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The prognostic value of the pretreatment serum albumin to globulin ratio for predicting adverse pathology in patients undergoing radical prostatectomy for prostate cancer

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Purpose: Few studies have demonstrated the clinical significance of pretreatment serum albumin and globulin in prostate cancer (PCa). This study evaluated the association between the pretreatment albumin to globulin ratio (AGR) and clinicopathologic characteristics of nonmetastatic PCa in a large multicenter setting in Korea.

Materials and Methods: This study involved 742 patients with nonmetastatic PCa who underwent radical prostatectomy (RP) in seven institutions between January 2011 and December 2012. The AGR was calculated as follows: albumin/(total protein-albumin). Patients were divided into low and high AGR groups by a cutoff value from a receiver operating characteristic curve analysis.

Results: The best cutoff for the AGR was set at 1.53. The area under the curve of the AGR was 0.624 (95% confidence interval, 0.557–0.671; p<0.001). Patients who had a lower pretreatment AGR (<1.53) were identified as the low AGR group (n=398, 53.6%) and the remaining patients as the high AGR group (n=344, 46.4%). Preoperative AGR was significantly lower in patients with non-organ-confined disease (≥pT3) than in those with organ-confined disease (≤pT2) (p<0.001). The low AGR group had higher aggressive pathologic Gleason scores (pGS) (≥8) than did the high AGR group (p=0.016). Furthermore, the AGR was an independent prognostic factor for high pGS (≥8) and non-organ-confined disease (≥pT3), according to multivariate logistic regression analysis.

Conclusions: A low AGR was closely associated with nonconfined disease (≥pT3) and high pGS (≥8). AGR can be a useful serological marker for predicting adverse pathology in patients with nonmetastatic PCa who undergo RP.

Keywords: Albumin; Globulin; Pathology; Prostate cancer; Prostatectomy

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INTRODUCTION

In Korea, prostate cancer (PCa) is the most common malignancy of the genitourinary tract and the fourth most common type of cancer among men [1]. Approximately 14,561 new PCa cases and 2,040 PCa-related deaths were reported in Korea in 2020 [2]. In addition to an increase in PCa-associated mortality [3], the incidence of PCa has been increasing in Korea owing to a modernized environmental lifestyle, more westernized dietary habits, medical advances in laboratory diagnosis, gradual implementation and widespread application of prostate-specific antigen (PSA) screening, and enhanced prostate biopsy skill [4-6].

Hypoalbuminemia is associated with a poor nutritional state and indicates systemic inflammation in patients with cancer [7]. Serum albumin and globulin are major components of human serum proteins that play important roles in the inflammatory reaction and immunity [8]. Besides hypoalbuminemia, hyperglobulinemia is also considered an indicator of chronic inflammation in patients with cancer [9]. Furthermore, a previous meta-analysis revealed that a low preoperative serum albumin to globulin ratio (AGR), which is computed as albumin divided by the value of total protein minus albumin, is related to worse prognosis in various human cancers [10].

To date, only two studies have been performed to determine the association between preoperative AGR and oncologic outcomes of PCa. However, these studies included patients with metastatic or recurrent PCa. Therefore, to demonstrate the clinical significance of pretreatment AGR, we evaluated the association between the AGR and clinicopathologic characteristics of patients with nonmetastatic PCa in a large-scale multicenter study in Korea.

MATERIALS AND METHODS

1. Ethics statement

This study was approved by the Institutional Review Board of Kyungpook National University, School of Medicine, Daegu, Korea (approval number: KNUH 2021-02-003). The study was carried out in agreement with applicable laws and regulations, good clinical practices, and ethical principles as described in the Declaration of Helsinki. The board exempted the requirement for informed consent because of the retrospective nature of the study.

2. Study population

The clinical data, including demographic characteristics and pathologic outcomes, of 742 patients who showed nonmetastatic PCa and underwent radical prostatectomy (RP) in seven institutions between January 2011 and December 2012 were analyzed. Seven surgeons representing the different institutions performed the RP. All patients were diagnosed with primary prostate adenocarcinoma on initial prostate biopsy and underwent prostate magnetic resonance imaging, computed tomography scan, and bone scan for clinical staging. Serum albumin and globulin were measured at least within 1 week of surgery. RP was performed in patients who did not show distant or nonregional lymph node metastasis or who did not have severe cardiopulmonary disease. Patients who received androgen deprivation therapy or radiotherapy and those with a history of other solid or hematologic malignancy were excluded. The decision to perform open, laparoscopic, or robotic RP was optimized by each of the operators according to patient characteristics.

3. Calculating albumin to globulin ratio

The AGR was calculated as follows: albumin/(total protein-albumin). Patients were divided into two groups according to the cutoff value derived from the receiver operating characteristic (ROC) curve analysis, with the best cutoff AGR value for predicting non-organ-confined disease set at 1.53 (Fig. 1). The area under the curve of the AGR was 0.624 (95% confidence interval, 0.557–0.671; p<0.001). Patients who had a lower pretreatment AGR (<1.53) were identified as the low AGR group (n=398, 53.6%) and the remaining patients as the high AGR group (n=344, 46.4%).

4. Statistical analysis

Student's t-test for continuous variables and the chi-square test for noncontinuous variables were used. The multivariate logistic regression model was used for predicting

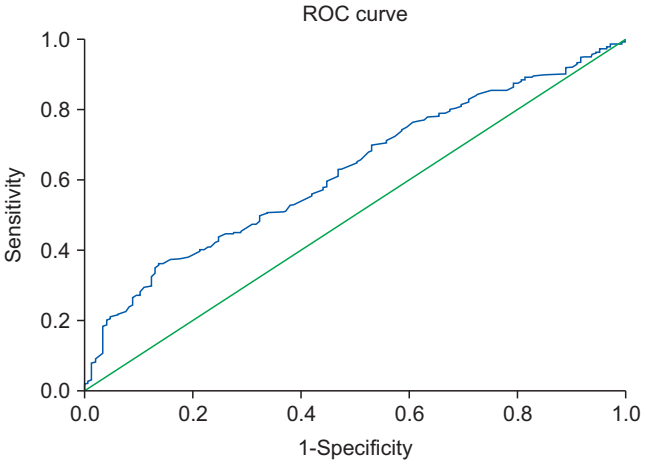

Fig. 1. Cutoff value of the serum albumin to globulin ratio from receiver operating characteristic (ROC) curve analysis.

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non-organ-confined disease (≥T3) and high Gleason scores (≥8). Statistical analyses were performed using SPSS for Windows, version 23 (IBM Corp., Armonk, NY, USA), and statistical significance was established with $p<0.05$.

RESULTS

Table 1 shows the clinical and pathologic characteristics of patients according to pretreatment serum AGR. The mean follow-up period, age, body mass index, preoperative PSA, and Gleason score on prostate biopsy did not differ significantly between the two groups. The mean prostate volume measured by preoperative transrectal ultrasound was 37.35±17.36 mL in the low AGR group and 34.46±15.23 mL in the high AGR group. The preoperative prostate volume was significantly different between the groups (p=0.019). The low AGR group had a significantly higher percentage of high cT stage (≥3) than did the high AGR group (17.8% vs. 9.6%; p=0.001). Significantly more robotic RP was performed in the low AGR group. The percentage of patients with high pathologic Gleason scores (≥8) was significantly higher in the low AGR group than in the high AGR group (21.4% vs. 14.5%; p=0.016). The low AGR group also had significantly more patients with a high pT stage (≥3) than did the high AGR group (24.6% vs. 13.7%; p<0.001). The pN stage did not differ significantly between the two groups. A total of 62 pa-

Table 1. Clinical and pathologic characteristics of the patients according to pretreatment serum AGR

Variable	Low AGR group, AGR <1.53 (n=398)	High AGR group, AGR ≥1.53 (n=344)	p-value
Follow-up period, mo	57.3 (48.2–72.7)	57.2 (41.9–74.8)	0.935
Age, y	66.88±6.30	66.83±6.12	0.913
BMI, kg/m^2	24.21±2.64	24.20±3.05	0.985
Preoperative PSA, ng/mL	11.56±11.07	12.75±17.05	0.270
Preoperative prostate volume, mL	37.35±17.36	34.46±15.23	0.019
Gleason score on prostate biopsy			0.482
≤7	356 (89.4)	313 (91.0)	
≥8	42 (10.6)	31 (9.0)	
cT Stage			0.001
≤2	327 (82.2)	311 (90.4)	
≥3	71 (17.8)	33 (9.6)	
cN stage			0.177
0	386 (97.0)	327 (95.1)	
1	12 (3.0)	17 (4.9)	
Operation technique			<0.001
Open	180 (45.2)	205 (59.6)	
Laparoscopic	62 (15.6)	46 (13.4)	
Robotic	156 (39.2)	93 (27.0)	
Pathologic Gleason score, sum			0.016
≤7	313 (78.6)	294 (85.5)	
≥8	85 (21.4)	50 (14.5)	
pT stage			<0.001
2	300 (75.4)	297 (86.3)	
≥3	98 (24.6)	47 (13.7)	
pN stage			0.594
0 or X	382 (96.0)	327 (95.1)	
1	16 (4.0)	17 (4.9)	
Upgrading	43 (10.8)	19 (5.5)	0.001
Upstaging	27 (6.8)	14 (4.1)	0.106
Postoperative prostate weight, g	40.60±17.01	37.36±16.16	0.011
Tumor volume, mL	11.59±15.38	16.68±20.34	0.002
Biochemical recurrence	97 (24.4)	72 (20.9)	0.265
Cancer-specific death	6 (1.5)	7 (2.0)	0.799

Values are presented as mean±standard deviation or number (%).
AGR, albumin to globulin ratio; BMI, body mass index; PSA, prostate-specific antigen.

tients (8.4%) showed upgrading and 41 (5.5%) showed upstaging. The ratio of upgrading was significantly higher in the low AGR group (10.8% vs. 5.5%; p=0.001). Postoperative prostate weight was significantly greater in the low AGR group than in the high AGR group (40.60±17.01 g vs. 37.36±16.16 g; p=0.011) but tumor volume was significantly lower (11.59±15.38 mL vs. 16.68±20.34 mL; p=0.002). Biochemical recurrence was shown in 169 patients (22.8%) and cancer-specific death in 13 (1.8%). Kaplan–Meier curve analysis showed that there were no significant differences in biochemical recurrence (Supplementary Fig. 1A) or cancer-specific death (Supplementary Fig. 1B) between the two groups.

Table 2 shows the mean AGR according to pathologic outcomes. Mean AGR was significantly lower in patients with a high pT stage (≥3) than in those with pT2 stage disease (1.46±0.21 vs. 1.59±0.28; p<0.001). The mean AGR did not differ significantly according to pN stage, pathologic Gleason score, or surgical margin status.

Table 2. Pretreatment serum albumin to globulin ratio (AGR) according to pathologic outcome

Pathologic outcome	Mean AGR	p-value
pT stage		<0.001
2	1.59±0.28	
≥3	1.46±0.21	
pN stage		
0 or X	1.56±0.27	0.955
1	1.56±0.31	
Pathologic Gleason score, sum		0.068
≤7	1.56±0.27	
≥8	1.51±0.26	
Surgical margin status		0.829
Negative	1.56±0.26	
Positive	1.55±0.29	

Values are presented as mean±standard deviation.

The results of the multivariate analysis for predicting non-organ-confined disease (≥pT3) are shown in Table 3. Gleason score on prostate biopsy, preoperative PSA, and AGR (continuous or categorical) were independent prognostic factors for predicting a high pathologic stage.

The results of the multivariate analysis for predicting high Gleason scores (≥8) are shown in Table 4. Preoperative PSA, cTN stage, and AGR (categorical) were independent prognostic factors for predicting a high Gleason score.

Table 5 shows the results of multivariable Cox regression analyses predicting biochemical recurrence. Preoperative PSA, pathologic Gleason score, tumor volume, and surgical margin status were independent prognostic factors for predicting biochemical recurrence. However, AGR (categorical) was not significantly associated with biochemical recurrence (p=0.180).

DISCUSSION

The results of this study demonstrated that a low preoperative AGR is associated with a high pT stage (≥3) and high Gleason score (≥8) in patients with PCa who undergo RP. To the best of our knowledge, this study, involving a relatively large cohort, is the first trial to demonstrate the significant association between a low AGR and adverse pathologic outcomes in patients with nonmetastatic PCa.

Recent advances in cancer biology have revealed that

Table 3. Multivariate analysis for predicting non-organ-confined disease (≥pT3)

Variable	Odds ratio (95% confidence interval)	p-value
pT stage, 2 vs. pT stage, ≥3		
Age	1.017 (0.984–1.051)	0.317
BMI	1.041 (0.971–1.116)	0.260
Preoperative prostate volume	0.992 (0.979–1.006)	0.246
Gleason score on prostate biopsy	2.648 (1.889–3.711)	<0.001
Preoperative PSA	1.020 (1.007–1.033)	0.002
AGR (continuous)	0.131 (0.056–0.306)	<0.001
pT stage, 2 vs. pT stage, ≥3		
Age	1.018 (0.985–1.052)	0.291
BMI	1.041 (0.971–1.115)	0.259
Preoperative prostate volume	0.993 (0.979–1.006)	0.276
Gleason score on prostate biopsy	2.628 (1.879–3.676)	<0.001
Preoperative PSA	1.018 (1.006–1.030)	0.002
AGR (categorical, high AGR vs. low AGR)	2.162 (1.430–3.269)	<0.001

BMI, body mass index; PSA, prostate-specific antigen; AGR, albumin to globulin ratio.

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Table 4. Multivariate analysis for predicting high Gleason score (≥8)

Variable	Hazard ratio (95% confidence interval)	p-value
Gleason score, ≤7 vs. Gleason score, ≥8		
Age	1.032 (0.998–1.068)	0.072
BMI	1.026 (0.953–1.105)	0.489
Preoperative prostate volume	0.997 (0.984–1.010)	0.671
Preoperative PSA	1.031 (1.018–1.045)	<0.001
cT stage	1.460 (1.241–1.718)	<0.001
cN stage	2.535 (1.067–6.023)	0.035
AGR (continuous)	0.449 (0.201–1.005)	0.051
Gleason score, ≤7 vs. Gleason score, ≥8		
Age	1.033 (0.998–1.069)	0.067
BMI	1.026 (0.953–1.105)	0.489
Preoperative prostate volume	0.997 (0.984–1.010)	0.669
Preoperative PSA	1.031 (1.018–1.044)	<0.001
cT stage	1.458 (1.239–1.715)	<0.001
cN stage	2.640 (1.110–6.280)	0.028
AGR (categorical, high AGR vs. low AGR)	1.795 (1.171–2.752)	0.007

BMI, body mass index; PSA, prostate-specific antigen; AGR, albumin to globulin ratio.

Table 5. Multivariable Cox regression analyses predicting biochemical recurrence

Variable	Hazard ratio (95% confidence interval)	p-value
Age, y	1.008 (0.979–1.037)	0.602
BMI, kg/m^2	1.004 (0.951–1.060)	0.877
Preoperative PSA, ng/mL	1.017 (1.011–1.023)	<0.001
Operative technique		
Open	1.00 (ref)	
Laparoscopic	1.366 (0.841–2.218)	0.208
Robotic	1.040 (0.701–1.544)	0.846
Pathologic Gleason score, sum		
≤7	1.00 (ref)	
≥8	1.789 (1.264–2.532)	0.001
pT stage		
2	1.00 (ref)	
≥3	1.145 (0.758–1.729)	0.520
pN stage		
0	1.00 (ref)	
1	1.350 (0.680–2.678)	0.391
Tumor volume, mL	1.014 (1.007–1.021)	<0.001
Surgical margin status	2.214 (1.579–3.105)	<0.001
AGR (categorical, high AGR vs. low AGR)	1.262 (0.898–1.773)	0.180

BMI, body mass index; PSA, prostate-specific antigen; AGR, albumin to globulin ratio.

systemic malnutrition and inflammation are associated with poor prognosis in cancer [11,12]. Hypoalbuminemia is induced in an inflammatory state as a result of increased capillary escape of serum albumin into the interstitium [10]. Necrosis of malignant cells and tumor-related tissue inhibits the synthesis of serum albumin [13]. In addition, the serum level of tumor necrosis factor-α is elevated in patients with cancer, which inhibits albumin synthesis at the transcriptional level even before the onset of weight loss [14]. Thus, malnutrition, by reducing muscle mass and subsequently affecting the functional status of patients with cancer, is a crucial risk factor for adverse perioperative outcomes. Similarly, increased concentrations of serum globulin are correlated with an inflammatory state. Serum globulin, another major

protein produced by immune organs that reflects the immune state, consists of various proinflammatory proteins, including C-reactive protein, complement components, and immunoglobulins [15,16]. An increase in the globulin level with the stimulation of inflammation is also associated with poor survival in patients with cancer [17].

The prognostic value of a low AGR in patients with cancer is considered to be associated with the potential mechanisms of inflammation and nutrition in a cancer environment [18]. Although proper nutrition before and after surgery is important for patients with cancer, malnutrition is relatively common. Furthermore, malnutrition often causes the development of cancer cachexia and is associated with cancer progression. Chronic inflammation is present in almost all cancer environments [19] owing to the release of many inflammatory factors during angiogenesis, tissue remodeling, and rehabilitation by malignant tumor cells [20]. Subsequently, changes in inflammatory factors in tumor microenvironments facilitate tumor growth [19,21]. Therefore, poor nutritional status is strongly related to the progression of cancer.

If we consider and apply these prognostic values of AGR, inflammatory processes can trigger PCa development and progression by causing dysregulation of oncogenes and tumor suppressors, thereby causing DNA damage and other processes that can induce tumor cell proliferation and growth [22]. Several environmental and biological factors including obesity, certain dietary practices, infectious agents, and hormones that can affect the production of circulating systemic inflammatory markers have been implicated in PCa development and progression by promoting carcinogenic processes, such as DNA damage and tumor cell growth and proliferation [22,23]. Histologic, genetic, and animal studies have provided compelling evidence suggesting that chronic systemic inflammation may be involved in the early prostate carcinogenic process [24,25].

Therefore, we hypothesized that nutritional status and systemic inflammatory response are adversely associated with pathologic outcomes in patients with PCa. Since serum albumin is affected by various factors, including stress, tissue necrosis, and cancers, albumin alone may be insufficient to be widely used in clinical practice for predicting the pathologic outcomes of patients with PCa, and the same applies to serum globulin. Thus, by combining two aspects of adverse outcomes, the AGR may be a superior predictor for patients with PCa compared with other nutritional or inflammatory indicators [15].

Recently, the relationship between pretreatment AGR and various malignancies has attracted the attention of many scientists. In 2014, Suh et al. [18] performed a retrospective cohort trial on 26,974 healthy people over the age of 30 years. They demonstrated that a low AGR was related with the occurrence of cancer and death from cancer in the short and long term in a population of generally healthy adults undergoing health checkups. Furthermore, some research has shown that a low AGR is associated with worse prognosis in breast [26], colorectal [27], nasopharyngeal [28], renal [12], and lung cancers [29]. Therefore, the AGR could serve as a marker of cancer-related inflammatory responses.

To date, two studies have evaluated low preoperative AGR as a poor predictive factor in PCa. In 2019, Wang et al. [15] evaluated the prognostic value of the pretreatment serum AGR for metastatic PCa treated with maximal androgen blockade (n=214). The cutoff value of the AGR was 1.45. The pretreatment AGR was an independent prognostic biomarker for progression-free survival and cancer-specific survival in patients with metastatic PCa receiving maximal androgen blockade. In 2020, Quhal et al. [30] evaluated the predictive value of preoperative AGR for oncologic outcomes in patients with radiation-recurrent PCa treated with salvage RP (n=214). The optimal cutoff for the preoperative AGR was 1.4. In patients with radiation-recurrent PCa undergoing salvage RP, a low preoperative AGR was associated with risk for biochemical recurrence in a univariate analysis only. Unlike the two studies described above, our study focused on the association between pathologic features (pT stage ≥3, pathologic Gleason score ≥8) and low AGR in patients with nonmetastatic PCa who underwent RP. We think that in the case of PCa, the AGR and oncological outcomes may be correlated only if the PCa has advanced. As shown in two articles mentioned above, the AGR was associated with survival and recurrence rate only in metastatic PCa or radiation-recurrent PCa, which is a different disease setting from the present study. In general, it is known that early PCa has a good prognosis compared with other cancers. Although malnutrition and chronic systemic inflammation are important factors for progression or metastasis of cancer, this hypothesis may not be applied to early PCa patients who can undergo RP.

The limitations of this study include the retrospective data collection and heterogeneous study collection. Many missing data, including data on perioperative complications, and heterogeneous surgeons are also weak points. Unlike the previous two studies described above, the result of the current study that a low AGR did not correlate significantly with oncologic outcomes is an important issue to be solved in the future. Owing to the retrospective nature of this study, selection bias was inevitable, and therefore conclu-

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sions should be carefully judged. Despite these limitations, this study may have many clinical implications. First, this is the first study with a relatively large cohort to demonstrate that a low AGR is associated with worse pathologic outcomes in patients with nonmetastatic PCa. Second, preoperative serum AGR can be measured easily and inexpensively. With these advantages, the AGR has potential as a convenient and simple marker to help urologists counsel patients with PCa during clinical decision-making. Currently, many factors including TNM stage, Gleason score, and serum PSA are being used to determine the prognosis of PCa. However, contemporary studies are discordant with regard to potential predictors of upgrading, including preoperative PSA, prostate volume, and obesity, when we considering active surveillance. Although the AGR cannot be superior to PSA, it is a simple, easy to access, and labor saving blood parameter that is helpful for predicting adverse pathology of PCa or for counselling patients who are eligible for active surveillance. Finally, preoperative evaluation of nutritional status and supplement of adequate nutrition should be performed in patients with a low AGR (<1.53). In the near future, further large-scale, population-based, prospective multi-institutional studies involving factors that may influence the outcomes of PCa should be performed.

CONCLUSIONS

We found that a low pretreatment AGR was closely associated with worse pathologic outcomes, such as nonconfined disease (≥pT3) and a high pathologic Gleason score (≥8). Our results suggest that the AGR may be a useful serological marker for further characterization of adverse pathology in patients with nonmetastatic PCa who undergo RP. Preoperative AGR is an easy-to-use inexpensive method, and therefore these findings may help urologists give preoperative advice to patients with a low AGR before surgical management of PCa.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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AUTHORS' CONTRIBUTIONS

Research conception and design: Jae-Wook Chung, Yun-Sok Ha, and Tae-Hwan Kim. Data acquisition: Sang Won Kim, Seung Chol Park, and Taek Won Kang. Statistical analysis: Jae-Wook Chung and Yun-Sok Ha. Data analysis and interpretation: Jae-Wook Chung, Young Beom Jeong, Sung-Woo Park, and Jinsung Park. Drafting of the manuscript: Jae-Wook Chung and Yun-Sok Ha. Critical revision of the manuscript: Eun Sang Yoo, Tae Gyun Kwon, Sung Pil Seo, Ho Won Kang, Won Tae Kim, Yong-June Kim, Sang-Cheol Lee, Wun-Jae Kim, and Seok Joong Yun. Obtaining funding: Jae-Wook Chung and Yun-Sok Ha. Administrative, technical, or material support: Jae-Wook Chung and Yun-Sok Ha. Supervision: Yun-Sok Ha and Tae-Hwan Kim. Approval of the final manuscript: Tae-Hwan Kim.

SUPPLEMENTARY MATERIAL

Supplementary material can be found via https://doi.org/10.4111/icu.20210105.

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