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The Role of Albumin to Globulin Ratio for Progression in Patients Underwent Active Surveillance for Prostate Cancer: Can It Use As an Selection Criteria for Active Surveillance? Retrospective Cohort Analyses

Prostat Kanseri Nedeniyle Aktif İzleme Alınan Hastalarda Albumin-Globulin Oranının Progresyondaki Rolü: Aktif İzleme Seçim Kriteri Olarak Kullanılabilir Mi? Retrospektif-Kohort Çalışma

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ABSTRACT Objective: In this study, we aimed to show whether albumin/globulin ratio (AGR) can predict progression in prostate cancer (pCA) patients in active surveillance (AS). **Material and Methods:** A retrospective analysis of data recorded in the electronic registration system of our hospital was conducted for patients who were under AS due to pCA between 2018 and 2022. The inclusion criteria for AS were as follows: prostate specific antigen (PSA)<10 ng/ml, Gleason score≤6, clinical stage T1c-T2a, ≤2 positive cores and ≤50% tumour cells in each positive core. A programme of periodic clinical assessments was implemented for all patients, incorporating digital rectal examination and a PSA test on a quarterly basis for a period of 1 year. Following the conclusion of the initial year, a second biopsy was conducted on all patients. Patients were divided into 2 groups according to their progression status. AGR and other clinicopathological features were then compared between these groups. **Results:** Receiver operating characteristic analysis was used to determine the optimum AGR cut-off value predicting progression and this value was determined as 1.6. Utilising the 1.6 cut-off point, the sensitivity and specificity of AGR the predictive values for progression were found to be 90% and 62.6%, respectively. The multivariate analysis indicated that low AGR values and the number of cores were more effective in explaining the progression of the disease than the other parameters. **Conclusion:** We propose that AGR values should be incorporated into AS criteria, in addition to other established criteria.

Keywords: Active surveillance; albumin; globulin; prostate cancer

ÖZET Amaç: Bu çalışmada, albümin/globulin oranının (AGR) aktif izlemdeki (Aİ) prostat kanseri (PK) hastalarında progresyonu öngörüp öngöremeyeceğini göstermeyi amaçladık. **Gereç ve Yöntemler:** 2018-2022 yılları arasında PK nedeniyle Aİ altında olan hastalar için hastanemizin elektronik kayıt sistemine kaydedilen verilerin retrospektif analizi yapıldı. Aİ dâhil etme kriterleri prostat spesifik antijen (PSA)<10 ng/ml, gleason skoru ≤6, klinik evre T1c-T2a, ≤2 kor pozitif ve her pozitif korda ≤%50 tümör hücresi olarak belirlendi. Tüm hastalar için 1 yıllık bir süre boyunca 3 ayda 1 dijital rektal muayene ve PSA testini içeren periyodik klinik değerlendirme programı uygulandı. İlk yılın tamamlanmasının ardından, tüm hastalara ikinci bir biyopsi yapıldı. Hastalar progresyon durumlarına göre 2 gruba ayrılmış ve AGR ve diğer klinikopatolojik özellikler gruplar arasında karşılaştırılmıştır. **Bulgular:** Progresyonu öngören optimal AGR kesme değerini belirlemek için alıcı işletim özelliği analizi kullanılmış ve bu değer 1,6 olarak belirlenmiştir. 1,6 kesme noktası kullanıldığında, AGR'nin progresyon için prediktif değerlerinin duyarlılığı ve özgüllüğü sırasıyla %90 ve %62,6 olarak bulunmuştur. Çok değişkenli analiz, düşük AGR değerlerinin ve kor sayısının hastalığın ilerlemesini açıklamada diğer parametrelere göre daha etkili olduğunu göstermiştir. **Sonuç:** Mevcut Aİ kriterlerine AGR eklenmesinin yararlı olacağını düşünüyoruz.

Anahtar Kelimeler: Aktif izlem; albümin; globulin; prostat kanseri

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Active surveillance (AS) is an option for patients with low-risk localized prostate cancer (pCA) because it can achieve similar results to radical prostatectomy or radiotherapy.[1] The fundamental objective of AS is to mitigate the occurrence of overtreatment, while ensuring the opportunity for curative treatment is not overlooked. The primary concerns in AS are the prevention of morbidity and comorbidities, and the maintenance of quality of life. A significant concern in AS is the upgrading of Gleason score (GSU), which consequently results in the delay of curative treatment.[1] GSU is a significant condition due to its association with elevated levels of biochemical recurrence, the potential for progression to systemic disease, and a low cancer-specific survival rate.[2] A preceding study demonstrated that up to 36% of patients who were categorised as low risk by prostate biopsy according to the prevailing AS criteria in fact exhibited high-grade disease following radical prostatectomy.[3] In order to address the discrepancy between the established criteria and the actual clinical outcomes, and to enhance the classification of pCA, there is a necessity for research to be conducted with a view to identifying new biomarkers.[4] It is hypothesised that, as a consequence of these studies, it may be feasible to identify patients with GSU earlier and more accurately.[1]

Systemic inflammatory status has been demonstrated to be a significant predictor of unfavourable outcomes in numerous types of cancer. A number of cytokines and mediators, which are produced as a secondary consequence of inflammation, have been observed to increase cell proliferation, invasion, and metastasis.[5] Serum albumin (A) and globulin (G) represent two of the most significant constituents of human serum proteins. They play pivotal roles in inflammatory responses.[6] A is also associated with systemic inflammation, although it is an indicator of nutritional status.[7] A low level of A in the blood has been linked to a lower chance of survival in patients with upper tract urothelial carcinoma.[8] Similarly, high levels of G in the blood are now seen as a sign of inflammation in cancer patients.[9] In view of the potential variability of A levels, which can be influenced by a variety of factors, including nutritional status and inflammation, there has been a concerted effort to identify a more reliable biomarker. This objective has been realised through the calculation of the albumin-to-globulin ratio (AGR), which serves as an additional parameter indicative of the inflammatory state. Previous studies have indicated that an operative low serum AGR is associated with a poor prognosis in various human cancers.[10-13]

To date, researchers have focused on investigating the efficacy of AGR in predicting the prognosis for men with advanced pCA prior to treatment. However, there is currently a lack of evidence regarding the ability of AGR to predict the progression of patients with AS. Previous studies have suggested a potential association between low AGR levels at the time of the initial biopsy and subsequent progression in patients with AS. The present study aims to address these research questions in 2 ways. Firstly, it will examine whether AGR can be utilised to predict progression in AS patients in comparison with the current criteria. Secondly, it will explore whether AGR can be employed as a criterion for AS in this group of patients.

MATERIAL AND METHODS

STUDY DESIGN

Data from 121 patients who were under active surveillance between 2018 and 2022 were retrospectively analysed in this study.

EVALUATION OF PATIENTS

The following data were collected and analysed from our hospital's electronic patient records: Prostate specific antigen (PSA) value before the 1st biopsy (PSA1) and the 2nd biopsy (PSA2), rectal examination results, clinical T stage status, maximum tumour length in one core and number of positive cores. A, G and total protein (TP) levels were recorded in addition to routine blood analyses.

A prostate biopsy is recommended when there are signs of problems during a digital rectal examination (DRE) and when the PSA level in the blood is above 2.5 ng/mL. Prior to undergoing the biopsy, all patients were subjected to a multiparametric magnetic resonance imaging (mpMRI) of the prostate. The initial biopsies were conducted under transrectal ultra-

sound, targeting peripheral zones with a minimum of 12 cores, and were also performed as magnetic resonance (MR) cognitive biopsies. Subsequent biopsies were undertaken as MR fusion biopsies. The evaluation of the first biopsy specimens was conducted by a different pathologist, while the second specimens were evaluated by the same pathologist. In accordance with the 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma, both specimens were awarded the Gleason score (GS).[14] Although there are many different inclusion criteria for AS published in the literature we used Prostate Cancer Research International: Active Surveillance (PRIAS) study criterias for selecting patients for AS.[15] According to this, our criterias are include: GS≤6, clinical stage based on DRE of the prostate T1c-T2a, PSA≤10 ng/mL, ≤2 positive cores, and PSA density (PSAD)≤0.2 ng/mL. A programme of periodic clinical assessments was implemented for all patients, incorporating DRE and a PSA test on a quarterly basis for a period of 1 year. Following the conclusion of the initial year, a 2nd biopsy was conducted on all patients. The definition of progression was established as any alteration in the histological pattern observed on subsequent biopsies. For instance, a shift from Gleason ISUP 1 to 2 or 3 could be indicative of progression.[16] Patients with active autoimmune disease, chronic inflammatory disease or haematological disease and a history of concomitant secondary cancer, were excluded from the study.

The AGR was calculated using this formula: albumin/globulin. Patients were divided into two groups according to their progression status, and AGR and other clinicopathological features were then compared between these groups.

STATISTICAL ANALYSES

The analysis was conducted utilising IBM SPSS Statistics 27.0. To ascertain the normality of numeric variables, the Kolmogorov-Smirnov test was employed. Numerical variables with a normal distribution were expressed as mean±standard deviation. Data exhibiting non-normal distribution were presented as median±interquartile range (IQR). Categorical variables were presented as number and percent. The statistical analysis employed a range of tests, including the t-test, Mann-Whitney U test, and chi-square test. The prediction of progression cut-off value of AGR was determined with receiver operating characteristic (ROC) analyses. The effect of AGR, the number of cores and tumour length in one core on progression risk was calculated using logistic regression analyses. P values less than 0.05 were considered statistically significant.

ETHIC

The study was compatible with the Helsinki Declaration for laws and regulations, good clinical practice, and ethical principles and was approved by the ethics committee of our hospital (date: November 14, 2022, no: 2022/326). Written informed consent was obtained from all participants.

RESULTS

Progression was observed in a total of 20 (16.5%) patients. The mean age of patients with no progression was 63.69±2.9 years and for patients with progression were 63.05±2.8 years. There were no statistically significant differences between the groups (p=0.376) (Table 1).

The median A level of patients demonstrating no progression was found to be 42 g/L (30-50), while the mean TP level was 67 g/L (44.4-81). In contrast, the median A levels in patients who exhibited progression were 39.5 g/L (28.7-46.9), while the median TP levels were 66.7 g/L (50.2-76). There was no clear difference in the groups when it came to A and TP (p=0.135 and p=0.451, respectively). The median G levels were further analysed according to progression status, revealing a median value of 27.2 g/L (20.1-33) in patients who progressed, as compared to 24 g/L (13-32) in those who did not. A significant statistical distinction was observed between the 2 groups regarding G (p=0.001). The mean AGR of the patients without progression was found to be 1.7 (SD=0.16), while the mean of the patients with progression was 1.4 (SD=0.18). This finding indicates a statistically significant difference between the groups in terms of mean AGR (p=0.001), as illustrated in Table 1.

TABLE 1: Group characteristics

		Progression		
		Yes	No	
Age	(year)	63.05±2.8	63.69+2.9	0.376[a]
Albumin	(g/L)	39.5 (28.7-46.9)	42 (30-50)	0.135[b]
Globulin	(g/L)	27.2 (20.1-33)	24 (13-32)	0.001[b*]
TP	(g/L)	66.7 (50.2-76)	67 (44.4-81)	0.451[b*]
AGR		1.4±0.18	1.7+0.16	**0.001**[a*]
PSA1	(ng/mL)	5.3 (3.5-8.4)	5.3 (3.3-9.6)	0.62[b]
PSA2	(ng/mL)	5.8 (3.6-8.5)	5.5 (3-9.8)	0.82[b]

[a]t-test; [b]Mann-Whitney U test; *statistically significant (p<0.05); AGR: Albumin to globulin ratio; PSA: Prostate specific antigen; TP: Total protein

Median PSAD was 0.1 (0.05-0.2) for the patients without progression and 0.09 (0.06-0.2) for the patients with progression. The results demonstrate a clear progression, with no statistically significant differences observed in the PSAD (p=0.496). The median tumor length in one core was 1.6 (1-2.5) cm. for the patients without progression and 2 (1.1-2.5) cm. for the patients with progression. There were statistically significant differences in the tumor length between groups (p=0.001). When the T stage and the number of cores involved with cancer were examined in terms of progression, T stage and the number of cores involved with cancer had a statistically significant effect on progression. All parameters which effect progression showed in Table 2.

The ROC curve was constructed to ascertain the distinctiveness of the AGR values in order to determine the progression. The area under the curve was found to be 0.881 (95% CI 0.790-0.971), indicating statistical significance. The ROC analysis was then utilised to determine the optimal AGR cut-off value, which was established to be 1.6. (Figure 1). In the absence of progression in 28 patients (38.4%) with low AGR values (<1.6), progression was observed in 18 patients (90 %) (p=0.001). Utilising the 1.6 cut-off point, the sensitivity and specificity of AGR the predictive values for progression were found to be 90% and 62.6 %, respectively (Figure 1).

There was no significant difference between the PSA1 and PSA2 levels in the groups that did and did not progress (p=0.62 and 0.82, respectively). However, a discrepancy was observed between the 2 PSA measurements in the progression group when the groups were evaluated within themselves (p=0.007 and 0.437, respectively). Of the 20 patients demonstrating progression, 16 exhibited higher PSA2 levels in comparison to PSA1 (Table 3).

Univariate analysis was conducted to ascertain the impact of various factors on tumour progression. The findings revealed that low AGR values, the number of cores involved, T stage and the length of the tumour in one core were significantly associated with

TABLE 2: Parameters that affect progression

		Progression		
		Yes	No	p value
PSAD (ng/mL^2)		0.09 (0.06-0.2)	0.1 (0.05-0.2)	0.496[a]
Length (cm)		2 (1.1-2.5)	1.6 (1-2.5)	0.01[a*]
AGR	<1.6	18 (90 %)	28 (38.4%)	0.01[b*]
	>1.6	2 (10 %)	73 (62.6%)	
T stage	T1c	9 (10.2 %)	79 (89.8%)	0.002[b*]
	T2a	11 (33.3 %)	22 (66.7%)	
Number of core	1	9 (8.7 %)	94 (91.3%)	0.001[b*]
	2	11 (61.1 %)	7 (38.9%)	

[a]Mann-Whitney U test; [b]Chi-Square Test; *statistically significant (p<0.05); PSAD: Prostate specific antigen density; AGR: Albumin to globulin ratio

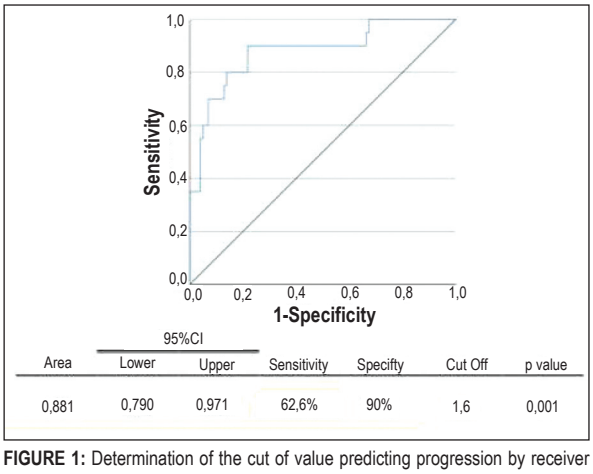

FIGURE 1: Determination of the cut of value predicting progression by receiver operating characteristic analysis; CI: Confidence interval.

TABLE 3: PSA variation within groups

	PSA 1 (ng/mL)	PSA 2 (ng/mL)	p value
Progression group	5.3 (3.5-8.4)	5.8 (3.6-8.5)	0.007[a*]
Non-progression group	5.3 (3.3-9.6)	5.5 (3-9.8)	0.437[a]

[a]Wilcoxon signed rank test; *statistically significant (p<0.05); PSA: Prostate specific antigen

TABLE 4: Results of the logistic regression analyses

	Univariate		95% CI		Multivariate		95% CI	
	p value	OR	Lower	Upper	p value	OR	Lower	Upper
T stage[a]	0.004*	4.389	1.615	11.926	0.053	4.296	0.982	18.799
Length	0.021*	3.980	1.237	12.803	0.053	5.370	0.975	29.557
Number of core[b]	0.001*	16.413	5.101	52.809	0.001*	18.625	3.262	106.343
AGR<1.6[c]	0.001*	23.464	5.109	107.763	0.001*	36.985	5.553	246.348

[a]ref T1c; [b]ref one core; [c]ref AGR>1.6; *statistically significant (p<0.05); AGR: Albumin to globulin ratio; CI: Confidence interval

progression. Low AGR (<1.6) was found to be a more effective indicator of progression than the length and T stage, but similar to the number of cores. The multivariate analysis indicated that low AGR values and the number of cores were more effective in explaining the progression of the disease than the other parameters. The findings of this study indicate that low AGR values (less than 1.6) are more effective in predicting disease progression than the number of cores (Table 4).

DISCUSSION

The present study demonstrated that AGR has the capacity to function as a valuable predictive instrument in determining progression in patients with AS. According to the results obtained, before the initial biopsy, AGR<1.6 was a predictor of progression. A review of the extant literature reveals that AS studies are predominantly grounded in pathological evaluation following radical prostatectomy.[17] The present study will be the first to investigate the effect of AGR on progression in patients under AS who did not undergo radical prostatectomy.

Recent advancements in the field of cancer biology have elucidated a correlation between systemic malnutrition and inflammation with unfavourable prognoses in cancer cases.[18,19] In the process of inflammation, there is an observed decrease in serum A levels, whilst G levels increase. Given that albumin levels can be low due to nutritional status outside of the inflammatory response, it was hypothesised that the AGR would be a more effective indicator of inflammation.[20,21] The present study lends support to this hypothesis. In this study, G levels were found to be higher in the group with progression compared to the group without progression, while A levels decreased in the group with progression. However, no statistical significance was observed. However, when AGR levels were analysed, a significant difference was found between the 2 groups.

The predictive role of AGR in pCA has been the subject of investigation in several studies. The majority of these studies were conducted in cases of advanced pCA.[22,23] The findings of these studies demonstrated that diminished AGR levels were associated with diminished cancer-specific survival (CSS), progression-free survival and earlier incidence of biochemical recurrence. Furthermore, Wang et al. demonstrated that AGR retained its efficacy in predicting CSS, irrespective of albumin levels. This finding corroborates the hypothesis that AGR exhibits an advantage over either parameter alone in demonstrating inflammation. Chung et al. evaluated the use of AGR in predicting gleason score up-grading in patients with organ-confined prostate cancer.[24] The study demonstrated that men who had low AGR before treatment had worse results, including nonconfined disease (≥pT3) and a high pathologic Gleason score (≥8). In the present study, low AGR was demonstrated to predict progression, a finding that aligns with the study conducted by Chung et al. Our study suggests that it would be better to choose active treatment instead of AS in patients with low AGR.

As a secondary objective of this study, regression analyses were conducted to ascertain the contribution of low AGR in predicting progression and to ascertain the feasibility of incorporating AGR into

the AS criteria. To this end, univariate and multivariate regression analyses were performed for T stage, number of involved cores, tumour length in a cord and AGR univariate and multivariate regression analyses. The findings of the regression analysis demonstrated that low AGR values were superior in predicting progression compared with other parameters.

The present study has some restricted. Firstly, the number of patients included was comparatively small. Secondly, the study was retrospective in nature. Furthermore, the fact that the initial prostate biopsy specimens were evaluated by a number of different pathologists may have resulted in a low GS. The low staging probability at the beginning may have resulted in a high progression rate. It is important to note that, due to the retrospective nature of this study, there is a possibility of selection bias. Therefore, it is essential to exercise caution when evaluating the results. Notwithstanding these restrictions, we did not consider our findings to be inconsistent with the current literature explaining the link between inflammation and cancer.

CONCLUSION

In this study, we show that low levels of AGR are a significant predictor of progression in patients with AS. Based on our results we can say low AGR can reflect the status of immune inflammation and can act as a indicator for AS. Consequently, we propose that AGR values should be incorporated into AS criteria, in addition to other established criteria. If our results are confirmed by further studies, pre-treatment AGR could be considered a commonly able to be used, affordable, objectively measurable, and avert reproducible biomarker. In this case, it may be beneficial in terms of accurately defining the AS patient groups.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Levent Özcan, Ömür Memik;* ***Design:*** *Emre Can Polat;* ***Control/Supervision:*** *Alper Ötünçtemur;* ***Data Collection and/or Processing:*** *Ahmet Boylu;* ***Analysis and/or Interpretation:*** *Levent Özcan;* ***Literature Review:*** *Ömür Memik;* ***Writing the Article:*** *Levent Özcan;* ***Critical Review:*** *Alper Ötünçtemur, Emre Can Polat;* ***References and Fundings:*** *Ahmet Boylu.*

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