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Clinical-Bladder cancer

Impact of preoperative serum albumin-globulin ratio on disease outcome after radical cystectomy for urothelial carcinoma of the bladder

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Abstract

Introduction: The Albumin-Globulin Ratio (AGR; albumin/total protein – albumin) has been associated with oncological outcome in various malignancies. However, its role in urothelial carcinoma of the bladder (UCB) has not been clearly established. In this study, we assessed the association of preoperative AGR (pAGR) with survival in patients who underwent radical cystectomy (RC) for UCB.

Material and Methods: We conducted a retrospective analysis of an established multicenter database of 4.335 patients who were treated with RC for UCB. The cohort was divided into 2 groups according to the pAGR status. Binominal logistic regression as well as uni- and multivariable Cox regression analyses were used. The predictive value of the models was assessed by calculating receiver operating characteristics curves and concordance-indices (C-Index). The additional clinical value was assessed using the decision curve analysis (DCA).

Disclosures: All authors have nothing to disclose.

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Results: Overall, 1.670 patients (38.5%) had a low pAGR. On multivariable logistic regression analyses, low pAGR was associated with an increased risk of ≥pT3 disease at RC (odds ratio [OR] 1.15, 95% confidence interval [CI] 1.01−1.31, P= 0.04). On multivariable Cox regression analyses, low pAGR remained associated with worse recurrence-free survival (RFS, HR 1.24, 95% CI 1.1−1.37, P< 0.001), cancer-specific survival (CSS, HR 1.23, 95% CI 1.1−1.38, P< 0.001) and overall survival (OS, HR 1.17, 95% CI 1.07−1.28, P< 0.001). The addition of pAGR to multiple prognostic models that were respectively fitted for clinical and postoperative variables did not improve the predictive accuracy.

Conclusion: pAGR status is an independent predictor of ≥pT3 disease, therefore it could help identify patients who have a higher likelihood to benefit from neoadjuvant systemic therapy. While pAGR was independently associated with RFS, CSS, and OS, it did not improve the predictive accuracy and clinical value beyond obtained by information already available. The predictive value of this biomarker in the age of immunotherapy needs further evaluation.

Keywords: MIBC; NMIBC; Bladder cancer; AGR; Biomarker; Transitional cell carcinoma

Abbreviations: AC, adjuvant chemotherapy; AGR, albumin-globulin ratio; AUC, area under the curve; C-Index, concordance-indices; CSS, cancer-specific survival; DCA, decision curve analysis; IQR, interquartile ranges; MIBC, muscle invasive bladder cancer; NIMBC, non-muscle invasive bladder cancer; NOCD, nonorgan confined disease; OS, overall survival; pAGR, preoperative albumin-globulin ratio; RC, radical cystectomy; RFS, recurrence-free survival; ROC, receiver operating characteristics; UCB, urothelial carcinoma of the bladder

1. Introduction

Radical cystectomy (RC) and neoadjuvant chemotherapy for cis-platin eligible patients is the standard treatment for muscle invasive bladder cancer [1]. RC is also indicated for very high risk and Bacillus Calmette-Guerin unresponsive non-muscle invasive bladder cancer [2,3]. Risk stratification is of the utmost importance in this disease, as urothelial carcinoma of the bladder (UCB) is a heterogeneous disease with a variable natural history. Therefore, it is important to identify patients which are at the highest risk of nonorgan confined disease (NOCD) or disease recurrence after RC [4−6]. Improved preoperative outcome prediction could allow better patient selection with respect to perioperative systemic therapy. Unfortunately, clinical stage is discrepant with final pathological stage [4,6]. Contemporary prognostic models rely on definitive clinicopathological features [7,8]. Therefore, novel biomarkers to improve the current prognostic models are necessary to capture the individual biologic and clinical tumor behavior [9]. Currently, individual molecular markers also do not add sufficient value on outcome prediction, and their cost-effectiveness and availability are still suboptimal [4,10,11].

Several blood-based inflammatory markers have been evaluated as potential biomarkers for UCB after RC [4,12−14]. Indeed, the tumor microenvironment creates a stimulation of the immune system [15]. Serum albumin and globulins are the 2 major serum proteins, and they can be used to measure this inflammatory process [16]. During inflammation, serum albumin levels will decrease, while globulin levels increase [17,18]. Nevertheless, serum albumin levels are affected by several variables such as hydration levels and nutritional status [19]. A combined biomarker, based on the ratio of preoperative albumin to globulins (preoperative AGR [pAGR]), is less affected by these conditions and is presumably more robust [20].

Low pAGR has been identified as a prognostic biomarker of poor survival in various malignancies. Lv et al. for example found in a meta-analysis including 15 different types of cancer, that low blood levels of pAGR were associated with a significantly higher 5-year mortality [21]. In UCB, several studies attempted to correlate pAGR with oncologic outcomes, but they did not evaluate the predictive capabilities of pAGR and were limited by their single center nature, small sample sizes and limitations in study design [22−24]. In order to conclusively analyze the prognostic value of pAGR, an external validation of its predictive capabilities in a large multicenter study is needed [11,25,26]. Therefore, the aim of this study was to assess the potential predictive value of blood levels of pAGR in a large multi-institutional cohort of patients. We focused on prediction of NOCD in order to identify patients who most likely would benefit from neoadjuvant systemic therapy. Beyond multivariable modeling, we used predictive accuracy testing and decision curve analysis (DCA) to assess real world clinical utility of pAGR in UCB patients treated with RC.

2. Subjects/patients

2.1. Patients selection

This retrospective study included patients who underwent open RC for nonmetastatic UCB between 1979 and 2012. All cases were histologically confirmed UCB with only minor variant component, if any. Patients were included from 12 different medical institutions. No patient received neoadjuvant chemotherapy. All patients underwent RC and standard lymph node dissection. The choice of urinary diversion was at the surgeon's discretion. Preoperative routine blood tests were done within 30 days before RC and included albumin and globulin levels. Patients with known autoimmune, chronic inflammatory, or hematological disorders, as well as patients with any concomitant

second malignancy other than UCB, concomitant upper urinary tract carcinoma or missing data were excluded. The study was approved by the local ethics committees at all participating institutions and informed consents were obtained from all eligible patients.

All specimens were histologically confirmed to be UCB, staged according to the American Joint Committee on Cancer Staging Manual (eighth edition or prior editions appropriate at the time of diagnosis) TNM classification and graded according to the 1973 World Health Organization grading system.

Adjuvant chemotherapy (AC) was administered at the discretion of the treating physician and according to guidelines. Clinical and radiological follow-up was performed in accordance with institutional protocols and current guidelines. For most patient's physical examination, radiological imaging, and urine cytology were obtained every 3 months for 2 years, then semiannually between the second and the fifth year. After 5 years, annual follow-up was performed. Tumor recurrence was defined as the occurrence of locoregional recurrence or distant metastasis on radiological imaging. Cause of death was abstracted from medical charts end/or from death certificates. Patient data were collected and stored in a common anonymized dataset.

2.2. Pretreatment AGR

As in previous studies, pAGR was calculated by dividing the albumin levels and the non-albumin protein levels (pAGR = albumin/total protein − albumin) [22−24]. The optimal pAGR cutoff value was defined by creating a time−dependent receiver operating characteristic (ROC) curve, analyzing the highest Youden index value. In summary, the Youden-index provides the optimal cut-off from a continuous variable by showing the score that offers the best trade-off between sensitivity and specificity. Using this score the overall population was divided into 2 separate pAGR groups (low vs. high).

Table 1
Association of pAGR with clinicopathologic characteristics in 4,335 patients treated with radical cystectomy for urothelial carcinoma of the bladder

	Overall	High pAGR	Low pAGR	*P*
n (%)	4335 (100%)	2665 (61.5%)	1670 (38.5%)	
Age (median [IQR])	67.02 [59.72, 73.12]	67.18 [60.01, 73.09]	66.72 [58.88, 73.20]	0.2
Male sex (%)	3464 (79.9%)	2119 (79.5%)	1345 (81.5%)	0.43
Clinical tumor stage (%)				0.48
cTa	141 (3.3%)	84 (3.2%)	57 (3.4%)	
cTis	308 (7.1%)	201 (7.5%)	107 (6.4%)	
cT1	1078 (24.9%)	676 (25.4%)	402 (24.1%)	
cT2	2372 (54.7%)	1451 (54.4%)	921 (55.1%)	
cT3	171 (3.9%)	97 (3.6%)	74 (4.4%)	
cT4	129 (3.0%)	78 (2.9%)	51 (3.1%)	
NA	136 (3.1%)	78 (2.9%)	58 (3.5%)	
Clinical tumor grade (%)				0.75
Grade 1	0 (0%)	0 (0%)	0 (0%)	
Grade 2	43 (1%)	28 (1.1%)	15 (0.9%)	
Grade 3	4156 (99%)	2559 (96.0%)	1597 (95.6%)	
NA	126 (3.1%)	78 (2.9%)	58 (3.5%)	
Pathological tumor stage (%)				0.23
pT0	227 (5.2%)	142 (5.3%)	85 (5.1%)	
pTa	123 (2.8%)	78 (2.9%)	45 (2.7%)	
pTis	424 (9.8%)	281 (10.5%)	143 (8.6%)	
pT1	585 (13.5%)	367 (13.8%)	218 (13.1%)	
pT2	1042 (24.0%)	646 (24.2%)	396 (23.7%)	
pT3	1371 (31.6%)	818 (30.7%)	553 (33.1%)	
pT4	563 (13.0%)	333 (12.5%)	230 (13.8%)	
Pathological tumor grade (%)				0.92
Grade 1	227 (5.2%)	142 (5.3%)	85 (5.1%)	
Grade 2	54 (1.2%)	34(1.3%)	20 (1.2%)	
Grade 3	4054 (93.6%)	2489 (93.3%)	1565 (93.7%)	
Positive STSM (%)	262 (6.0%)	**139 (5.2%)**	**123 (7.4%)**	**<0.01**
LVI (%)	1475 (34.0%)	890 (33.4%)	585 (35.0%)	0.28
Concomitant CiS (%)	2154 (49.7%)	1339 (50.2%)	815 (48.8%)	0.37
pN+ (%)	1127 (26.0%)	701 (26.3%)	426 (25.5%)	0.59
Numbers of lymph nodes removed (median) [IQR]	18.00 [11.00, 31.00]	18.00 [11.00, 30.00]	18.00 [11.00, 31.00]	0.77
Use of AC (%)	985 (22.7%)	611 (22.9%)	374 (22.4%)	0.71

AC, adjuvant chemotherapy; CiS, carcinoma in situ; IQR, interquartile range; LVI, lymphovascular invasion; NA, not available; p, *P* value; pAGR, preoperative albumin/globulin ratio; pN+, lymph node involvement; STSM, soft tissue surgical margins.

All p values <.0.05 that were statistically significant were bolded.

Table 2
Univariable and multivariable logistic regression predicting pN+ and ≥pT3 or any nonorgan confined disease in 4,335 patients treated with radical cystectomy for urothelial carcinoma of the bladder

		pN+			≥ pT3			Any NOCD (≥pT3 and/or pN+)		
Univariable analysis		*OR*	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*p*
	pAGR (low)	0.96	0.83−1.1	0.56	1.03	0.88−1.2	0.71	1.1	0.98−1.25	0.12
	Sex (male)	0.92	0.78−1.09	0.36	0.9	0.75−1.08	0.25	0.95	0.81−1.1	0.46
	Age	1.0	1.0−1.01	0.53	1.0	1.0−1.02	**0.01**	1.02	1.01−1.02	**<0.001**
	≥cT3	2.72	2.14−3.45	**<0.001**	3.41	2.67−4.34	**<0.001**	5.59	4.09−7.64	**<0.001**
Multivariable analysis		OR	95%CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
	pAGR (low)	0.91	0.79−1.05	0.21	1.15	1.01−1.31	**0.04**	1.08	0.94−1.23	0.21
	Sex (male)	0.91	0.76−1.09	0.31	0.98	0.83−1.15	0.79	0.97	0.83−1.13	0.72
	Age	1.01	0.99−1.01	0.86	1.02	1.02−1.03	**<0.001**	1.02	1.01−1.02	**<0.001**
	≥cT3	1.73	1.59−1.89	**<0.001**	2.35	2.16−2.57	**<0.001**	5.64	4.16−7.8	**<0.001**
	AUC with pAGR	0.56			0.62			0.60		
	AUC without pAGR	0.55			0.61			0.60		
	Difference between AUC	0.97% (*P*= 0.14)			0.22% (*P*= 0.32)			0.12% (*P*= 0.51)		

AUC; area under the curve; OR, odds ratio; NOCD, any nonorgan confined disease; pAGR, preoperative albumin/globulin ratio; p, *P* value; pN+, lymph node involvement; 95% CI, 95% confidence interval.

All p values <.0.05 that were statistically significant were bolded.

2.3. Statistical analysis

Report of categorical variables included frequencies and proportions. Reporting of continuous coded variables focused on medians and interquartile ranges (IQR). With respect to pAGR status, comparisons were performed using the chi-squared and Mann-Whitney *U* tests, as appropriate.

Binominal logistic regression was used for testing the association of preoperative variables with pN+, ≥pT3 or any nonorgan confined disease (defined as ≥pT3 and/or pN+) at RC pathology report. The predictive accuracy of the model was tested with ROC curves derived area under the curve (AUC). Kaplan-Meier survival curves and log-rank tests analyzed the association between pAGR and oncological outcome parame-

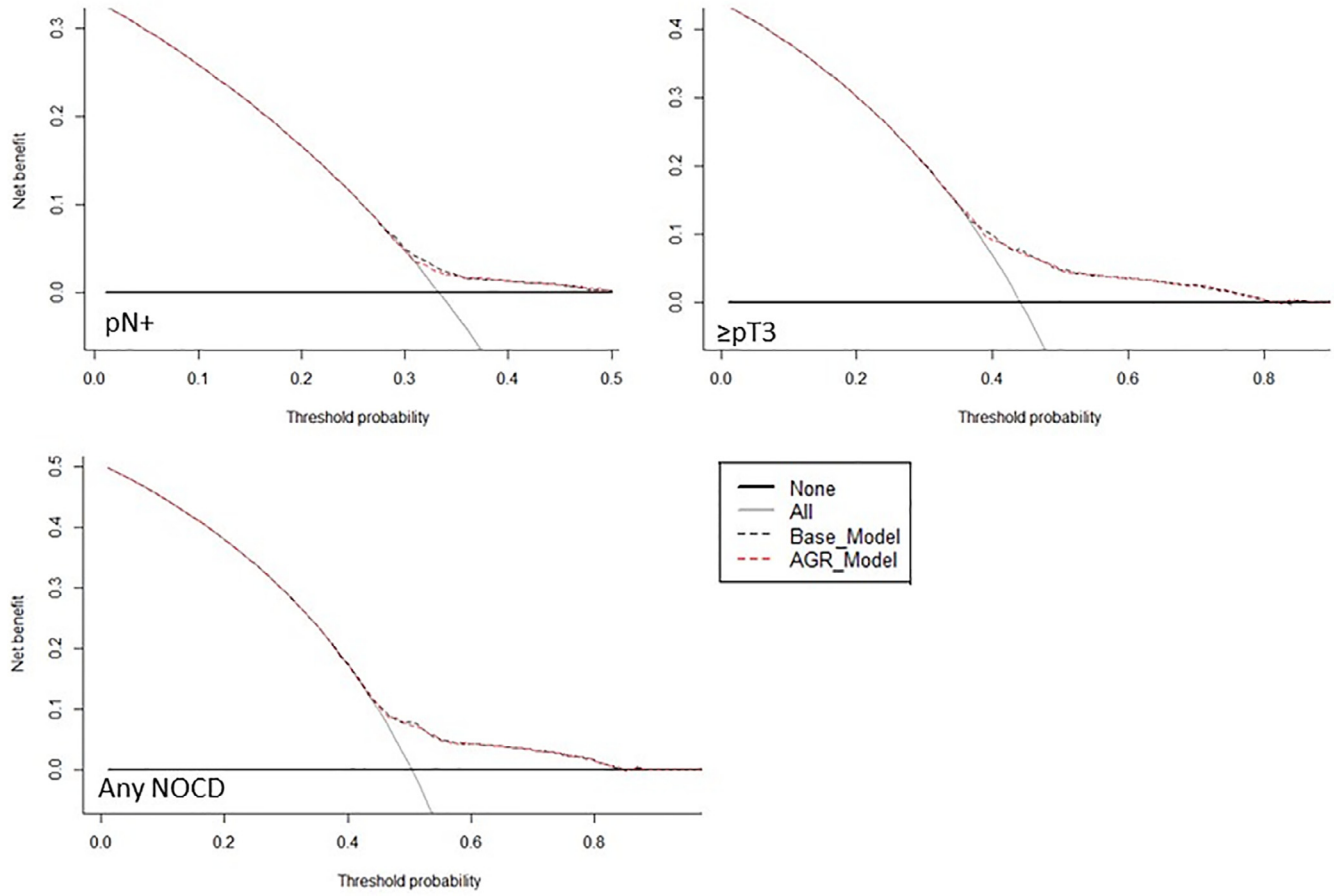

Fig. 1. Decision curve analysis (DCA) for the net-benefit of pAGR based on a preoperative model (including age, sex, and clinical staging) for the prediction of PN+, ≥PT3, or any nonorgan confined disease.

ters such as recurrence-free survival (RFS), cancer-specific survival (CSS), and overall survival (OS). Association between prognostic variables and RFS, CSS, and OS was assessed in univariable and multivariable Cox regression models. Separate models were respectively fitted for the testing of preoperative and postoperative predictor variables. Tumor grade was excluded as variable for the predictive models, since virtually all RC patients had high grade UCB. The discrimination of Cox regression models was tested with Harrel's concordance index (C-index) [27]. The additional clinical net-benefit was evaluated using the decision curve analysis (DCA) [28]. All reported *P* values were 2-sided, and statistical significance was set at 0.05. Statistical analyses were performed using R Version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria, 2020).

3. Results

3.1. Association with clinicopathologic features

A total of 4.335 patients were included in the analyses. The median age of the entire cohort was 67 years (IQR 59.7−73.1), with 79.9% of the cohort being males. Median pAGR was 1.52 (IQR 1.37−1.59). ROC analysis showed that the highest Youden Index was found at 1.42. According to this cutoff for pAGR, 1.670 (38.5%) had a low pAGR. There were no significant differences between the low and high pAGR group, except for a higher positive soft tissue surgical margin rate in the low pAGR group (5.2 vs. 7.4%, *P*= 0.005; Table 1).

On multivariable logistic regression models, pAGR was significantly associated with an increased risk of ≥pT3 disease (OR 1.15, 95%CI 1.01−1.31, *P*= 0.04) at RC (Table 2). Lymph node involvement (OR 0.91, 95%CI 0.79−1.05, *P*= 0.21) or any NOCD (OR 1.08, 95%CI 0.94−1.23, *P*= 0.21) were not significantly influenced by pAGR. In ROC curve analyses, the addition of pAGR to a predictive model based on sex, age and clinical staging did not improve its discriminating ability for prediction of pN+, ≥pT3 or any NOCD by any prognostic margin (change in AUC <1%). On DCA, the inclusion of pAGR did not improve the clinical net-benefit of the prognostic models relative to models that did not rely on pAGR (Figure 1).

3.2. Association with survival outcome

The median follow-up was 31.5 months (IQR: 13.3−72.3). During this period, 1.457 (33.6%) patients

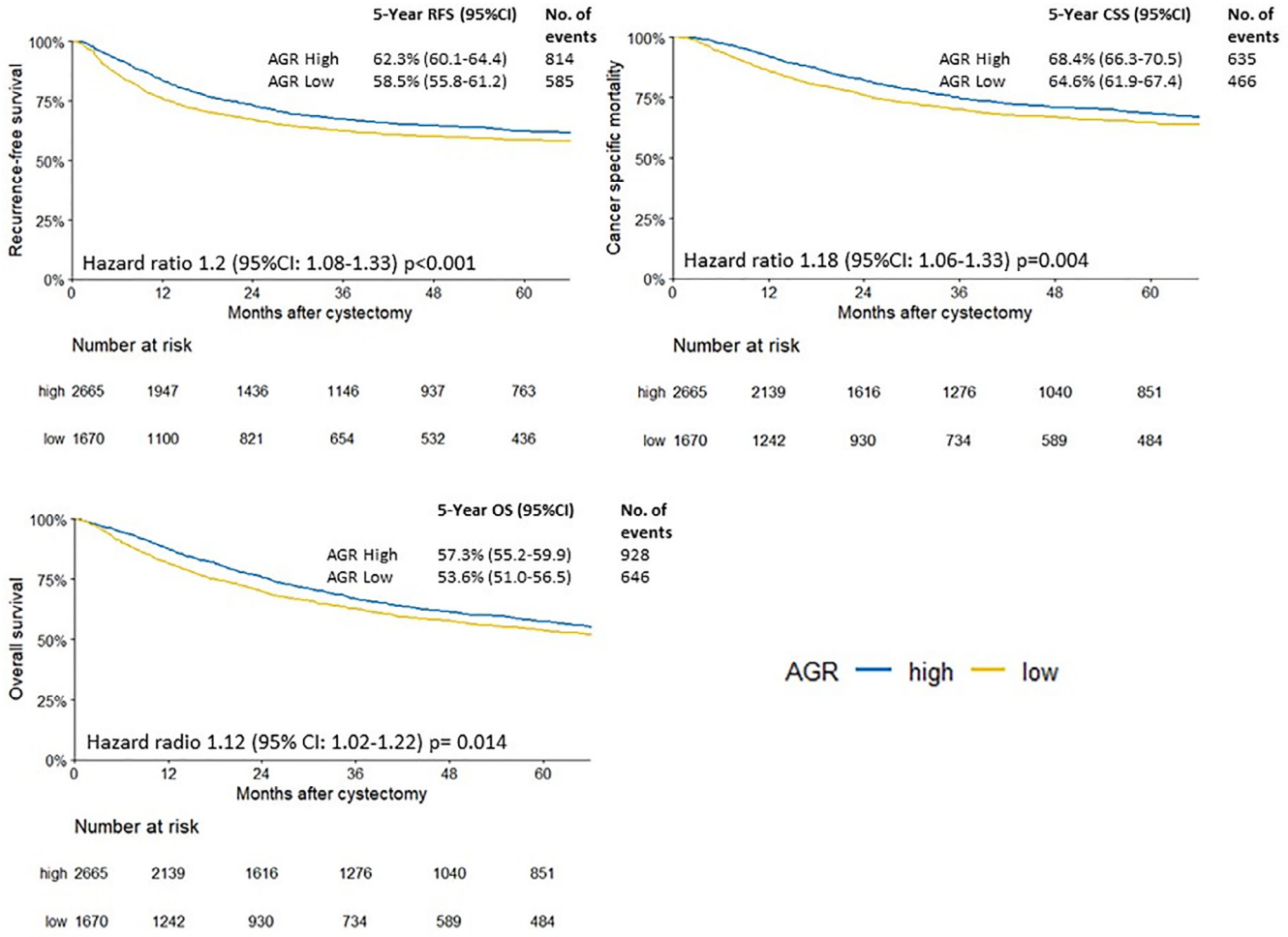

Fig. 2. Kaplan-Meier + log rank test for 5-year recurrence-free survival; cancer-specific survival and overall survival according to preoperative AGR status.

experienced disease recurrence, 2.034 (46.9%) patients died and 1.205 (27.8%) patients died of UCB. The 5-Year OS estimate was 55.9% (95%CI: 54.2−57.6), with a significant lower 5-year OS for patients with a low pAGR (57.3% vs. 53.7%, HR 1.12, *P*= 0.001). The 5-year RFS and CSS estimates were 60.8% and 66.9%, respectively. At 5 years, low pAGR was significantly associated with worse RFS (62.3% vs. 58.5%, HR 1.2, *P*< 0.001) and CSS (68.4% vs. 64.6% HR 1.18, *P*= 0.004; Figure 2).

In multivariable Cox regression models, pAGR was independently associated with worse RFS (HR 1.24; 95% CI 1.1−1.37, *P*< 0.001), CSS (HR 1.23, 95%CI 1.1−1.38, *P*< 0.001), and OS (HR 1.17, 95% CI 1.07−1.28, *P*< 0.001). Other factors that were associated with worse oncological outcomes included sex, age, use of adjuvant chemotherapy, tumor stage, pN+ disease, lymphovascular invasion, and positive soft tissue surgical margins (Table 3).

The addition of pAGR did not improve the discrimination ability of a base model that included preoperative clinical variables (sex, age, and clinical staging) for prediction of RFS, CSS, and OS (change of C-Index <1% for all). Similarly, the addition of pAGR to a model based on established postoperative variables also did not improve its discrimination ability (change of C-Index <1% for RFS, CSS, and OS). On DCA, the inclusion of pAGR did not improve the clinical net-benefit of models that either included preoperative or postoperative variables (Figures 3 and 4).

4. Discussion

With the advent of the genetic and immunotherapeutic revolution, the landscape of UCB is rapidly changing. Despite this progress, risk stratification for UCB remains a challenge, hampering a precision medicine-based approach.

Table 3
Univariable and multivariable cox regression analyses of factors associated with disease recurrence-free survival (RFS), cancer-specific survival (CSS) and overall survival (OS)

		Recurrence-free survival			Cancer-specific survival			Overall survival		
		HR	95% CI	*P*	HR	95%CI	p	HR	95%CI	*P*
Univariable analysis	pAGR (low)	1.2	1.08−1.33	**<0.001**	1.18	1.06-1.33	**0.004**	1.12	1.02-1.22	**0.014**
	Age	1.02	1.01−1.02	**<0.001**	1.02	1.01-1.03	**<0.001**	1.04	1.03-1.04	**<0.001**
	Gender (male)	0.87	0.77−0.98	**0.024**	0.79	0.69-0.91	**<0.001**	0.89	0.8-0.98	**0.024**
	Tumor stage pTa*	1.14	0.59−2.22	0.7	1.37	0.63-2.99	0.42	1.08	0.68-1.71	0.74
	Tumor stage pTis*	1.21	0.74−1.98	0.45	1.33	0.73-2.42	0.36	1.15	0.83-1.59	0.41
	Tumor stage pT1*	1.88	1.2−2.95	**0.006**	2.15	1.24-3.72	**0.006**	1.48	1.1-2.01	**0.011**
	Tumor stage pT2*	3.1	2.03−4.75	**<0.001**	3.62	2.14-6.1	**<0.001**	1.98	1.49-2.64	**<0.001**
	Tumor stage pT3*	6.27	4.14−9.51	**<0.001**	8.14	4.87-13.6	**<0.001**	3.61	2.73-4.79	**<0.001**
	Tumor stage pT4*	9.85	6.46−15.0	**<0.001**	12.72	7.56-21.4	**<0.001**	5.05	3.78-6.75	**<0.001**
	Positive STSM	3.3	2.81−3.87	**<0.001**	3.98	3.37-4.71	**<0.001**	2.85	2.45-3.31	**<0.001**
	Concomitant CIS	0.91	0.82−1.0	0.6	0.92	0.82-1.03	0.13	0.98	0.9-1.07	0.7
	LVI	3.08	2.77−3.41	**<0.001**	3.31	2.95-3.71	**<0.001**	2.35	2.15-2.56	**<0.001**
	pN+	3.6	3.24−3.99	**<0.001**	4.11	3.67-4.61	**<0.001**	2.66	2.43-2.92	**<0.001**
	No. of lymph nodes removed	1.0	1.0−1.0	0.52	1.0	1.0-1.0	0.67	1.0	1.0-1.0	0.46
	Use of AC	2.26	2.03−2.51	**<0.001**	2.19	1.95-2.46	**<0.001**	1.42	1.29-1.57	**<0.001**
		Recurrence-free survival			Cancer specific survival			Overall survival		
		HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Multivariable anylsis	pAGR (low)	1.24	1.11−1.37	**<0.001**	1.23	1.1 - 1.38	**<0.001**	1.17	1.07−1.28	**<0.001**
	Age	1.01	1.01−1.02	**0.02**	1.01	1.01−1.02	**<0.001**	1.03	1.03−1.04	**<0.001**
	Gender (*male*)	0.85	0.75−0.96	**0.01**	0.79	0.69−0.9	**<0.001**	0.91	0.82−1.01	0.09
	Tumor stage pTa*	1.13	0.58−2.2	0.72	1.37	0.63−2.99	0.43	1.11	0.7−1.75	0.67
	Tumor stage pTis*	1.21	0.73−2	0.45	1.33	0.72−2.45	0.36	1.09	0.78−1.53	0.61
	Tumor stage pT1*	1.73	1.1−2.73	**0.02**	1.98	1.14−3.44	**0.02**	1.38	1.01−1.88	**0.04**
	Tumor stage pT2*	2.33	1.51−3.58	**<0.001**	2.62	1.54−4.44	**<0.001**	1.59	1.18−2.13	**<0.001**
	Tumor stage pT3*	3.56	2.33−5.46	**<0.001**	4.38	2.59−7.39	**<0.001**	2.4	1.8−3.22	**<0.001**
	Tumor stage pT4*	4.72	3.05−7.32	**<0.001**	5.64	3.3−9.62	**<0.001**	2.94	2.17−3.99	**<0.001**
	Positive STSM	1.55	1.31−1.85	**<0.001**	1.77	1.47−2.12	**<0.001**	1.43	1.22−1.69	**<0.001**
	Concomitant CIS	1.02	0.91−1.14	0.74	1.02	0.90−1.15	0.74	1.08	0.98−1.19	0.12
	LVI	1.54	1.37−1.74	**<0.001**	1.58	1.39−1.8	**<0.001**	1.42	1.29−1.58	**<0.001**
	pN+	2.08	1.83−2.34	**<0.001**	2.43	2.11−2.79	**<0.001**	2.02	1.81−2.26	**<0.001**
	No. of lymph nodes removed	0.99	1.0−1.0	0.25	1.0	1.0−1.0	0.93	1.0	1.0−1.0	0.73
	Use of AC	0.96	0.85−1.09	0.55	0.86	0.75−0.99	**0.03**	0.73	0.65−0.82	**<0.001**

AGR, albumin/globulin ratio; HR, hazard ratio; 95% CI, 95% confidence interval; p, *P* value; CIS, carcinoma in situ; STSM, soft tissue surgical margins; LVI, lymphovascular invasion; pN+, lymph node involvement; AC, adjuvant chemotherapy.
*Reference, pT0.

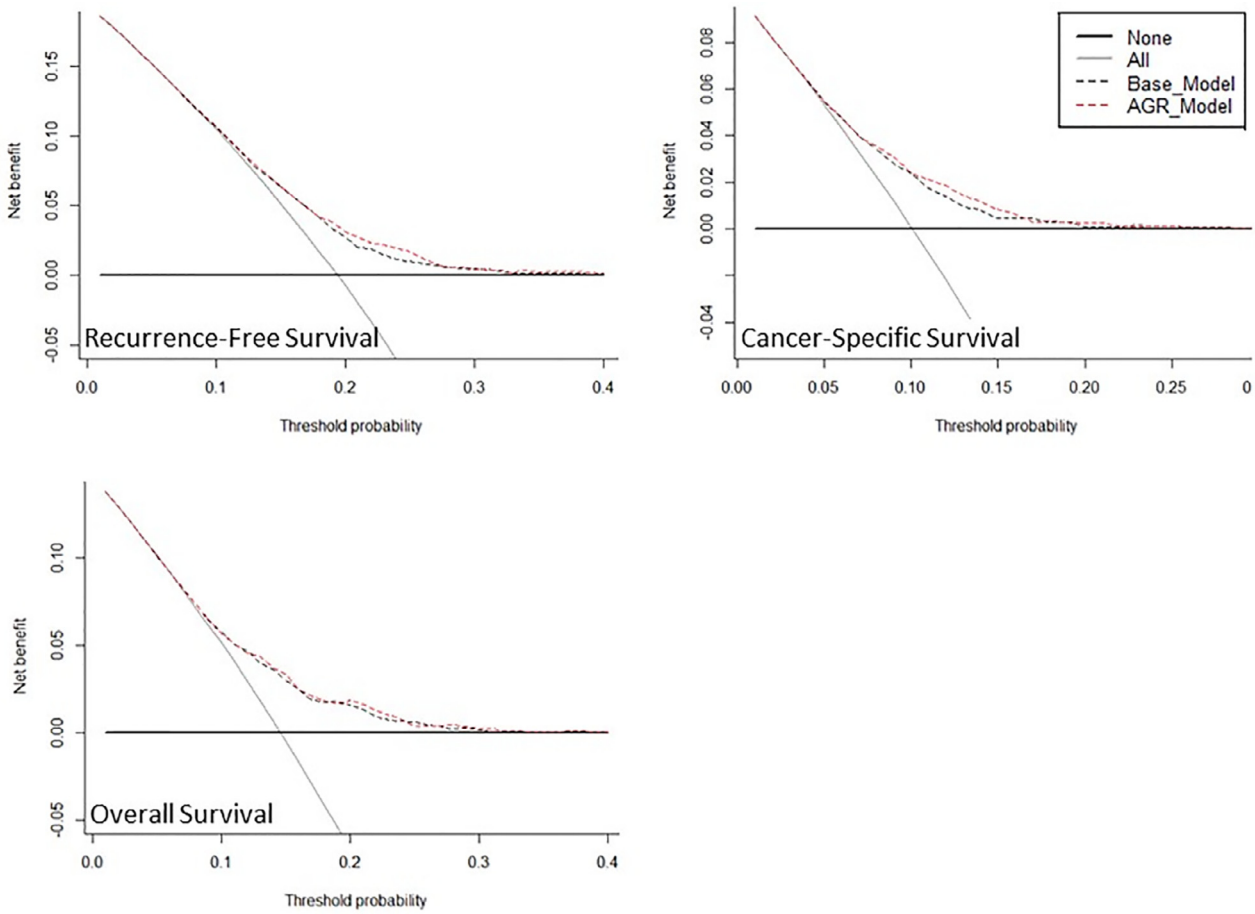

Fig. 3. Decision curve analysis (DCA) for the net-benefit of pAGR based on a preoperative model (including age, sex, and clinical staging) for the prediction of recurrence at 12 months.

Biomarkers can improve risk stratification through estimating the probability of treatment failure [29]. However, there is a persistent lack of clinically beneficial biomarkers in UCB [9,11]. Novel predictive molecular markers often lack external validation or are too expensive for clinical utilization [4,7,9,10,26]. Systemic inflammatory markers, such as pAGR, have the potential to predict UCB disease courses. We therefore analyzed the predictive and prognostic value of pAGR in patients undergoing RC for UCB in a large multicenter cohort. In our study, low pAGR was an independent predictor of ≥pT3 disease at RC. Low pAGR was also associated with worse RFS, CSS, and OS.

For UBC, 3 studies evaluated the association of pAGR with oncological outcomes. All 3 studies used a similar cutoff as we did (1.6 by Niwa et al. [23] and J. Liu et al. [24], 1.55 by Z. Liu et al. [22]). In a study of 364 patients with NMIBC, Niwa et al. found that low pAGR was associated with higher recurrence and progression rates [23]. For muscle invasive bladder cancer, a monocentric study that analyzed 296 patients who underwent RC, found low pAGR to be associated with worse RFS and CSS. However, baseline characteristics were unbalanced between the pAGR groups, and they did not analyze the effect on OS [24]. Another study confirmed that low pAGR was an independent risk factor for OS, RFS, and CSS using propensity score matching analyses [22]. However, this study had a small sample size and a short follow-up. Our findings, based on a much larger, multi-institutional cohort of patients of all stages with longer follow-up validated the independent ability of pAGR to predict OS, RFS and CSS.

Despite reports implying independent predictive status of pAGR, no previous study further analyzed the discrimination ability of pAGR through the creation of predictive models, where pAGR is allowed to add to discrimination ability of established predictor variables. Showing that low pAGR is an independent predictor in UCB with conventional multivariable models is insufficient to fully endorse a novel biomarker [11]. To validate whether pAGR can improve an existing model based on established clinical and pathological factors, we analyzed AUC values for different logistic models, C-indices for Cox regression models and clinical net-benefit of DCA [11]. Unfortunately, despite the large number of patients included, we were not able to show a relevant improvement in C-index through the addition of pAGR. Our logistic regression models for nonorgan confined disease also did not show a relevant change in

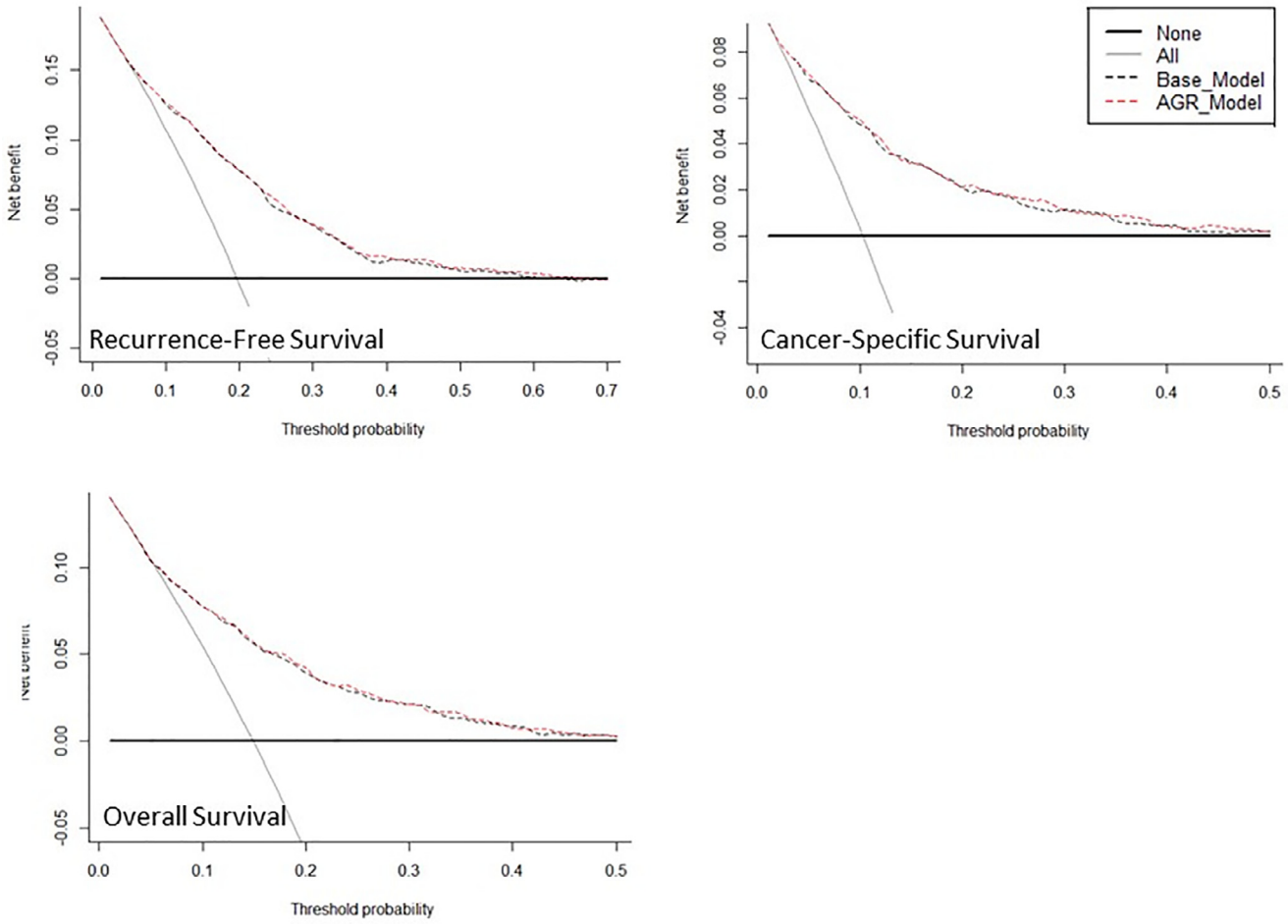

Fig. 4. Decision curve analysis (DCA) for the net-benefit of pAGR based on a postoperative model (including tumor stage, soft tissue surgical margin status, concomitant carcinoma in situ, lymphovascular invasion, pN+, no. of lymph nodes removed and use of adjuvant chemotherapy) for the prediction of recurrence at 12 months.

AUC after addition of pAGR as a factor. On DCA, our data showed that pAGR did not offer a relevant clinical net-benefit over the established clinical and histopathological factors.

Despite these negative findings, pAGR should be evaluated in further studies. It is unlikely that a single biomarker will have perfect predictive accuracy for a specific malignancy or tumor stage [26]. Furthermore, pAGR holds certain advantageous features, which could prove useful in combination with other markers. Unlike classical clinicopathological parameters, which can only be assessed postoperatively, pAGR offers the potential for a preoperative risk stratification. Future studies could enable a better patient selection for bladder sparing strategies or neoadjuvant chemotherapy utilization. Since pAGR is an inflammatory marker, it might also have great potential especially in the prediction of responses to new systemic treatments such as immunotherapy. Indeed, in patients with non-small cell lung carcinoma, pAGR has been attributed with the ability to predict the antitumor effect of anti-PD-1 antibody therapies [30].

While the strength of the cohort is its size and purity in treatment allocation, it is limited by its retrospective design and that none of the patients received NAC. Another limitation is that only the pretreatment pAGR was assessed in this study. There is no correlation to other inflammatory biomarkers (e.g., cytokine levels), as these have not been measured. Furthermore, confounding conditions such as undiagnosed infectious diseases or unknown drug interaction could affect pAGR. Data on therapies before RC which might alter pAGR, such as intravesical instillations, are unavailable. Due to the time of recruitment of this study, there is no information available on the predictive value of pAGR with respect to immunotherapies. Prospective trials that validate our cut-off and that evaluate the predictive value of pAGR with respect to NAC and immunotherapies are needed.

5. Conclusion

We confirmed that low pAGR is an independent risk factor for survival in patients with bladder cancer undergoing

RC. However, pAGR showed no value in improving the predictive and prognostic ability of models that relied on either clinical or pathological variables. In combination with other inflammatory markers, pAGR could be included in future models, especially in the era of new systemic therapies. Being inexpensive and broadly available, pAGR holds potential in identifying patients who are at risk of ≥pT3 disease or recurrence and might benefit from additional therapy.

Author Contributions

All authors made substantial contributions to the conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article and revising it critically for important intellectual content as well as final approval of the version to be submitted

Conflicts of interest

All authors have no conflict of interest.

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