Original Article

Establishing a model predicting Gleason grade group upgrading in prostate cancer

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Background: Gleason grade group (GG) upgrading is associated with increased biochemical recurrence (BCR), local progression, and decreased cancer-specific survival (CSS) in prostate cancer (PCa). However, descriptions of the risk factors of GG upgrading are scarce. The objective of this study was to identify risk factors and establish a model to predict GG upgrading.

Methods: There were 361 patients with PCa who underwent radical prostatectomy between May 2011 and February 2022 enrolled. Univariate and multivariate logistic regression analyses were identified and nomogram further narrowed down the contributing factors in GG upgrading. The correction curve and decision curve were used to assess the model.

Results: In the overall cohort, 141 patients had GG upgrading. But the subgroup cohort (GG ≤2) showed that 68 patients had GG upgrading. Multivariate logistic regression analysis showed that in the overall cohort, total prostate-specific antigen (tPSA) ≥10 ng/mL, systemic immune-inflammation index (SII) >379.50, neutrophil-lymphocyte ratio (NLR) >2.13, the GG of biopsy ≥3, the number of positive cores >3 were independent risk factors in GG upgrading. In the cohort of biopsy GG ≤2, multivariate logistic regression showed that the tPSA ≥10 ng/mL, SII >379.50 and the number of positive cores >3 were independent risk factors in GG upgrading. A novel model predicting GG upgrading was established based on these three parameters. The area under the curve (AUC) of the prediction model was 0.759. The C-index of the nomogram was 0.768. The calibration curves of the model showed good predictive performance. Clinical decision curves indicated clinical benefit in the interval of 20% to 90% of threshold probability and good clinical utility.

Conclusions: Combined levels of tPSA, SII and the positive biopsy cores distinguish patients with high-risk GG upgrading in the group of biopsy GG ≤2 and are helpful in the decision of treatment plans.

Keywords: Prostate cancer (PCa); Gleason grade group upgrading; systemic immune-inflammation index (SII); prediction model

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Introduction

Prostate cancer (PCa) is one of the most common malignancies and the fifth leading cause of cancer-related death in male worldwide (1). Prostatic biopsy is widely used in PCa diagnosis, and based on the aggressiveness of the cancer, patients may undergo radical prostatectomy (RP), active surveilling (AS), external beam radiotherapy, watchful waiting or androgen deprivation therapy (2). Since Gleason grade group (GG) established by the International Society of Urological Pathology (ISUP) is highly related to both cancer aggressiveness and prognosis, GG has been used as a critical parameter in decision-making of the treatments including intra-fascial prostatectomy and pelvic lymph node dissection (3).

Despite the growing concerns about overtreatment of insignificant PCa in recent decades (4,5), undertreatment of PCa is also significant. Due to the design of prostate biopsy sampling, GG often fails to represent the pathological grade of the tumor with only 40–60% of GG obtained from prostate biopsy being consistent with that from RP (5,6). Since AS is usually preferred for patients with low-risk and favorable intermediate-risk, if a patient is misleadingly diagnosed with a low- or favorable intermediate-risk, an increased risk of tumor progression and mortality is unavoidable. Multiple lines of evidence indicate that GG upgrading is associated with increased biochemical recurrence (BCR), local progression, and decreased cancer-specific survival (CSS) (7). It would be ideal to take the advantage of the simplicity of biopsy GG combined with other parameters to predict potential GG upgrading. Multiple factors including age, body mass index (BMI), prostate volume (PV), total prostate-specific antigen (tPSA), prostate-specific antigen density (PSAD), and neutrophil-to-lymphocyte ratio (NLR) have been shown to be associated with GG upgrading (7-9). In this study, we first evaluated the contributing factors in GG upgrading and established a novel prediction model for GG upgrading. We present this article in accordance with the TRIPOD reporting checklist (10,11) (available at https://tau.amegroups.com/article/view/10.21037/tau-24-155/rc).

Highlight box

Key findings

- This study found that systemic immune-inflammation index (SII) is an independent predictor of Gleason grade group (GG) upgrading in the overall cohort and in the biopsy GG ≤2 cohort.

What is known and what is new?

- Currently, there are several nomograms to predict the GG upgrading after radical prostatectomy, but they did not include the SII.
- In this study, we found that SII >379.50 is an independent predictor of GG upgrading in the overall cohort and in the biopsy GG ≤2 cohort. And we have established a novel model that consists of three parameters [total prostate-specific antigen (tPSA), SII and the number of biopsy-positive cores] to predict GG upgrading at RP from biopsy through a single center retrospective study.

What is the implication, and what should change now?

- Combined levels of tPSA, SII and the positive biopsy cores distinguish patients with high-risk GG upgrading in the group of biopsy GG ≤2 and are helpful in the decision of treatment plans.

Methods

Study subjects and inclusion/exclusion criteria

This retrospective study enrolled 361 PCa patients (May 2011 to February 2022) who underwent ultrasound-guided transrectal biopsy and laparoscopic or robot-assisted laparoscopic RP. Two senior pathologists conducted pathological examinations and diagnoses on both biopsy and postoperative specimens. The GG was determined based on the 2014 ISUP Consensus Conference on Gleason Grading of Prostatic Carcinoma. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and has been approved by the Ethics Committee of Daping Hospital (No. 2023_232). Individual consent for this retrospective analysis was waived.

The inclusion criteria for AS according to the European Association of Urology guidelines were low-risk PCa (life expectancy >10 years, ISUP grade 1, cT1c or cT2a, PSA <10 ng/mL and PSAD <0.15 ng/mL^2), favorable intermediate-risk PCa (life expectancy >10 years, PSA <10 ng/mL, the number of positive puncture needles ≤3 and the tumors tissue of positive cores ≤50%) and the patients are fully informed of the risks (2). The clinical T-staging ≥ cT2b based on the multiparametric magnetic resonance imaging (mpMRI) changes and patients' willingness were valid reasons for switching from AS to active treatment during the follow-up. The results from repeated biopsy's pathology indicated that the highest pattern's Gleason score (GS) was 4 or 5, and other pathological types such as neuroendocrine differentiation or intraductal carcinoma were also deemed a valid rationale (2).

The population of enrollment required transrectal ultrasound-guided prostate biopsy and RP to identify

primary prostatic acinar adenocarcinomas. Patients with a prior medical history of autoimmune or inflammatory disease, underwent any surgical intervention within the past month, received chemotherapy or radiotherapy, experienced acute or chronic infections, or had malignant tumors in other tissues/organs that could potentially influence the levels of complete blood count were excluded.

We defined GG upgrading as the GG of the specimen from RP being greater than that of the biopsy specimen (2). BCR is defined as a PSA level higher than 0.2 ng/mL over two sequential tests, 2 weeks apart (for patients after RP) (2), and the recurrence date is assigned to the day when the PSA level becomes ≥0.2 ng/mL.

Variables

Both preoperative and postoperative data were collected and de-identified all enrolled patients. The BMI and serological indicators were calculated as following: BMI = weight (kg)/height^2 (m^2); albumin-to-alkaline phosphatase ratio (AAPR) = serum albumin (g/dL)/serum alkaline phosphatase (IU/L); NLR = neutrophil count/lymphocyte count; systemic immune-inflammation index (SII) = platelet count × neutrophil count/lymphocyte count. SII was presented as a combination of NLR and platelet-to-lymphocyte ratio (PLR) (12,13). The continuous variables of these factors were converted to binary variables for further classification using the median as the cut-off point. The cut-off points are as following: free PSA (fPSA) (2.10 ng/mL), AAPR (0.54), lactate dehydrogenase (165.20 U/L), NLR (2.13), SII (379.50) and tPSA (10 ng/mL). The clinical T-staging, biopsy GG, the GG of RP, the number and percentage of positive cores, and preoperative neoadjuvant therapy were considered categorical variables.

Statistical analysis

All the statistical analyses were performed with IBM SPSS Statistics 26, GraphPad Prism 8, and R-software (version 4.2.2). The measurement data that conformed to a normal distribution was expressed as mean ± standard deviation. For skewed distributions, the measurement data was expressed as median [interquartile range (IQR)]. Enumeration data was expressed as the total number of cases and their respective percentages. Kaplan-Meier analysis showed differences in BCR-free survival in patients. Univariate and multivariate Cox regression analyses were performed to examine the independent factors associated with BCR. Univariate and multivariate logistic regression analyses were performed to examine the independent factors associated with GG upgrading. The odds ratio (OR) with 95% confidence interval (CI) was reported based on the results of the logistic regression analysis. Furthermore, based on the results of the multivariable logistic analysis in the biopsy GG ≤2 sub-group, predictive nomogram for GG upgrading were developed. Receiver operating characteristic (ROC), C-index, and calibration curves were used to evaluate their performance. Statistically significant levels were set at $P<0.05$ using a two-tailed approach.

Results

GGs variables from biopsied and surgical tumors

Among the 361 patients, 141 (39.1%), 161 (44.6%), and 59 (16.3%) had upgraded, unchanged, and downgraded GG, respectively. Among the subgroup of GG ≤2, 68 (52.3%), 55 (42.3%), and 7 (5.4%) had upgraded, unchanged, and downgraded GG, respectively. The related information of the patients is shown in Tables S1,S2.

The pathological results of the prostate specimens were provided in Table S1. Of note, all the samples were adenocarcinoma. One sample with invasive cribriform pattern, two samples with neuroendocrine differentiation, two samples with intraductal carcinoma, forty-three samples with perineural invasion (PNI), 14 samples with lymph vascular invasion (LVI), two samples with PNI and LVI. To analyze the association of adverse features with BCR, we utilized univariate and multivariate Cox analysis in overall cohort and biopsy GG ≤2 cohort (Tables S3,S4). Our findings indicated that GG upgrading was the risk factor of BCR. Nevertheless, no statistically significant difference was observed in adverse pathological features. We conducted Kaplan-Meier survival analysis and found that compared to the patients without GG upgrading, the BCR-free period in patients with GG upgrading was significantly shorter in both overall cohort [42.75 (IQR, 26.33, 63.63) *vs.* 21.03 (IQR, 8.30, 46.43) months, *Figure 1A*] and biopsy GG ≤2 sub-cohort [50.00 (IQR, 31.88, 66.77) *vs.* 23.43 (IQR, 8.23, 45.85) months, *Figure 1B*] indicating patients with GG upgrading was associated with poor prognosis.

In addition, three patients in the GG ≤2 sub-cohort switched from AS to RP due to elevated PSA levels in their follow-ups (*Figure 2* and Table S5). Postoperative pathologies indicate that 2 of the 3 who had upgraded GG also had shortened periods to BCR (less than 18 months). On the

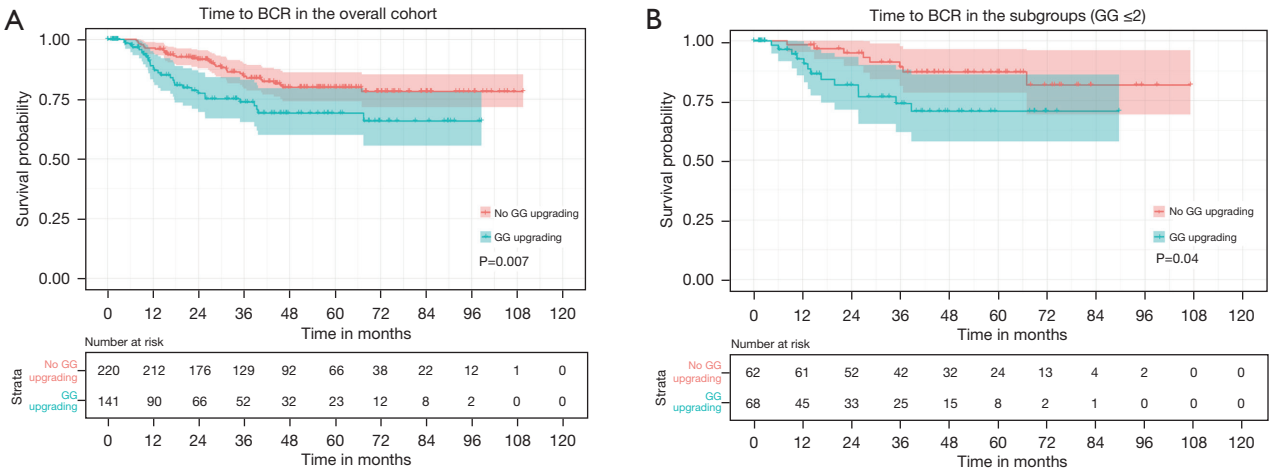

Figure 1 Kaplan-Meier curves showing differences in BCR-free survival in patients with (A) overall cohort (no GG upgrading *vs.* GG upgrading); (B) biopsy GG ≤2 cohort (no GG upgrading *vs.* GG upgrading). BCR, biochemical recurrence; GG, Gleason grade group.

other hand, the GG of the first patient remained unchanged and undetectable PSA in his 3-year follow-up (*Figure 2*).

Contributing factors in GG upgrading

To identify contributing factors in GG upgrading, we examined 15 parameters including 3 basic, 6 serological, and 6 pathological parameters (Table S1). We first conducted univariate and multivariate logistic regression analyses with the overall cohort (Table S6). Univariate analysis found that age (P=0.03), tPSA ≥10 ng/mL (P=0.004), SII >379.50 (P=0.001), NLR >2.13 (P=0.001), biopsy GG ≥3 (P<0.001), the number of positive cores >3 (P=0.003), and the positive rate of biopsy >25% (P=0.02) affect GG upgrading. We then conducted multivariate logistic regression analysis and found that tPSA ≥10 ng/mL (P=0.006), SII >379.50 (P=0.045), NLR >2.13 (P<0.001) are positive factors for GG upgrading; biopsy GG ≥3 (P=0.001) and the number of positive cores >3 (P=0.02) are negative factors for GG upgrading.

Since AS is generally suggested for patients with GG ≤2, we are more interested in identifying contributing factors in GG upgrading for patients with GG ≤2 (Table S7). We conducted univariate and multivariate logistic regression analyses for patients in the biopsy GG ≤2 sub-group (*Table 1*). The univariate analysis found that tPSA ≥10 ng/mL (P<0.001), SII >379.50 (P<0.001), NLR >2.13 (P<0.001), clinical stage ≥ cT3 (P=0.009), the number of positive cores >3 (P=0.01), and the positive rate of biopsy >25% (P=0.03) are statistically correlated with GG upgrading. The multivariate logistic regression analysis found that tPSA ≥10 g/mL (P=0.03), SII >379.50 (P=0.001) are risk factors for GG upgrading, while the number of positive cores >3 (P=0.009) is protective factors for GG upgrading. ROC analysis found that the tri-factor (PSA, SII, and number of positive cores) model is better than the mono- and di-factor models (*Figure 3A*) in predicting GG upgrading [area under the curve (AUC) =0.759 (95% CI: 0.677–0.841, P<0.001)]. Moreover, the nomogram (*Figure 3B*) indicates the association between this panel and GG upgrading has a concordance index of 0.768 (95% CI: 0.682–0.854, P<0.001). The calibration curve of the prediction models showed good predictive performance (*Figure 3C*). Clinical decision curves indicate the clinical benefit in the interval of 20% to 90% of threshold probability and good clinical utility (*Figure 3D*).

Discussion

Prostate biopsy is currently the gold standard for PCa diagnosis. However, both transrectal and transperineal biopsies have certain degree of under-detection due to the way of sampling. Previous studies have shown that GG plays a critical role in the decision-making of treatment and GG upgrading affects the prognosis (14-17). Therefore, it is ideal to accurately predict GG upgrading especially for patients with GG ≤2 who would undergo AS. In this study, we found that tPSA ≥10 ng/mL, SII >379.50, NLR >2.13, biopsy GG ≥3, the number of positive cores >3 were all independent risk factors for GG upgrading in the overall cohort. More importantly, in the biopsy GG ≤2 cohort,

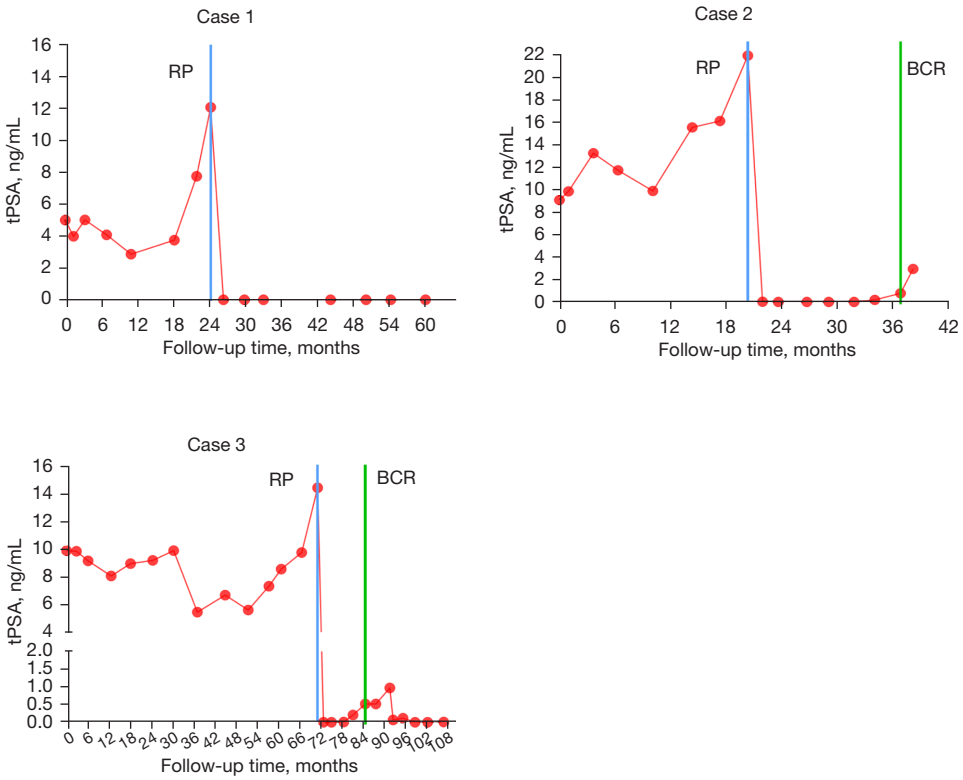

Figure 2 The trend of tPSA during the follow-up. BCR, biochemical recurrence; RP, radical prostatectomy; tPSA, total prostate-specific antigen.

Table 1 Univariate and multivariate analysis of predictors associated with GG upgrading after RP in biopsy GG ≤2 cohort

Predictors	Univariate analysis		Multiple analysis	
	OR (95% CI)	P	OR (95% CI)	P
Age (years)	1.050 (0.981, 1.124)	0.16	–	–
BMI (kg/m^2)	0.988 (0.879, 1.111)	0.84	–	–
tPSA ≥10 (ng/mL)	3.431 (1.633, 7.210)	<0.001	2.645 (1.084, 6.456)	0.03
fPSA >2.10 (ng/mL)	1.599 (0.641, 3.988)	0.31	–	–
AAPR >0.54	1.449 (0.726, 2.893)	0.29	–	–
LDH >165.20 (U/L)	1.079 (0.541, 2.153)	0.83	–	–
SII >379.50	4.276 (2.036, 8.98)	<0.001	4.602 (1.940, 10.915)	0.001
NLR >2.13	4.481 (2.137, 9.396)	<0.001	–	–
Clinical stage (cT3 + cT4)	4.104 (1.42, 11.859)	0.009	–	–
Number of positive cores >3	0.374 (0.173, 0.806)	0.01	0.313 (0.131, 0.746)	0.009
The percentage of positive cores >25%	0.431 (0.201, 0.923)	0.03	–	–
Preoperative neoadjuvant therapy (yes)	0.905 (0.249, 3.288)	0.88	–	–

Preoperative neoadjuvant therapy: LHRH agonists including Goserelin or leuprorelin. GG, Gleason grade group; RP, radical prostatectomy; BMI, body mass index; tPSA, total prostate-specific antigen; fPSA, free prostate-specific antigen; AAPR, albumin-to-alkaline phosphatase ratio; LDH, lactate dehydrogenase; SII, systemic immune-inflammation index; NLR, neutrophil-lymphocyte ratio; OR, odds ratio; CI, confidence interval; LHRH, luteinizing hormone-releasing hormone.

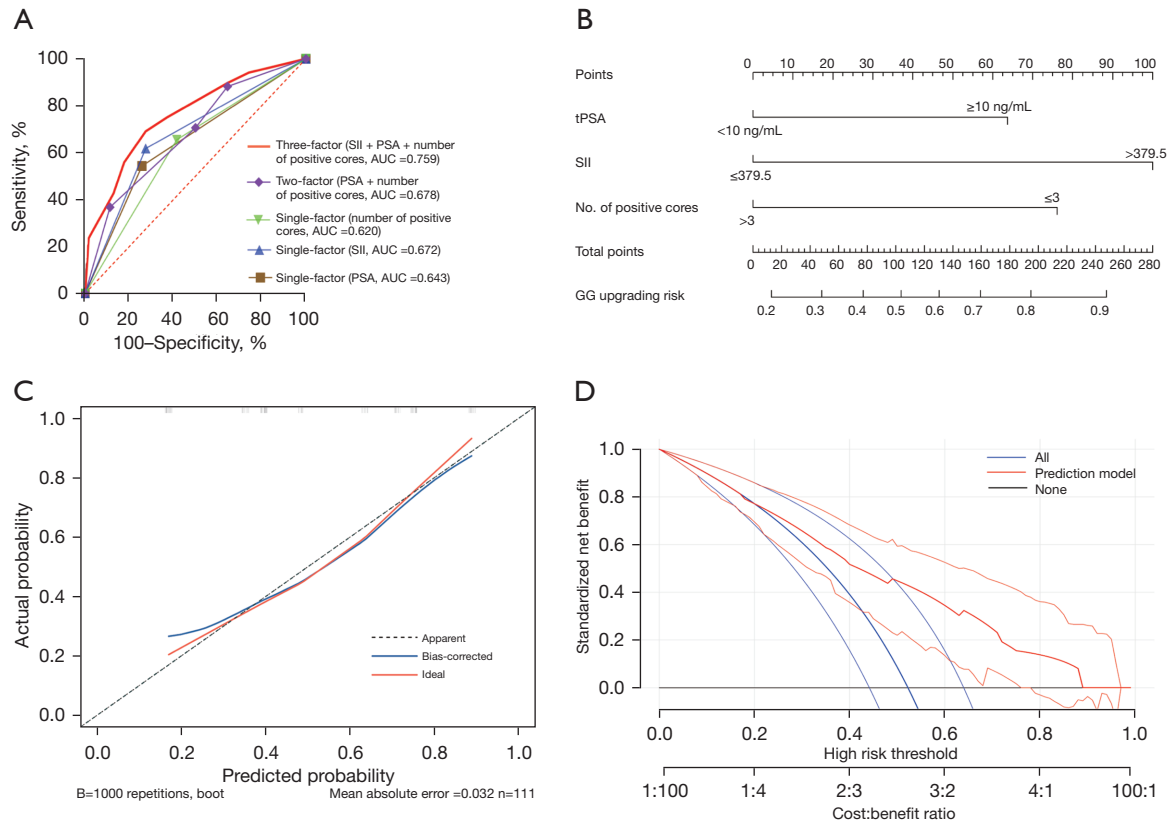

Figure 3 Establishing a model predicting Gleason grade group upgrading in prostate cancer. (A) ROC curve for prediction model in biopsy GG ≤2 cohort; (B) a nomogram for predicting GG upgrading (three-factor prediction model in biopsy GG ≤2 cohort); (C) calibration curve; (D) clinical decision curves. SII, systemic immune-inflammation index; PSA, prostate-specific antigen; AUC, area under the curve; tPSA, total PSA; ROC, receiver operating characteristic; GG, Gleason grade group.

tPSA ≥10 ng/mL, SII >379.50 and the number of positive cores >3 were independent risk factors of GG upgrading. The prediction model based on these factors showed good predictive performance, which can provide a reference for clinical decision-making when the patients choose AS.

GG upgrading affects the survival, recurrence, and progression (14). Ham *et al.* showed that GG upgrading is associated with BCR (15). Kovac *et al.* found that GG upgrading significantly reduces 10-year CSS (16). Marra *et al.* revealed that biopsy GS 6 is frequently upgraded and has less optimal oncological control (17). However, the roles of GG upgrading and its prediction models have been less thoroughly investigated in the Chinese population. This is of significant importance due to the considerable variation in the epidemiology and genomic features of PCa among individuals in China, Western countries, and elsewhere (18). For example, in China, the majority of newly diagnosed PCas are found to be at advanced stages. In our study, we found that PCa with GG upgrading often progress to BCR more quickly. In addition, GG upgrading is more important for localized PCa with biopsy GG ≤2 because PCa patients with localized biopsy GG ≤2 would choose AS, which might have an increased risk of tumor progression and mortality; while patients with localized PCa and biopsy GG >2 would still undergo RP although a higher GG tumor is missed at prostate biopsy. In the present study, three PCa patients with biopsy GG ≤2 changed their treatment from AS to RP based on their elevated PSA. Of note, two patients with GG upgrading also had shortened BCR-free survival. Thus, predicting GG is rather important for patients with localized biopsy GG ≤2. When tPSA ≥10 ng/mL, SII >379.50 and the number of positive cores ≤3 in patients with localized PCa and biopsy GG ≤2, AS should be considered carefully before treatment decision-making.

Several factors including basic information, serological indicators, pathological features, mpMRI, prostate-

specific membrane antigen (PSMA) positron emission tomography/computed tomography (PSMA PET/CT) and gene sequencing might be associated with GG upgrading. Huang *et al.* found that the PV (<38 mL) and PSAD (>0.26 ng/mL^2) were associated with increased risk of GS upgrading (19). Kim *et al.* proposed that higher numbers of biopsy-positive cores and biopsy-positive rates indicate a greater number of tumor cells (20). We found that the number of positive cores >3 is a protective factor in GG upgrading because higher cores more likely represent the tumor grade. In addition, Ferro *et al.* have shown that NLR, eosinophil-to-lymphocyte ratio, and PLR are significant predictors of GG upgrading (21). Özsoy *et al.* found that high NLR is associated not only with the aggressiveness but also GG upgrading (22). Additionally, age, tPSA, Prostate Imaging-Reporting and Data System (PI-RADS) score in MRI, the minimum apparent diffusion coefficient (ADCmin) of MRI and PNI have also been suggested as predictors in GG upgrading (23-27). Esen *et al.* found that high prostatic PSMA uptake (maximum standardized uptake value ≥5.6) was a highly reliable predictor of GG upgrading (28). Cooperberg *et al.* reported that the biomarker signatures based on analyses of both DNA and RNA significantly and independently predict adverse pathology and GG upgraded but it's expensive (29). Flood *et al.* reported that the presence of cribriform morphology for percent Gleason pattern 4 on biopsy is strongly associated with GG upgrading at RP whereas ill-defined glands, fused glands, and glomerulations were not useful (30). Although there are so many previously reported models, the prediction accuracy is limited. Additionally, it is more expensive to use PSMA PET-CT or DNA/RNA sequencing (29,30). In our study, we have established a novel model to predict GG upgrading at RP from biopsy with unique advantages. Our model only consists of three parameters (tPSA, SII and the number of biopsy-positive cores), which could be easily acquired. Of note, serological indicators (tPSA and SII) could be obtained by blood tests, while pathological indicators (the number of biopsy-positive cores) could be obtained from the information of prostate needle biopsy. The AUC of the prediction model was 0.759, which is slightly higher than that of Zhou's prediction model based on MRI (0.751) (27). Therefore, our model is both simple and effective.

Multiple lines of evidence imply that inflammatory factors are closely related to tumor initiation and progression (31,32). Our previous studies have shown that tumor-associated inflammatory infiltration and inflammation-related signaling pathways play crucial roles in PCa plasticity and castrate-resistant prostate cancer (CRPC) progression (33-36). SII is a novel inflammatory biomarker that combines components of NLR and PLR. Comparing to other inflammatory indexes, SII reflects more on systemic inflammatory response. High levels of SII indicate non-specific inflammation and weaker adaptive immune response which is promotive to tumor formation (37). In PCa patients, SII is also associated with BCR and CRPC (38,39). However, the role of SII in GG upgrading has not been previously examined. Our model innovatively included the parameter and discovered that SII is an independent predictor of GG upgrading, with an optimal cutoff of 379.50 in the overall cohort and in the biopsy GG ≤2 cohort. The AUC of the three-factor model with SII incorporated into the prediction model was significantly higher than that of the two-factor model (*Figure 3A*). Since SII can be obtained easily by routine bloodwork, we strongly recommend the levels of SII should be considered when selecting AS as the preferred treatment for patients with biopsy GG ≤2.

There are some limitations in this study which can be addressed in the future research. First, this is a retrospective and single-centered study with relatively smaller sample size. Prospective and multi-centered studies with larger sample sizes are needed to confirm these findings. Second, some parameters such as PI-RADS scores and the digital rectal examinations were unavailable due to the retrospectivity. Third, patients with infection and inflammatory diseases were excluded from our study, factors related to infection and inflammation could have been missed.

Conclusions

GG upgrading is highly associated with BCR and survival especially in biopsy GG ≤2 subgroup. We found the tri-parameter (tPSA, SII and the number of positive biopsy cores) model can predict GG upgrading in PCa with biopsy GG ≤2, which is helpful in treatment decision-making.

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Footnote

Reporting Checklist: The authors have completed the

TRIPOD reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-24-155/rc

Data Sharing Statement: Available at https://tau.amegroups.com/article/view/10.21037/tau-24-155/dss

Peer Review File: Available at https://tau.amegroups.com/article/view/10.21037/tau-24-155/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-24-155/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and has been approved by the Ethics Committee of Daping Hospital (No. 2023_232). Individual consent for this retrospective analysis was waived.

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