.92)	0.009	
≥.0	0.71 (0.57, 0.88)	0.002		0.76 (0.61, 0.95)	0.018		0.76 (0.60, 0.95)	0.019	
Tumor Size (cm)			0.745			0.709			0.415
<3	0.77 (0.53, 1.10)	0.154		0.73 (0.48, 1.09)	0.124		0.67 (0.43, 1.06)	0.085	
3≥	0.78 (0.66, 0.91)	0.002		0.80 (0.68, 0.94)	0.006		0.77 (0.65, 0.93)	0.006	
Number of tumors			0.547			0.550			0.326
Single	0.75 (0.62, 0.89)	0.001		0.76 (0.63, 0.91)	0.003		0.68 (0.55, 0.86)	0.001	
Multiple	0.79 (0.62, 1.02)	0.068		0.83 (0.64, 1.07)	0.143		0.84 (0.65, 1.08)	0.174	
pT Stage			0.153			0.242			0.093
2	0.68 (0.51, 0.92)	0.011		0.68 (0.49, 0.94)	0.019		0.66 (0.48, 0.92)	0.013	
3–4	0.87 (0.75, 1.01)	0.074		0.84 (0.71, 1.01)	0.064		0.85 (0.71, 1.03)	0.101	
pN stage			0.352			0.113			0.063
0	0.73 (0.62, 0.86)	<0.001		0.72 (0.61, 0.86)	<0.001		0.69 (0.57, 0.84)	<0.001	
10.00	0.89 (0.67, 1.19)	0.4455		0.97 (0.71, 1.32)	0.845		0.97 (0.69, 1.36)	0.861	
Pathological Grade			0.163			0.340			0.296
High Grade	0.78 (0.68, 0.90)	0.001		0.79 (0.68, 0.92)	0.002		0.77 (0.65, 0.91)	0.002	
Low Grade	Δ	Δ		Δ	Δ		Δ	Δ	
Hydronephrosis			0.642			0.221			0.435
No	0.71 (0.59, 0.85)	<0.001		0.68 (0.55, 0.83)	<0.001		0.65 (0.52, 0.80)	<0.001	
YES	0.93 (0.76, 1.14)	0.510		0.99 (0.82, 1.20)	0.923		0.99 (0.79, 1.25)	0.948	
Hypertension			0.874			0.728			0.537
No	0.78 (0.67, 0.91)	0.001		0.79 (0.67, 0.93)	0.004		0.77 (0.64, 0.92)	0.004	
Yes	0.60 (0.38, 0.95)	0.030		0.60 (0.38, 0.95)	0.030		0.61 (0.38, 0.99)	0.045	

(*Continued*)

Table 5 (Continued).

Characteristic	OS			CSS			RFS		
	HR (95% CI)	*P* value	*P* for Interaction	HR (95% CI)	*P* value	*P* for Interaction	HR (95% CI)	*P* value	*P* for Interaction
Diabetes			0.503			0.617			0.625
No	0.77 (0.66, 0.89)	0.001		0.79 (0.68, 0.92)	0.002		0.77 (0.66, 0.91)	0.003	
Yes	Δ	Δ		Δ	Δ		Δ	Δ	
ASA level			0.086			0.114			0.201
1–2	0.80 (0.65, 1.00)	0.046		0.80 (0.64, 1.01)	0.061		0.81 (0.64, 1.02)	0.073	
3–4	0.74 (0.61, 0.90)	0.002		0.76 (0.62, 0.92)	0.006		0.68 (0.53, 0.88)	0.003	
Adjuvant chemotherapy			0.103			0.510			0.573
NO	0.66 (0.53, 0.83)	<0.001		0.70 (0.55, 0.89)	0.004		0.63 (0.46, 0.86)	0.004	
YES	0.87 (0.72, 1.05)	0.137		0.84 (0.69, 1.03)	0.090		0.85 (0.69, 1.04)	0.116	

Notes: Each stratification was adjusted for all the factors (sex, age, bmi, tumor size, tumor number, pT stage, pN stage, pathological grade, hydronephrosis, ASA level, hypertension, diabetes, adjuvant chemotherapy), except for the stratification factor itself. ΔThe model failed because of the small sample size.

proteins and alkaloids.[25] Alkaline phosphatase is expressed at expressed high levels in disease of the liver, kidney and bone.[26–28] Alkaline phosphatase has anti-inflammatory property, it can inhibit inflammatory reaction and it is also associated with the nutritional status of the body.[29] Previous studies have shown that alkaline phosphatase is correlated with the prognosis of esophageal cancer, colorectal cancer, nasopharyngeal cancer and renal cancer.[30,31] Alkaline phosphatase is expressed at different levels in bladder tumor tissues. It has been used as marker for bone metastasis of bladder cancer.[32]

AAPR, a ratio of albumin and alkaline phosphatase, reflects the systemic inflammatory response, immune status and nutritional status under the influence of tumors at some level. Patients with a low AAPR ratio may have malnutrition, strong systemic inflammatory response and low immune function. These factors indirectly suggest that the tumor cells are highly aggressive, have a relatively high probability of recurrence and metastasis after surgery, and a poor prognosis.

Our study first investigated the prognostic value of AAPR in Patients with Muscle-Invasive Bladder Cancer after Radical Cystectomy, the result showed a linear correlation between preoperative AAPR and outcomes (OS, CSS and RFS). Compared with patients with low AAPR group, patients with high AARP group had better prognosis. This negative effect was evident in all subgroups considered and after careful adjustment. However, Our study showed that there was no correlation between preoperative AAPR and pathological outcomes (pT stage and pN stage), although tumor invasion and lymph node metastasis were recognized as the most important prognostic factor. As a novel serum marker, AAPR can be used to evaluate the prognosis of patients with MIBC undergoing radical cystectomy, but the mechanism underlying the interaction between AAPR and prognosis is still unclear, and needs to be further basic reach.

The limitations of this study should be described. 1. Our study was a retrospective single-center study with a small sample size, possibly giving rise to selection bias. The results of this study need to be confirmed by a multicenter study in large clinical trials. 2. Although the Cox proportional risk regression model in this study adjusted for a series of confounding factors, many unknown factors affecting AAPR have not been completely excluded. 3. We only explored the prognostic value of preoperative AAPR in Patients with MIBC, the prognostic

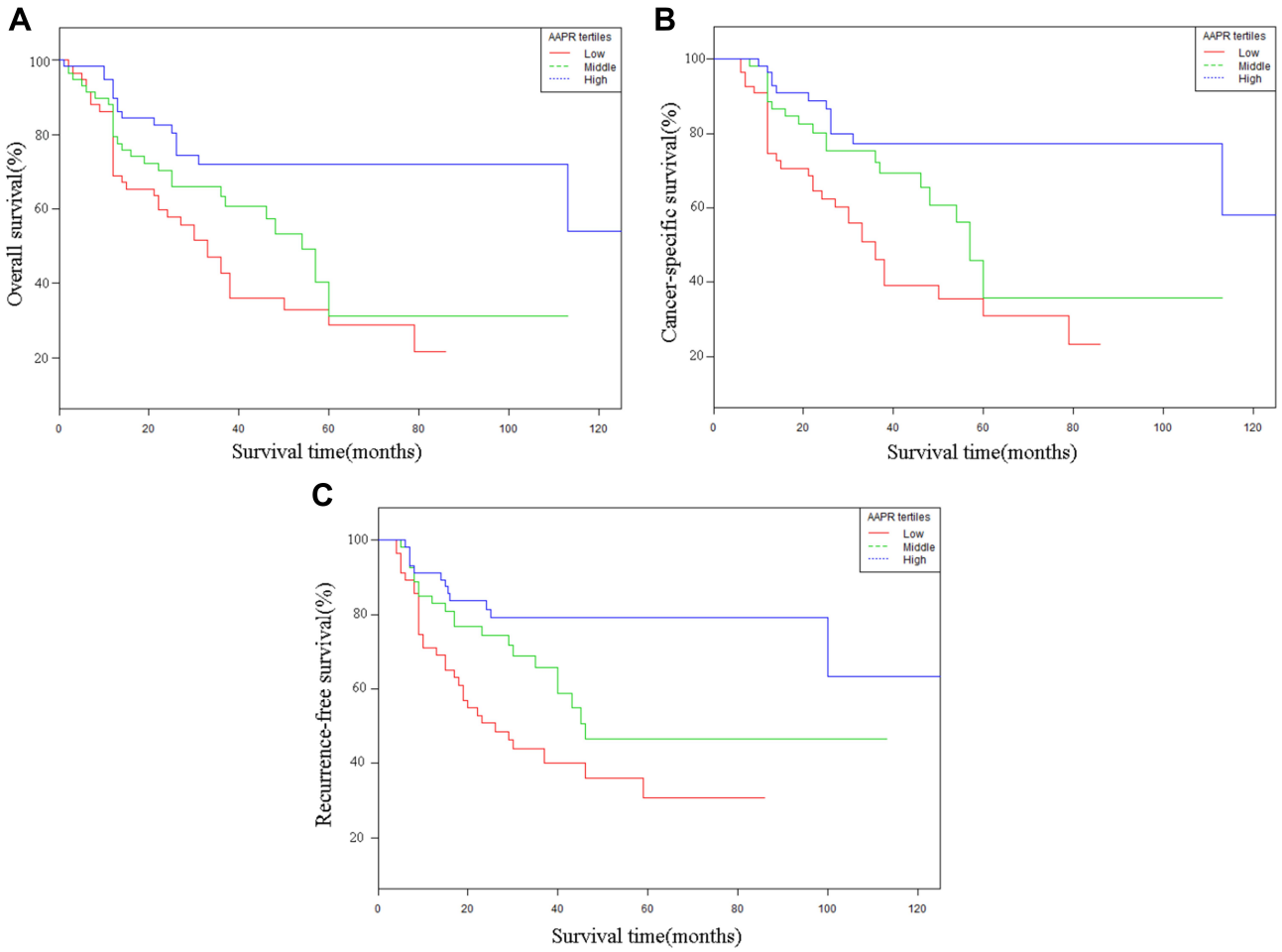

Figure 1 Kaplan–Meier curves of OS (**A**), CSS (**B**) and RFS (**C**) according to albumin-to-alkaline phosphatase ratio (AAPR) level in all patients.

value of AAPR dynamic changes remains to be explored in future research. 4. The advantages of AAPR compared to other inflammatory markers and Whether AAPR can be combined with other inflammatory markers for patient risk-stratification should be evaluated in the further studies. 5. Our study included patients with the urothelial carcinoma of bladder, Whether the results are appropriate for patents with squamous cell carcinoma and adenocarcinoma remains to be studied.

Conclusions

AAPR was a potentially valuable prognostic maker in patients with Muscle-Invasive Bladder Cancer after Radical Cystectomy.

Disclosure

The authors report no conflicts of interest for this work.

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