Prognostic value of the pre-operative serum albumin to globulin ratio in patients with non-metastatic prostate cancer undergoing radical prostatectomy

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Abstract

Purpose To evaluate the potential predictive value of the preoperative serum albumin to globulin ratio (AGR) for oncological outcomes in patients treated with radical prostatectomy (RP) for clinically non-metastatic prostate cancer (PCa).

Methods Pre-operative AGR was assessed in a multi-institutional cohort of 6041 patients treated with RP. Logistic regression analyses were performed to assess the association of the AGR with advanced disease. We performed Cox regression analyses to determine the relationship between AGR and biochemical recurrence (BCR).

Results The optimal cut-off value was determined to be 1.31 according to receiver operating curve analysis. Compared to patients with a higher AGR, those with a lower preoperative AGR had worse BCR-free survival (P < 0.01) in the Kaplan–Meier analysis. Pre- and post-operative multivariable models that adjusted for the effects of established clinicopathologic features, confirmed its independent association with BCR [hazard ratio (HR) 1.52, 95% confidence interval (CI) 1.31–1.75, P < 0.01, HR 1.55, 95% CI 1.34–1.79, P < 0.01, respectively]. However, the addition of AGR to established prognostic models did not improve their discrimination.

Conclusion While AGR is significantly associated with BCR, in the present study, the clinical impact of AGR was not large enough to affect patient management. Longer follow-up is necessary to observe the true effect of AGR.

Keywords Albumin · Globulin · Radical prostatectomy · Prostate cancer

Introduction

Prostate cancer (PCa) is estimated to be the most commonly diagnosed cancer in men and the second leading cause of cancer-related deaths in the United States in 2020 [1]. While there are several treatment options for PCa depending on the risk stratification, radical prostatectomy (RP) is currently the most common treatment for patients with clinically non-metastatic PCa who have long life expectancy [2–5]. However, despite adequate surgery, a significant proportion of patients experience disease recurrence and progression due to clinically occult micrometastases and underestimating tumor aggressiveness [6–9].

Chronic inflammation plays a vital role in carcinogenesis and progression. Inflammatory mediators such as cytokines, chemokines, growth factors, prostaglandins, reactive oxygen, and nitrogen species have been shown to exhibit biomarker potential for PCa [6, 7, 9]. Although clinical parameters such as prostate-specific antigen (PSA), imaging, and Gleason score allow certain risk stratification, they remain suboptimal for staging and prognostication [5]. Preoperative biomarkers could offer a personalized treatment approach for patients. However, preoperative biomarkers that can predict either treatment response or other oncological outcomes in patients with non-metastatic PCa lack standardization, as they need to be better than what we have while remaining simple and cost-effective [10–12]. Among these biomarkers, is the serum albumin to globulin ratio (AGR); in which...
albumin reflects the body’s nutritional status and globulin reflects the immunological status through its roles in immu-
nity and inflammation [13]. Several studies have shown an
inverse association between blood-based AGR and different
cancer prognoses [14–16]. To date, the staging and prognos-
tic value of noninvasive AGR have not yet been investigated
in patients with non-metastatic PCa.

This study aimed to assess whether preoperative serum
AGR could be a reliable biomarker of oncological out-
comes in patients undergoing RP for non-metastatic PCa.
We hypothesized that preoperative serum AGR could predict
outcomes after RP with significant accuracy.

Materials and methods

Patient selection

We performed a retrospective analysis of patients treated
with RP from our multi-institutional database. Between 2000
and 2011, a total of 6,041 patients with clinically non-met-
astatic PCa were identified. Due to the retrospective nature
of the study, the preoperative staging was not standardized.
Non-metastatic disease was defined as no cancer spread from
the primary site to different sites in the body. All patients
did not receive preoperative or post-operative adjuvant hor-
monal and radiation therapy. The local ethics committees
approved the study at all institutions.

Intervention

According to the guideline recommendations at the time of
recruitment and the surgeon discretion, all patients were
treated by RP with or without pelvic lymph node dissec-
tion. Dedicated genitourinary pathologists analyzed the
specimens at each center. The pathologic stage and grade
were assigned using the 2009 American Joint Committee on
Cancer TNM staging system and the International Society of
Urological Pathology (ISUP) 2014. Lymphovascular inva-
sion (LVI) was defined as the unequivocal presence of tumor
cells within an endothelium-lined space without underlying
muscular walls [17].

Preoperative AGR was calculated as
AGR = albumin/(total protein − albumin) and assessed
within 30 days before RP as part of the preoperative workup.

Follow-up

Due to the retrospective nature of the study, the follow-
up was not standardized. Patients were generally followed
by physical examination and PSA measurements taken
every three months in the first year of surgery, every six
months from the 2nd to 5th year and annually after that.

The definition of biochemical recurrence (BCR) was two
consecutive PSA readings of more than 0.2 ng/ml [18]. The
date of the first rise was considered as the date of BCR. The
time to event was calculated from the date of RP to the date
of BCR.

Statistical analyses

The chi-squared test and the Mann–Whitney U test were
used to compare the distribution of categorical and continu-
ous variables between patients with preoperative AGR > 1.31
and AGR ≤ 1.31, respectively. Cox regression analysis was
used to investigate the association of preoperative AGR
with BCR-free survival. Kaplan–Meier curves were used to
estimate the survival function visually. Two multivariable
Cox regression models, including pre- and post-operative
clinicopathologic features, were built. The discrimination
of these models was assessed using Harrel’s concordance index
(C-index). On exploratory analyses, logistic regression mod-
eling was used to investigate preoperative AGR association
with lymph node metastasis, positive surgical margin, LVI,
and non-organ confined disease (NOCD), defined as ≥pT3
and/or N + disease. If the 2-sided P value was < 0.05, we
considered the results to be significant. Data analyses were
performed using R (R project, Vienna, Austria).

Results

Identification of the optimal cut-off value
and association with clinicopathologic features

The preoperative AGR cut-off value was determined by
receiver operating characteristics curve analysis using the
Youden index [19]. The optimal cut-off in our cohort was
1.31. Using the identified cut-off value, 4038 patients (67%) had
an AGR > 1.31 and 2003 (33%) had an AGR ≤ 1.31. Patients characteristics are shown in (Table1). There were no
significant differences in clinicopathologic features between
patients with AGR > 1.31 and AGR ≤ 1.31 (all P > 0.05).

Association with biochemical recurrence

During a median follow-up of 45 months (interquartile range
35–58), 681 patients experienced BCR. In all, 278 (40.8%)
had a preoperative AGR ≤ 1.31, and 403 (59.2%) had a pre-
operative AGR > 1.31. On univariable Cox regression analy-

sis, preoperative AGR ≤ 1.31 was associated with a higher
risk of BCR [hazard ratio (HR) 1.40; 95% confidence inter-
val (CI) 1.21–1.62; P < 0.01] (Fig. 1).

On multivariable Cox regression analyses that adjusted
for preoperative and post-operative variables, AGR ≤ 1.31
remained significantly associated with BCR. The addition

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of AGR to the base models did not improve their discrimination (Table 2).

**Association of AGR with perioperative outcomes**

Preoperative AGR was not associated with positive surgical margin, LVI, lymph node metastasis, or NOCD (all $P \geq 0.4$) on exploratory logistic regression analyses. (Table 3).

We also performed a sub-group analysis according to the European Association of Urology (EAU) risk group classification [20]. We found that the AGR status did not show an association between AGR and adverse perioperative features (all $P$ value $> 0.05$).

**Discussion**

To our knowledge, this is the first study to evaluate preoperative serum AGR as a biomarker to predict BCR and oncological outcomes after primary RP for localized prostate cancer patients. Emerging evidence has shown that AGR could predict cancer diagnosis and prognosis in several malignancies, including colorectal [21], gastric [22], lung [23], and breast [24]. Our results demonstrated that low AGR was significantly associated with the risk of BCR in patients with localized prostate cancer undergoing RP. One of the factors that may explain this association is the increase in the concentration of free testosterone secondary to the low albumin-bound testosterone, which
eventually can influence disease recurrence and progression. Moreover, the consequence of inflammatory mediators during systematic inflammation can also be associated with tumor progression [25]. Indeed, it is well-known that inflammation has an essential role in tumor progression.

In our study, none of the biological aggressiveness indicators were correlated with low AGR level. Therefore, the precise mechanism in which AGR can influence BCR is still unknown. Notably, we assessed if the AGR level could predict lymph node metastasis, LVI, positive surgical margin, or NOCD. A low preoperative AGR was not found to be correlated with any of these outcomes. A possible explanation of why AGR may not be associated with perioperative outcomes in PCa is that patients chosen for RP as a treatment are presumed to be healthy with no significant comorbidities, and they are also presumed to have localized disease. This is contrary to other malignancies and to advanced PCa patients who could be offered hormonal or radiation treatment. Besides, due to PSA screening, the disease is detected in an early stage.

While low preoperative serum AGR was not associated with aggressive disease features such as pathological Gleason score and LN metastasis, the association with BCR could be important for decision making based on prognostic risk estimations. Despite the promising role of this biomarker in our study, only one study has evaluated the association of AGR in patients with metastatic PCa receiving androgen deprivation therapy and showed that a low serum AGR was an independent predictor of progression and cancer-specific mortality [26]. Because of the literature paucity, further studies should investigate AGR role in different stages of PCa to validate this conclusion.

Several limitations of the present study should be taken into consideration. The main limitation is the retrospective design and multicentric nature of this study. In addition, one of the major limitations of the study is the short follow-up. Another limitation is the lack of standardization of clinical staging for patients. Furthermore, as this is a multicentric study, the surgeries were performed by different surgeons and the RP specimens were analyzed in different laboratories. Moreover, we could not investigate the overall survival and cancer-specific survival because of the lack of mortality data. Despite these limitations, we provided the first reliable study to evaluate the AGR as a biomarker in patients with non-metastatic PCa patients who underwent RP.

Conclusion

While AGR is significantly associated with BCR, in the present study, the clinical impact of AGR was not large enough to affect patient management. Further studies with longer follow-up are necessary to further understand the prognostic impact of AGR in patients with prostate cancer.
Table 2 Cox regression analyses for the prediction of biochemical recurrence

| Variable                     | Univariable analysis     | Multivariable analysis    |
|------------------------------|--------------------------|---------------------------|
|                              | HR (95% CI)              | P                         | HR (95% CI) | P       |
| **Pre-operative model**      |                          |                           |             |         |
| Total PSA before RP          | 1.05 (1.05–1.06)         | <0.01                     | 1.05 (1.04–1.05) | <0.01  |
| Biopsy tumor ISUP            |                          |                           |             |         |
| ISUP1                        | Ref                      | Ref                       |             |         |
| ISUP2                        | 1.96 (1.63–2.35)         | <0.01                     | 1.87 (1.56–2.25) | <0.01  |
| ISUP3                        | 3.25 (2.67–3.96)         | <0.01                     | 3.07 (2.52–3.74) | <0.01  |
| ISUP4                        | 4.77 (3.73–6.09)         | <0.01                     | 4.23 (3.30–5.41) | <0.01  |
| ISUP5                        | 8.14 (5.88–11.26)        | <0.01                     | 5.78 (4.13–8.11) | <0.01  |
| **Clinical tumor stage**     |                          |                           |             |         |
| T2                           | Ref                      | Ref                       |             |         |
| T3                           | 7.80 (4.88–12.47)        | <0.01                     | 4.61 (2.86–7.44) | <0.01  |
| AGR                          | 1.40 (1.21–1.62)         | <0.01                     | 1.50 (1.30–1.74) | <0.01  |
| **Accuracy without AGR**    | 0.7388                   |                           |             |         |
| **Accuracy with AGR**        | 0.7410                   |                           |             |         |
| **Post-operative model**     |                          |                           |             |         |
| Total PSA before RP          | 1.05 (1.05–1.06)         | <0.01                     | 1.04 (1.03–1.04) | <0.01  |
| Positive surgical margin     | 3.74 (3.21–4.34)         | <0.01                     | 2.02 (1.72–2.37) | <0.01  |
| Pathological tumor stage     |                          |                           |             |         |
| T2                           | Ref                      | Ref                       |             |         |
| T3                           | 5.31 (4.60–6.13)         | <0.01                     | 2.70 (2.29–3.18) | <0.01  |
| Lymph node metastasis        | 14.71 (11.73–18.45)      | <0.01                     | 3.52 (2.68–4.62) | <0.01  |
| Pathological ISUP            |                          |                           |             |         |
| ISUP1                        | Ref                      | Ref                       |             |         |
| ISUP2                        | 1.57 (1.24–1.98)         | <0.01                     | 1.24 (0.97–1.57) | <0.08  |
| ISUP3                        | 4.05 (3.26–5.03)         | <0.01                     | 2.38 (1.89–2.99) | <0.01  |
| ISUP4                        | 9.33 (7.05–12.34)        | <0.01                     | 3.43 (2.53–4.64) | <0.01  |
| ISUP5                        | 13.72 (10.44–18.04)      | <0.01                     | 3.47 (2.51–4.80) | <0.01  |
| AGR                          | 1.40 (1.21–1.62)         | <0.01                     | 1.58 (1.36–1.83) | <0.01  |
| **Accuracy without AGR**    | 0.8124                   |                           |             |         |
| **Accuracy with AGR**        | 0.8164                   |                           |             |         |

*AGR Albumin to globulin ratio, PSA Prostatic Specific Antigen, ISUP International Society of Urological Patho*
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Declarations

Conflict of interest All authors state that they have no conflict of interest that might bias this work.

Ethical approval This study has been approved by the appropriate ethics committee.

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