Decrease of Preoperative Serum Albumin-to-Globulin Ratio as a Prognostic Indicator after Radical Cystectomy in Patients with Urothelial Bladder Cancer

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Purpose: This study aims to evaluate whether preoperative serum albumin-to-globulin ratio (AGR) could predict the prognosis of patients with urothelial bladder cancer (UBC) after radical cystectomy (RC).

Materials and Methods: A total of 176 patients with UBC who underwent RC in a tertiary hospital between 2008 and 2019 were retrospectively analyzed. The AGR was calculated as albumin/(total protein − albumin). In addition, the AGR was divided into two groups for the time-dependent receiver operating characteristic curve (ROC) analysis. Survival was estimated using the Kaplan–Meier analysis and compared using the log-rank test. Cox proportional-hazards models were used for multivariate survival analysis.

Results: The best cutoff AGR value for metastasis prediction was 1.32 based on the ROC curve analysis. Patients who had lower pretreatment AGR (<1.32) values composed the low-AGR group (n = 57; 32.4%). On the other hand, the remaining patients (n = 119; 67.6%) composed the high-AGR group. The patients in the low-AGR group had more advanced stage tumors compared with the patients in the high-AGR group. The Kaplan–Meier curves revealed that the patients in the low-AGR group had significantly lower rates of metastasis-free survival (MFS) and cancer-specific survival (CSS). The multivariate Cox regression analysis showed that preoperative AGR was an independent prognostic factor for MFS and CSS.

Conclusion: In this single-institution retrospective study, lower preoperative AGR values demonstrated a poor prognostic effect on MFS and CSS in patients with UBC who underwent RC.

Keywords: cystectomy; prognosis; serum albumin; serum globulins; survival; urinary bladder neoplasms

INTRODUCTION

Bladder cancer (BC) is the tenth most frequent type of neoplasms globally, and Europe and North America have higher age-standardized incidence rates for BC[1]. In the USA, BC is the sixth most frequent cancer and the seventh most frequent cause of cancer mortality[2]. In Korea, the incidence rate of BC is lower than in the USA. However, the 5-year survival rates in the USA and Korea are similar (77% vs. 76.8%, respectively)[2,3]. Nearly 90% of BC cases are urothelial bladder cancer (UBC)[4]. Radical cystectomy (RC) accompanied by extended pelvic lymph node dissection is the approved management for patients with muscle-invasive BC (MIBC) and those at the highest risk for bacillus Calmette–Guérin unresponsive nonmuscle invasive BC[5,6]. The 5-year relative survival rates of patients with regional and distant diseases are still lower than those with other genitourinary cancers despite the increase in the 5-year relative survival rate of BC from 70% to 76.8% over the past 20 years[3]. Recently, several prognostic markers have been studied in patients with MIBC[7-10]. However, no biological markers can be recommended for routine clinical use to make clinical decisions for patients with MIBC[6,7]. Factors, such as skeletal muscle index, require using a commercially available software by a subspecialty-trained urogenital radiologist to quantitatively calculate muscle areas[8]. However, a preoperative routine laboratory blood test is one of the fastest, most convenient, and lowest-cost clinical investigations[9]. To date, various preoperative laboratory tests have been studied to predict the prognosis of patients with UBC who have undergone RC. Prognostic indicators, such as the De Ritis ratio, platelet-to-lymphocyte ratio (PLR), and neutrophil-to-lymphocyte ratio (NLR), have been reported to be able to predict the prognoses of patients with BC after RC[9,10]. Serum albumin is a biochemical marker for malnutrition and has been associated with systemic inflammation[11,12]. In addition, serum globulin has been related to cancer-related inflammation[13]. The albumin-to-globulin ratio (AGR), which is computed by albumin/(total protein − albumin), is a good indicator of the nutritional and systemic inflammatory state of patients because it combines these two states in a single measurement[14].

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Table 1. Patient demographics and preoperative characteristics.

Variables[a]	Total (N = 176)	Low-AGR group AGR < 1.32 (N = 57)	High-AGR group AGR ≥ 1.32 (N = 119)	*P* value
Age, years	68.05 ± 8.96	69.32 ± 9.34	67.44 ± 8.75	.194
Sex (male/female)	151/25 (85.8/14.2)	48/9 (84.2/15.8)	103/16 (86.6/13.4)	.677
BMI, kg/m²	23.01 ± 2.99	23.57 ± 3.24	22.75 ± 2.83	.090
Diversion type				.408
Conduit	119 (67.6)	38 (66.7)	81 (68.1)	
Neobladder	31 (17.6)	8 (14.0)	23 (19.3)	
PCN, ureterostomy	26 (14.8)	11 (19.3)	15 (12.6)	
NAC	35 (19.9)	12 (21.1)	23 (19.3)	.788
AC	58 (33.0)	18 (31.6)	40 (33.6)	.788
MIBC	110 (62.5)	34 (59.6)	76 (63.9)	.589
Operation method				.503
Open	68 (38.6)	20 (35.1)	48 (40.3)	
Robot	108 (61.4)	37 (64.9)	71 (59.7)	
Total protein (g/L)	7.13 ± 0.60	7.39 ± 0.58	7.00 ± 0.57	< 0.001
Serum albumin (g/L)	4.14 ± 0.32	4.04 ± 0.30	4.19 ± 0.33	.005
AGR	1.41 ± 0.24	1.22 ± 0.11	1.50 ± 0.17	< 0.001

[a]Values are presented as mean ± standard deviation or number (%) unless otherwise indicated.
Abbreviations: AGR, albumin-to-globulin ratio; BMI, body mass index; PCN, percutaneous nephrostomy; NAC, neoadjuvant chemotherapy; AC, adjuvant chemotherapy; MIBC, muscle-invasive bladder cancer.

To date, two retrospective studies conducted in China have evaluated the efficiency and efficacy of pretreatment AGR as a prognostic factor in patients with BC after undergoing RC[15,16]. These studies demonstrated in a multivariable analysis that AGR, pathological tumor stage, and lymph nodes metastasis were independent prognostic predictors[15,16]. However, only a few studies have exhibited the prognostic predictive value of preoperative AGR in patients with BC in Korea. Thus, this retrospective study aims to evaluate the correlation between preoperative AGR and prognosis of patients with BC who underwent RC in Korea.

MATERIALS AND METHODS

Study population

The medical records of 183 patients with nonmetastatic UBC who underwent cystectomy at the authors' hospital (one institution) between August 2008 and May 2019 were reviewed retrospectively. Patients who underwent partial cystectomy (three), has a history of radiation therapy of the pelvis (three), and has a history of combination surgery (one) were excluded. A total of 176 patients were enrolled in this retrospective study. Of the patients, 146 (83.0%) underwent transurethral resections of the bladder tumors (TURBTs) before RC and 110 (62.5%) were diagnosed with MIBC before RC (**Figure 1**).

The institutional review board (IRB) of Kyungpook National University Chilgok Hospital, Daegu, Republic of Korea, approved the present trial (approval number: KNUMC 2020-04-037). The study was conducted in compliance with the relevant laws and regulations,

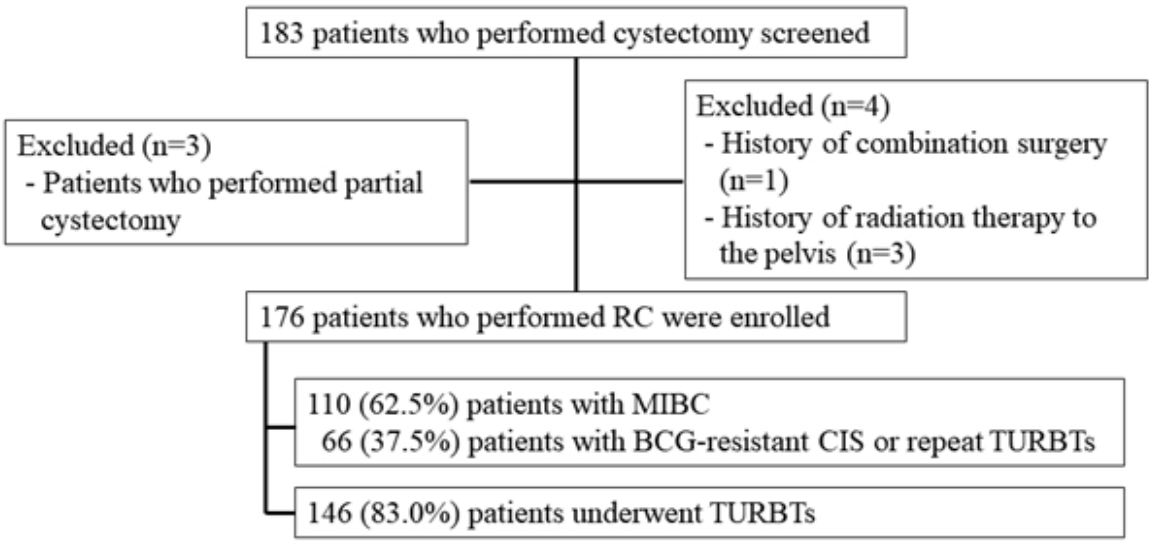

Figure 1. Flowchart of participants in the study.

Table 2. Comparison of clinicopathological variables.

Variables[a]	Total (N = 176)	Low-AGR group AGR < 1.32 (N = 57)	High-AGR group AGR ≥ 1.32 (N = 119)	*P* value
Pathological tumor stage				.080
≤T2	103 (58.5)	28 (49.1)	75 (63.0)	
≥T3	73 (41.5)	29 (50.9)	44 (37.0)	
Histological grade				.470
Low	8 (4.5)	6 (5.9)	2 (2.7)	
High	168 (95.5)	96 (94.1)	72 (97.3)	
Lymph nodes Involvement	40 (22.7)	15 (26.3)	25 (21.0)	.432
LVI	35 (19.9)	12 (21.1)	23 (19.3)	.788
Follow-up period[b], Months	32.4 (0.2–95.3)	32.6 (4.4–95.3)	32.2 (0.2–92.1)	.794
Metastasis	52 (29.5)	27 (47.4)	25 (21.0)	< 0.001
Cancer-related mortality	41 (23.3)	22 (38.6)	19 (16.0)	.001

[a]Values are presented as mean ± standard deviation or number (%) unless otherwise indicated.
[b]Values are presented as median (range)
Abbreviations: AGR, albumin-to-globulin ratio; LVI, lymphovascular invasion.

good clinical practices, and ethical principles described in the World Medical Association's Declaration of Helsinki. Requiring patients to provide informed consent was waived by the IRB because of the retrospective feature of the present study.

Inclusion and exclusion criteria

The current study included patients with MIBC without distant metastases, recurred multifocal superficial refractory tumor, repeated TURBTs, and bacillus Calmette–Guérin-resistant carcinomas in situ. In addition, the patients with a history of radiation therapy to the pelvis, clinical-stage M1, and history of combination surgery were excluded from the study. The 7th edition of the American Joint Committee on Cancer TNM staging system for BC was utilized in estimating the clinical tumor stage[17]. Histological grades were defined in accordance with the 2004 World Health Organization classification system[18].

Evaluations

Imaging investigation, histopathological analyses, and routine preoperative laboratory tests were performed before RC. The chest, abdominal, and pelvic computed tomography, and/or pelvic magnetic resonance imaging were performed to determine the clinical stage of the patients with BC. A bone scan was performed to evaluate bone metastasis. Laboratory tests for AGR were performed before neoadjuvant chemotherapy (NAC) for patients who underwent cisplatin-based NAC. Otherwise, laboratory tests were performed within 1 month before RC.

RC was performed after completing these preoperative workups. The patients with pathological tumor stage > 3 and node-positive diseases who have a good performance status underwent cisplatin-based adjuvant chemotherapy (AC) for at least four cycles. On the other hand, the patients with clinical tumor stage > 3 and node-positive diseases (based on the imaging investigation) who have a good performance status underwent cisplatin-based NAC for at least three cycles. Follow-up and management were performed for all the patients after RC according to published guidelines[19].

Statistical analysis

The time-dependent receiver operating characteristic (ROC) curve of the AGR for tumor metastasis was utilized in computing the ideal cutoff level by using the R Package Survival ROC, version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria). Areas under the curve were calculated for AGR. The best cutoff value was calculated to be 1.32 in the ROC curve at 12 months based on the highest Youden Index score. The decision curve analysis was utilized in evaluating the effectiveness of their marker in a decision-making process by using R package rmda, version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

Consequently, the patients with AGR values ≥ 1.32 composed the high-AGR group, while patients with AGR values < 1.32 composed the low-AGR group. The normal distribution of the continuous variables was evaluated by histogram and analytical methods (Kolmogorov–Smirnov and Shapiro–Wilk tests). Other continuous variables had normal distributions and were shown as mean ± standard deviation except for the fol-

Table 3. Multivariable Cox regression analysis for metastasis.

Variables	HR	95% CI	*P* value
Age	0.993	0.959–1.028	.680
Sex (female vs. male)	0.978	0.413–2.325	.960
Pathological tumor stage (≤ T2 vs. ≥ T3)	2.254	1.178–4.312	.014
Lymph nodes involvement (no vs. yes)	1.899	0.966–3.734	.063
Histological grade (low vs. high)	0.532	0.155–1.820	.314
LVI (no vs. yes)	1.950	1.002–3.792	.049
AGR (< 1.32 vs. ≥ 1.32)	0.435	0.248–0.763	.004

Abbreviations: AGR, albumin-to-globulin ratio; CI, confidence interval; HR, hazard ratio; LVI, lymphovascular invasion.

Table 4. Multivariable Cox regression analysis for cancer-specific mortality.

Variables	HR	95% CI	*P* value
Age	0.993	0.956–1.031	.705
Gender (female vs. male)	0.988	0.380–2.569	.980
Pathological tumor stage (≤ T2 vs. ≥ T3)	3.349	1.640–6.839	.001
Lymph node involvement (no vs. yes)	1.060	0.503–2.232	.878
Histological grade (low vs. high)	0.973	0.126–7.494	.920
LVI (no vs. yes)	2.660	1.297–5.457	.008
AGR (< 1.32 vs. ≥ 1.32)	0.488	0.257–0.924	.028

Abbreviations: AGR, albumin-to-globulin ratio; CI, confidence interval; HR, hazard ratio; LVI, lymphovascular invasion.

low-up period with non-normal distribution. Moreover, the follow-up period was shown as median (range). Student's t-test for the continuous variables with normal distribution, Mann–Whitney test for the continuous variable with non-normal distribution, and the chi-squared test for the categorical variables were used to compare the clinicopathological features between the two groups. The Kaplan–Meier method was utilized to calculate the survival spreads including metastasis-free survival (MFS) and cancer-specific survival (CSS). A log-rank test was performed to compare survival distributions between the two groups. For MFS, the dependent and independent variables were metastasis and the MFS period, respectively. For CSS, the dependent and independent variables were cancer-related mortality and the CSS period, respectively. The factors independently related to MFS and CSS were estimated using a multivariate Cox proportional-hazards regression model with hazard ratios (HR) and 95% confidence intervals (CI) calculated for each factor. The same statistical analyses aforementioned were done for the subgroup without NAC. All statistical analyses except for time-dependent ROC curves were performed using the Statistical Package for the Social Sciences, version 18.0 (IBM, Chicago, IL, USA). *P* values < .05 were considered statistically significant.

RESULTS

A time-dependent ROC analysis for AGR was conducted to evaluate the preoperative AGR for metastasis prediction. The areas under the curves for AGR at 12, 18, and 24 months were 0.632, 0.596, and 0.608, respectively (**Figure 2**). The best cutoff AGR value was determined to be 1.32 in the ROC curve at 12 months (**Figure 3A**). Moreover, the best cutoff AGR value was determined to be 1.32 in patients without NAC (**Figure 3B**). The standardized net benefit of AGR was higher than that of albumin and globulin in the decision curve analysis for metastasis prediction (**Figure 4**).

The demographics and preoperative characteristics of the patients in the two groups are shown in **Table 1**. The mean age of all the patients was 68.05 ± 8.96 years. The mean body mass index (BMI) was 23.01 ± 2.99 kg/m^2. The mean age and BMI were not statistically different between the two groups. Among the patients, 14.2% were females. Of the patients, 62.5%, 19.9%, and 33.0% were diagnosed with MIBC before RC, underwent NAC, and patients underwent AC, respectively. The ratio of females, diversion type, operation methods, MIBC, NAC, and AC were not significantly different between the two groups. The mean total protein, mean serum albumin, and mean AGR were 7.13 ± 0.60, 4.14 ± 0.32, and 1.41 ± 0.24 g/L, respectively. The mean total protein in the low-AGR group was significantly higher than that in the high-AGR group (7.39 ± 0.58 vs. 7.00 ± 0.57; *P* < .001). On the other hand, the mean serum albumin (4.04 ± 0.30 vs. 4.19 ± 0.33; *P* = .005) and mean AGR (1.22 ± 0.11 vs. 1.50 ± 0.17; *P* < 0.001) were significantly lower in the low-AGR group than those in the high-AGR group.

A comparison of the clinicopathological characteristics of the patients between the two groups is shown in

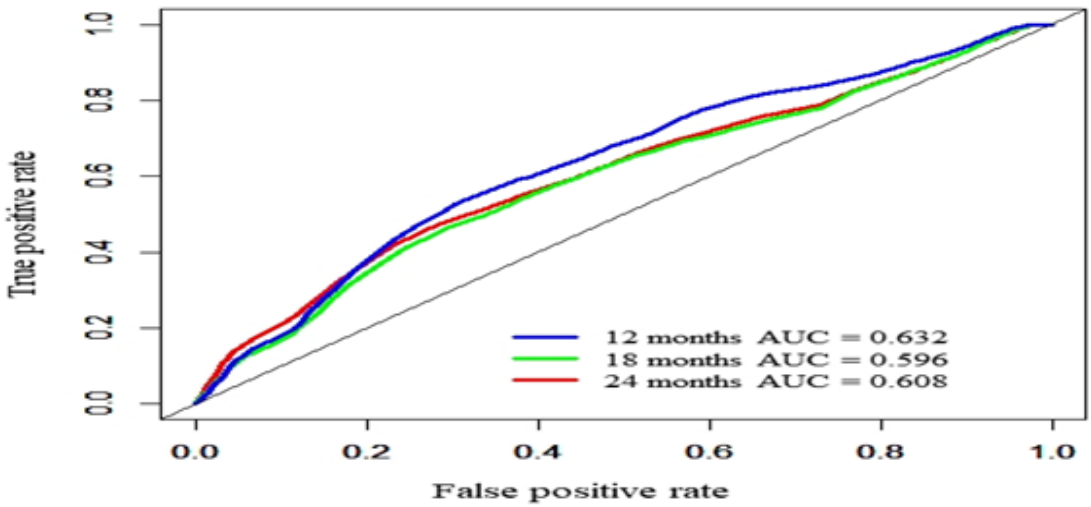

Figure 2. Time-dependent ROC curves of preoperative AGR according to times from RC for metastasis.

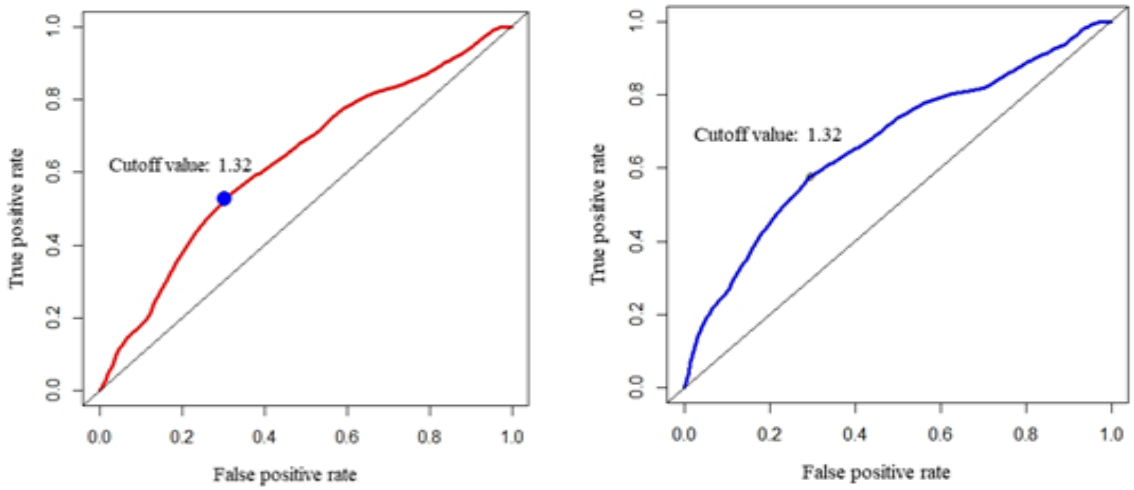

Figure 3. The best cutoff value of AGR was calculated with time-dependent ROC curves for metastasis at 12 months in the study population **(A)** and patients without NAC **(B)**.

Table 2. The mean follow-up period in this study was 32.4 months (range, 0.2–95.3 months). The histological subtype (low vs. high grade), lymphovascular invasion (LVI), and pathological tumor stages between the two groups were not statistically different. Metastasis rates were significantly higher in the low-AGR group than in the high-AGR group (47.4% vs. 21.0%; $P < .001$). In addition, cancer-related mortality rates were significantly higher in the low-AGR group than in the high-AGR group (38.6% vs. 16.0%; $P = .001$).

The Kaplan–Meier curve analysis demonstrated that the patients in the low-AGR group had significantly lower rates of MFS than those in the high-AGR group (52.6% vs. 79.0%; $P = .001$; **Figure 5A**) and lower rates of CSS compared with the high-AGR group (61.0% vs. 84.0%; P = .003; **Figure 5B**). NMIBC has a higher survival rate than MIBC, so an additional analysis was done only for patients with MIBC. For patients with MIBC, the Kaplan-Meier curves were utilized to calculate MFS and CSS. MFS was significantly different between the two groups (44.7% vs. 70.1%; $P = .015$) (**Figure 6A**). The CSS in the low-AGR group was lower than that in the high-AGR group, but not statistically significant (53.8% vs. 74.8%; $P = .053$) (**Figure 6B**).

The multivariate analysis for metastasis is shown in **Table 3**. The pathological tumor stage ≥ T3 (HR = 2.254; 95% CI = 1.178–4.312; $P = .014$), LVI (HR = 1.950; 95% CI = 1.002–3.792; $P = .049$), and AGR ≥ 1.32 (HR = 0.435; 95% CI = 0.248–0.763; $P = .004$) were shown to be independent predictive prognostic factors for metastasis. **Table 4** shows the multivariate analysis for cancer-related mortality. Consequently, the pathological tumor stage ≥ T3 (HR = 3.349; 95% CI = 1.640–6.839; $P = .001$), LVI (HR = 2.600; 95% CI = 1.297–5.457; $P = 0.008$), and AGR ≥ 1.32 (HR = 0.488; 95% CI = 0.257–0.924; $P = .028$) were shown

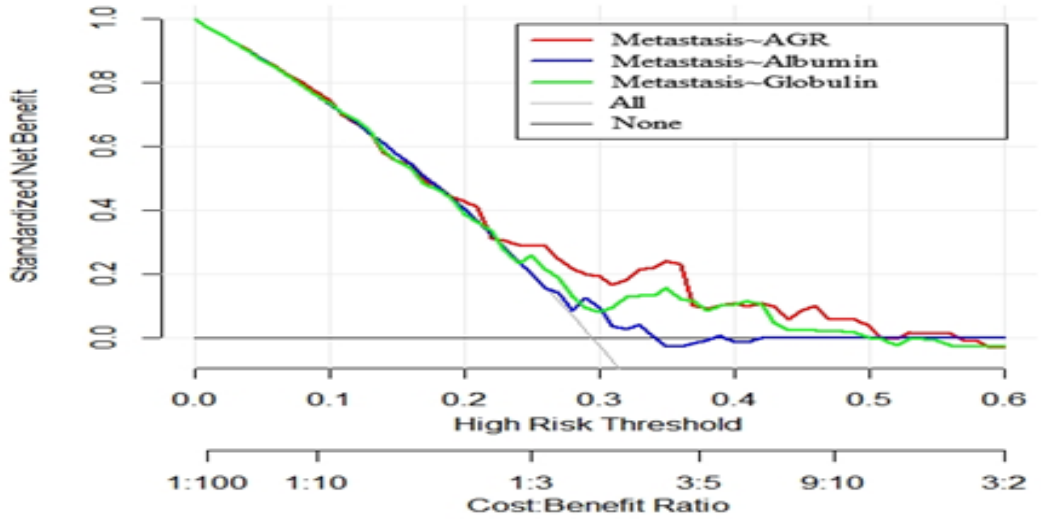

Figure 4. Decision curve analysis for AGR, albumin, and globulin predicting metastasis.

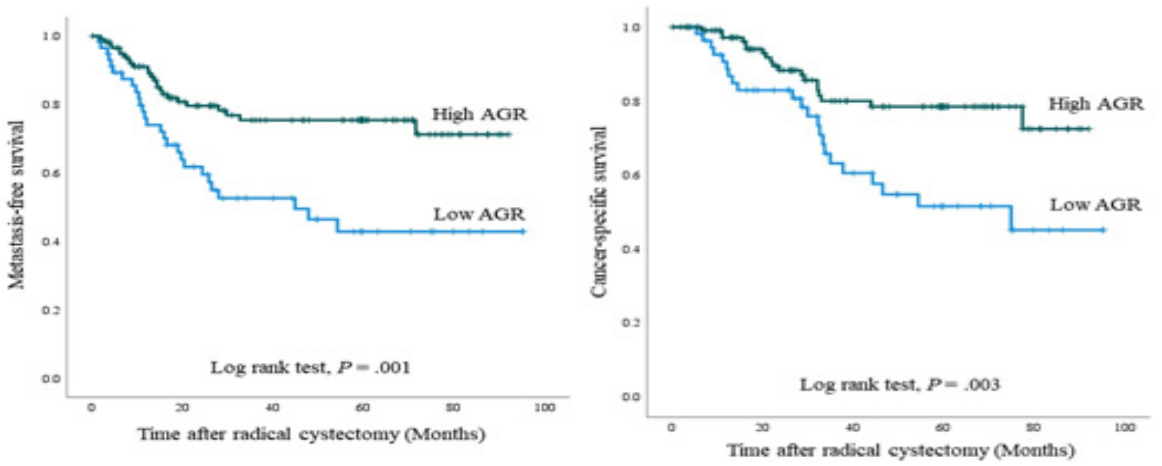

Figure 5. The Kaplan–Meier curves showing MFS (A) and CSS (B) between low- and high-AGR groups.

to be independent predictive factors for cancer-related mortality.

DISCUSSION

This retrospective study showed that preoperative AGR can be valuable as a predictive factor in estimating CSS and MFS in patients with UBC who have undergone RC. This study is one of the first studies conducted in Korea to assess the efficiency and accuracy of preoperative AGR as a predictive prognostic factor in estimating MFS and CSS in patients with UBC who have undergone RC although some retrospective studies previously demonstrated that preoperative AGR is related to the prognosis after RC of patients with UBC in China[15,16]. It is generally accepted that inflammation is related to cancer[20]. Cancer-related inflammation, which consists of local immune and systemic inflammatory responses, is common in advanced cancer and is associated with shorter overall survival (OS)[13,21,22]. Variable biomarkers from laboratory tests were studied (including C-reactive protein, albumin, Glasgow prognostic score (GPS), modified GPS, PLR, NLR, and lymphocyte-to-monocyte ratio) to estimate cancer-related systemic inflammation[23].

Serum albumin, a component of systemic inflammation, has several crucial physiological functions, including maintaining colloidal osmotic pressure, binding charged compounds, and doing antioxidant activities[13,24]. Decreased serum albumin and increased serum globulin level is associated with cancer-related systemic inflammation and tumor progression[12,13]. AGR is a factor that reflects both low albumin level and high globulin level in cancer-related systemic inflammation[14].

Several studies have examined the efficiency and accuracy of preoperative AGR as a predictive prognostic factor for diverse human cancers in the past 10 years[25]. In a healthy screening population, low AGR is a risk factor for the occurrence of malignancies and malignancy-related mortality in the short- and long-term

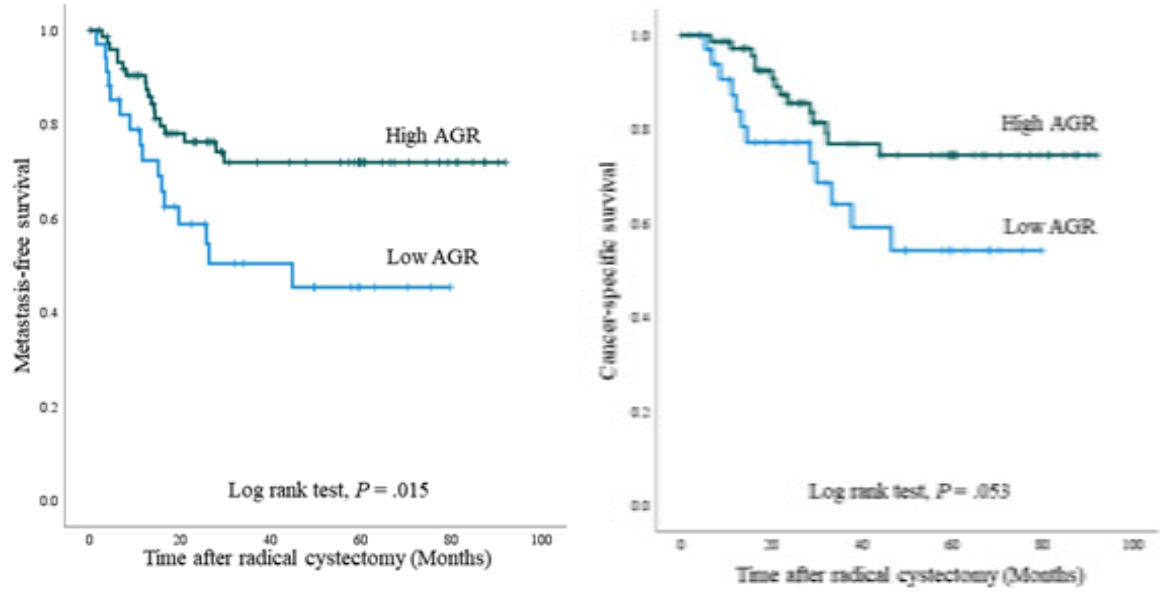

Figure 6. The Kaplan–Meier curves showing MFS **(A)** and CSS **(B)** between low- and high-AGR groups in patients with MIBC.

periods[26]. A meta-analysis of preoperative AGR and human cancers reported that low preoperative AGR values are related to poor OS, progression-free survival (PFS), and disease-free survival in patients with malignancies[25].

To date, two retrospective AGR studies in China have been conducted involving patients with BC who underwent RC[15,16]. Liu et al.[15] carried out a retrospective study involving 296 patients with UBC who underwent RC. They determined the cutoff value of AGR as 1.6 and reported that high-AGR values are a strong independent predictive factor of long-term recurrence-free survival and CSS in patients with UBC undergoing RC. Moreover, Liu et al.[16] reported a retrospective cohort study involving 189 patients with primary high-grade UBC using a propensity score-matched analysis and determined that the cutoff value of AGR was 1.55. Their study demonstrated that preoperative AGR, age (≥ 60 years), before and after propensity score-matched analysis, the pathological tumor stage, and lymph nodes metastasis were independent components in predicting PFS, CSS, and OS in multivariate Cox regression analyses.

This study was a retrospective study involving 176 patients with UBC who underwent RC. In contrast to the previous two studies, this study included patients with clinical T3 or T4 who received NAC. The cutoff value for AGR in the current study was defined to be 1.32, which is lower than those in other studies. The ratio of pathologic tumor stage ≥ T3 (41.5% vs. 34.4%–36.5%) (15,16) and the ratio of the histological high-grade tumor (95.5% vs. 74.7%) were higher compared with other studies[15]. Considering that cancer progression is related to local and systemic inflammatory responses, these differences may be the reason why the cutoff value for AGR in this study is lower than other studies[15,16,20]. Moreover, the study population included NAC patients with clinical tumor stages 3–4 and node-positive disease. The downstaging effect of NAC was not affected in these patients because preoperative laboratory tests were performed before NAC[27]. These points may also be the reason why the cutoff value for AGR is lower than in other studies.

The pathological tumor stage, LVI, and AGR were independent predictive prognostic factors in the multivariate Cox regression analyses for metastasis and cancer-specific mortality. Moreover, a meta-analysis demonstrated that LVI is a significant component in predicting cancer recurrence and cancer-specific mortality in patients with BC[28].

Among the three studies that investigated the association between AGR and UBC, one study[15] did not include LVI as a variable. In another study[16], LVI was not an independent factor for CSS, PFS, and OS in multivariate Cox regression analysis. In this study, the difference in LVI (in percent) between the low- and high-AGR groups was smaller than that of another study (18.1% vs. 19.8% and 36.4% vs. 20.3%, respectively)[16]. In contrast to these two studies, the involvement of the lymph nodes was not an independent factor for metastasis and cancer-specific mortality in this study. The ratio of the involvement of the lymph nodes was higher in the low-AGR group in these two studies (31.8% vs. 9.9% and 21.8% vs. 11.4%; respectively) [15,16]. However, the difference in the involvement of the lymph nodes between the two groups in this study was smaller than that of the other studies (26.3% vs. 21.0%). Patients with clinical tumor stages of 3 or 4 and lymph node-positive diseases in this study received neoadjuvant cisplatin-based chemotherapy. NAC decreases residual cancer burden in patients with advanced UBC[29]. Nearly half of the patients with UBC treated with RC achieved pathological downstaging through NAC[27]. Therefore, NAC may be the cause of the lower differences in the involvement of the lymph nodes and LVI between the two groups in this study.

This study evaluated AGR as a prognostic factor for recurrence and survival in BC in Korea and included patients who underwent NAC (< 20%). However, this study had some limitations, including its retrospective study design and the shortest follow-up period (32 months) among the three studies investigating the association between UBC and AGR. These limitations could affect subsequent results. Furthermore, other prognostic factors from routine preoperative laboratory testing were not included. Finally, the single-institutional database of this study did not contain data from other institutions. This could lead to imperfect reflections of the whole population of patients with UBC treated with RC in Korea. Therefore, a larger-scale, multi-institutional, and prospective study is required to provide a better conclusion.

CONCLUSIONS

AGR, which is an easily accessible and inexpensive marker, is an important predictive factor in patients with UBC treated with RC. The pathological tumor stage, metastasis, and cancer-specific mortality were significantly correlated with low AGR values. Low AGR values showed a poor prognostic effect on CSS and MFS in patients who underwent RC for the treatment of UBC. Preoperative AGR is a readily accessible and inexpensive prognostic marker that can be utilized to predict outcomes in patients with UBC treated with RC.

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CONFLICT OF INTEREST

None declared.

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