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Neutrophil, Platelets, and Eosinophil to Lymphocyte Ratios Predict Gleason Score Upgrading in Low-Risk Prostate Cancer Patients

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Keywords
Neutrophil to lymphocyte ratio · Platelets to lymphocyte ratio · Eosinophil to lymphocyte · Prostate cancer

Abstract
Background: Several biochemical and clinical markers have been proposed for selecting patients for active surveillance (AS). However, some of these are expensive and not easily accessible. Moreover, currently about 30% of patients on AS harbor aggressive disease. Hence, there is an urgent need for other tools to accurately identify patients with low-risk prostate cancer (PCa). ***Patients:*** We retrospectively reviewed the medical records of 260 patients who underwent radical prostatectomy and were eligible for AS according to the following criteria: clinical stage T2a or less, prostate-specific antigen level <10 ng/mL, 2 or fewer cores involved with cancer, Gleason score (GS) ≤6 grade, and prostate-specific antigen density <0.2 ng/mL/cc. ***Methods:*** Univariate and multivariate analyses were performed to evaluate the association of patient and tumor characteristics with reclassification, defined as upstaged (pathological stage >pT2) and upgraded (GS ≥7) disease. A base model (age, prostate-specific antigen, prostate volume, and clinical stage) was compared with models considering neutrophil to lymphocyte ratio (NLR) or platelets to lymphocyte ratio (PLR), monocyte to lymphocyte (MLR), and eosinophil to lymphocyte ratio (ELR). OR and 95% CI were calculated. Finally, a decision curve analysis was performed. ***Results:*** Univariate and multivariate analyses showed that NLR, PLR, and ELR upgrading were significantly

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associated with upgrading (ORs ranging from 2.13 to 4.13), but not with upstaging except for MLR in multivariate analysis, showing a protective effect. ***Conclusion:*** Our results showed that NLR, PLR, and ELR are predictors of Gleason upgrading. Therefore, these inexpensive and easily available tests might be useful in the assessment of low-risk PCa, when considering patients for AS.

Introduction

The widespread use of prostate-specific antigen (PSA) increased the number of tumors diagnosed at early stages [1], but it also led to over-diagnosis and over-treatment of a considerable number of patients with clinically insignificant prostate cancer (PCa) [2]. The proportion of men with low-risk PCa ranged from 16% in 2000 to 21% in 2006. Accordingly, an increase of "watchful waiting option" from 0 to 39% over the same period was observed [3]. PIVOT study [4] showed favorable outcomes of watchful waiting; clinically insignificant disease was treated excessively and active follow up of these patients preferred instead of radical treatment. Active surveillance (AS) is an alternative to initial radical treatment of low-risk PCa, even if the current parameters used for selection and follow up, such as clinical T stage, total PSA, PSA density, Gleason score (GS), and number of positive prostate biopsy cores, incorrectly exclude some patients eligible for AS and misclassify some who actually harbor significant disease [5]. Currently, the available preoperative tools used in this clinical setting, such as PSA, digital rectal examination, and biopsy results fail to accurately predict PCa aggressiveness and distinguish between insignificant PCa and clinically significant PCa and underestimates the GS compared to prostatectomy specimens in up to 66% of patients, based on PSA levels, biopsy GS, and clinical stage [6].

Besides these variables, which have been incorporated in a validated predictive model to predict Gleason upgrading [7], a number of biomolecular markers have been associated with Gleason upgrading [4, 6]. Recently numerous preoperative prognostic tools analyzed the ability of prostate cancer antigen 3 (PCA3), sarcosine, [–2]proPSA, and Prostate Health Index in predicting the pathological features at radical prostatectomy (RP) [8, 9].

Furthermore, the PCA3 score was strongly indicative of a cancer ≥0.5 cm^3 and significant PCa in men eligible for AS, supporting the hypothesis that the PCA3 score may be a useful marker for improving the selection of these patients [10]. Many studies available on the role of mpMRI during PCa-AS have shown the ability to reduce re-biopsies [11, 12], not always MRI lesions correspond to guided biopsy or RP specimen findings [12]. Recently, preoperative neural network software, based on mpMRI variables, PSA level, and GS has been reported to predict insignificant prostate cancer, particularly in the context of clinically non-palpable tumors, suggesting a prognostic and pathologic predictive role in very low-risk PCa [13]. Some authors suggested that risk scores based on the mRNA liquid biopsy assay combined with traditional clinical risk factors identified men at risk of harboring high-grade PCa on prostate biopsy, suggesting the use of epigenetic testing for prostate cancer detection using methylation-specific PCR and cancer-associated epigenetic biomarkers in predicting pathological features at RP [14, 15].

Neutrophil-to-lymphocyte ratio (NLR) has been proposed as an indicator of cancer-related inflammation and unfavorable prognosis in several types of cancer [16, 17]. In PCa, higher NLR was associated with disease aggressiveness in metastatic patients. It has been demonstrated that preoperative NLR is an independent prognostic factor for overall- and cancer-specific survival after RP [18]. Gokce et al. [19] showed that higher GS was associated with higher NLR.

In this study, we evaluated the ability of NLR, monocyte to lymphocyte ratio MLR), platelets to lymphocyte ratio (PLR), and eosinophil to lymphocyte ratio (ELR) to predict Gleason upgrading and upstaging in low- and very low-risk PCa patients eligible for AS.

Materials and Method

We retrospectively reviewed the medical records of patients who underwent robotic RP for prostate cancer between November 2006 and May 2013. None of the patients included in the current study received neoadjuvant androgen-deprivation therapy or drugs that could alter the PSA values, such as dutasteride and finasteride, or a history of prostate surgery. Patients with evidence of acute prostatitis, no biopsy slide or incomplete data were excluded. Patients with evidence of acute prostatitis, no biopsy slide or incomplete data were excluded [20]. In total, 260 patients fulfilled the inclusion criteria for "Prostate Cancer Research International: AS" [21] defined as follows: clinical stage T2a or less, PSA <10 ng/mL, 2 or fewer cores involved with cancer, GS ≤6 grade, and PSA density ≤0.2 ng/mL/cc. We compared the pathological findings between prostate biopsies and specimens after RP. RP specimens were processed and evaluated according to the Stanford protocol [22] by a single, experienced, genitourinary pathologist (G.R.) blinded to index test results. PCa was identified and graded according to the definitions of the 2005 consensus conference of the International Society of Urological Pathology [23].

Study End Points

The primary end points of the study were to determine the accuracy of NLR, MLR, PLR, and ELR in predicting upgrading and upstaging.

Statistical Analysis

Reclassification of outcomes were: upgrading (GS ≥7) and upstaging (pathologic stage >pT2).

Informative parameters for the distribution of continuous variables (age, PSA, prostate volume, NLR, MLR, PLR, and ELR) were calculated, and their distributions tested for normality by the Kolmogorov-Smirnov test.

Univariate analyses were performed to evaluate the association of patient and tumor characteristics with upgrading and upstaging. The association of continuous variables was assessed by *t* test or non-parametric 2-sample Wilcoxon test, as appropriate, and by chi-square test for clinical stage.

Multivariate unconditional logistic regression models were performed to assess the independent contribution of patient and tumor characteristics in the prediction of upgrading and upstaging. A base model with age, PSA, prostate volume, and clinical stage was compared with models based on the previous one, adding NLR or PLR, MLR, and ELR, OR and 95% CI were calculated. For multivariate analysis, all ratios were divided based on their best cut-off obtained by maximizing the sum of sensitivity and specificity. Finally, to graphically evaluate the net benefit for the models with and without inclusion of ratios, a decision-curve analysis was performed. Decision curves were constructed by plotting the net benefit against the threshold probability, as previously described [24].

Statistical significance was defined as $p < 0.05$. Statistical analysis was performed using SAS software, version 9.4.

Table 1. Characteristics of the study cohort

	Mean ± SD and *n* (%)
Age, years	62.2±6.4
PSA	5.8±1.9
Prostate volume	51.9±17.7
NLR	2.3±1.0
PLR	117.8±34.1
MLR	0.3±0.1
ELR	0.1±0.1
Clinical stage	
T1c	231 (88.8)
cT2a	29 (11.2)
Pathological stage	
T2a	31 (11.9)
T2b	8 (3.1)
T2c	150 (57.7)
T3a	68 (26.2)
T3b	3 (1.2)
Total Gleason score	
5	2 (0.8)
6	164 (63.1)
7	92 (35.4)
8	2 (0.8)
Upgrading (GS >7)	
No	166 (63.8)
Yes	94 (36.2)
Upstaging (pT >3a)	
No	189 (72.7)
Yes	71 (27.3)

Results

Most of the patients (89%) had clinical stage cT1c. Pathological stage pT2c was found in 58% of patients, followed by pT3a (26%). A total of 164 patients had a GS = 6, and 92 patients had a GS = 7. There were 94 patients (36%) with upgrading and 71 patients (27%) with upstaging. The mean age (±SD) of the study subjects was 63 (±6) years, and the mean PSA was 5.6 (±1.9; Table 1).

Univariate analysis showed that upgrading (Table 2), but not upstaging (Table 4), was significantly associated with NLR, PLR, and ELR, with *p* values <0.0001, 0.0142, and 0.0403, respectively.

Multivariate analysis confirmed the association of upgrading with NLR, PLR, and ELR, with ORs ranging from 2.13 to 4.13. Furthermore, we found an association between upgrading, age, and prostate volume (Table 3). The differences between areas under the ROC curve were statistically significant for Model 2 and Model 5 when compared with the base model (Model 1), showing *p* values for the differences of 0.0055 and 0.0253, respectively. Upstaging (Table 5) was associated only with MLR, with a protective effect (OR 0.37; 95% CI 0.19–0.72).

Decision curve analyses are shown in Figures 1 and 2. Models including NLR or ELR resulted in greater net benefit for upgrading compared to models without NLR over almost all the range of probabilities, while no differences are observed for models including PLR in predicting upgrading or models with MLR in predicting upstaging when compared with base models.

Discussion

AS remains a tool that is able to prevent the side effects associated with RP. This is particularly relevant for men harboring low-risk PCa. Currently, patient stratification in risk class is based on D'Amico criteria (clinical stage, GS, and PSA). So, GS upgrading is a major concern. Literature data suggest about 30% higher Gleason at RP [25].

Despite several clinical and biochemical parameters being proposed as a means to select the best candidates

Table 2. Univariate analysis for the association between upgrading (GS ≥7) and patients and tumor characteristics

Variables	Upgrading		*p* value
	no, mean (SD)	yes, mean (SD)	
Age, years	61.7 (6.1)	63.1 (6.8)	0.0580
PSA	5.7 (1.9)	5.8 (2.0)	0.7343
Prostate volume	53.3 (19.0)	49.4 (14.8)	0.1496
NLR	2.1 (0.9)	2.6 (1.1)	**<0.0001**
PLR	114.4 (34.4)	123.7 (33.0)	**0.0142**
MLR	0.3 (0.1)	0.3 (0.1)	0.4037
ELR	0.1 (0.1)	0.1 (0.1)	**0.0403**

	Upgrading		Overall, *n* (%)	*p* value
	no, *n* (%)	yes, *n* (%)		
Clinical stage				0.3083
cT1c	145 (87.3)	86 (91.5)	231 (88.8)	
cT2a	21 (12.7)	8 (8.5)	29 (11.2)	

Significant *p* values are in bold.

Table 3. Multivariate analysis for the association between upgrading (GS ≥7) and patients and tumor characteristics

Variables	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Age, years	**1.05 (1.00–1.09)**	1.04 (0.99–1.09)	**1.05 (1.00–1.09)**	1.04 (0.99–1.09)	**1.05 (1.00–1.09)**
PSA	1.06 (0.92–1.22)	1.04 (0.89–1.20)	1.05 (0.91–1.21)	1.06 (0.92–1.22)	1.04 (0.90–1.20)
Prostate volume	**0.98 (0.97–0.99)**	0.98 (0.97–1.00)	**0.98 (0.97–0.99)**	**0.98 (0.97–0.99)**	**0.98 (0.96–0.99)**
Clinical stage					
cT1c	Reference	Reference	Reference	Reference	Reference
cT2a	0.54 (0.22–1.32)	0.50 (0.20–1.24)	0.51 (0.21–1.25)	0.55 (0.23–1.35)	0.52 (0.21–1.28)
NLR*					
<1.8687	–	Reference	–	–	–
≥1.8687	–	**4.13 (2.20–7.74)**	–	–	–
PLR*					
<86.9198	–	–	Reference	–	–
≥86.9198	–	–	**2.13 (1.04–4.36)**	–	–
MLR*					
<0.2468	–	–	–	Reference	–
≥0.2468	–	–	–	1.27 (0.73–2.21)	–
ELR*					
<0.0428	–	–	–	–	Reference
≥0.0428	–	–	–	–	**2.69 (1.40–5.17)**
AUC	0.613	0.700	0.647	0.619	0.670
p value for the difference between models	Reference	**0.0055**	0.1110	0.5283	**0.0253**

* Best cut-off for ratios were identified by maximizing the sum of sensitivity and specificity; significant values are in bold.

for AS in recent times [14, 26–28], the possibility of misclassification of cancer or missing a high-risk cancer remains a relevant clinical issue.

Several authors reported that inflammatory response in tumor microenvironment plays a key role in cancer malignant phenotype [29, 30]. On this basis, immune cells from blood samples might potentially be used as a prognostic predictor in cancer patients [31].

Several reports showed that NLR and PLR might be useful as predictors of outcome [32–34]. Neutrophil and

Table 4. Univariate analysis for the association between upstaging (pT ≥3a) and patients and tumor characteristics

Variables	Upstaging		*p* value
	no, mean (SD)	yes, mean (SD)	
Age, years	62.5 (6.1)	61.6 (7.1)	0.5705
PSA	5.8 (1.8)	5.7 (2.1)	0.6054
Prostate volume	53.1 (18.3)	48.8 (15.7)	0.0966
NLR	2.3 (1.1)	2.2 (0.9)	0.4402
PLR	117.2 (34.0)	119.2 (34.6)	0.4402
MLR	0.3 (0.1)	0.3 (0.1)	0.4402
ELR	0.1 (0.1)	0.1 (0.1)	0.8750
	Upstaging	Overall, *n* (%)	*p* value
	no, *n* (%)	yes, *n* (%)	
Clinical stage			0.9715
cT1c	168 (88.9)	63 (88.7)	231 (88.8)
cT2a	21 (11.1)	8 (11.3)	29 (11.2)

Table 5. Multivariate analysis for the association between upstaging (pT ≥3a) and patients and tumor characteristics

Variables	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR 95% CI)	OR (95% CI)
Age, years	0.98 (0.94–1.03)	0.99 (0.94–1.03)	0.98 (0.94–1.03)	1.00 (0.95–1.04)	0.98 (0.94–1.03)
PSA	0.99 (0.85–1.15)	1.00 (0.86–1.17)	0.99 (0.85–1.16)	1.00 (0.86–1.17)	0.99 (0.85–1.16)
Prostate volume	0.99 (0.97–1.00)	0.99 (0.97–1.00)	0.99 (0.97–1.00)	0.98 (0.97–1.00)	0.99 (0.97–1.00)
Clinical stage					
cT1c	Reference	Reference	Reference	Reference	Reference
cT2a	1.00 (0.41–2.45)	1.00 (0.41–2.46)	0.98 (0.40–2.39)	1.08 (0.44–2.67)	1.03 (0.42–2.51)
NLR*					
<2.1993	–	Reference	–	–	–
≥2.1993	–	0.70 (0.40–1.24)	–	–	–
PLR*					
<133.6	–	–	Reference	–	–
≥133.6	–	–	1.47 (0.81–2.64)	–	–
MLR*					
<0.2134	–	–	–	Refernce	–
≥0.2134	–	–	–	**0.37 (0.19–0.72)**	–
ELR*					
<0.0526	–	–	–	–	Reference
≥0.0526	–	–	–	–	0.79 (0.45–1.40)
AUC	0.566	0.582	0.592	0.621	0.568
p value for the difference between models	Reference	0.5008	0.3514	0.1159	0.9372

* Best cut-off for ratios were identified by maximizing the sum of sensitivity and specificity; significant values are in bold.

platelets are associated with adverse outcomes, whereas lymphocyte is associated with favorable disease.

In this study, we found that high NLR, PLR, and ELR were significantly associated with upgrading, but not with upstaging in patients without systemic or prostate-related inflammation. These findings suggest that these less expensive and easily accessible tests deserve more attention as potential tools for selecting eligible patients for AS.

Van Soest et al. [35] demonstrated that higher NLR is a predictor of aggressive disease and drug resistance

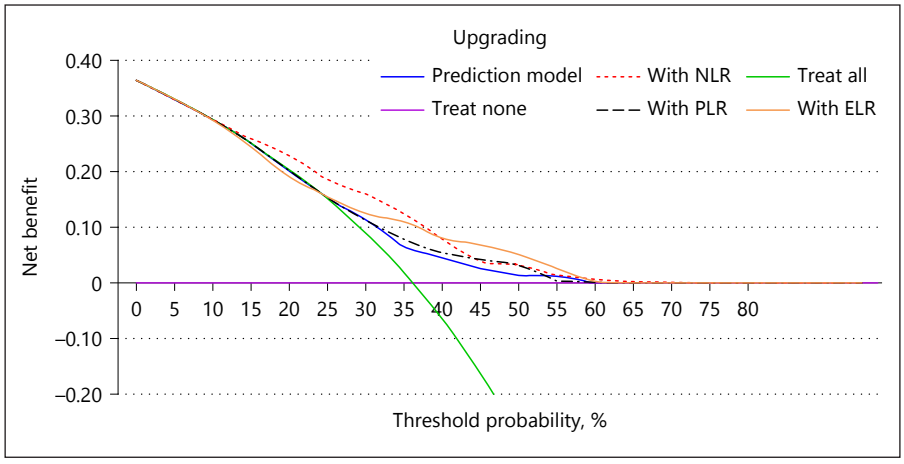

Fig. 1. Violet line: assume no patients have upgrading, Green line: assume all patients have upgrading. Blue line: base prediction model with age, PSA, prostate volume, and clinical stage. Dotted red line: prediction model adding MLR. Dotted black line: prediction model adding PLR. Orange line: prediction model adding ELR. The graph gives the expected net benefit per patient relative to the base model with age, PSA, prostate volume and clinical stage ("treat none"). The unit is the benefit associated with one upgraded patient evaluated with three different predicted models (including NLR, PLR, and ELR, respectively). PSA, prostate-specific antigen; MLR, monocyte to lymphocyte; NLR, neutrophil to lymphocyte ratio, ELR, eosinophil to lymphocyte ratio; PLR, platelets to lymphocyte ratio.

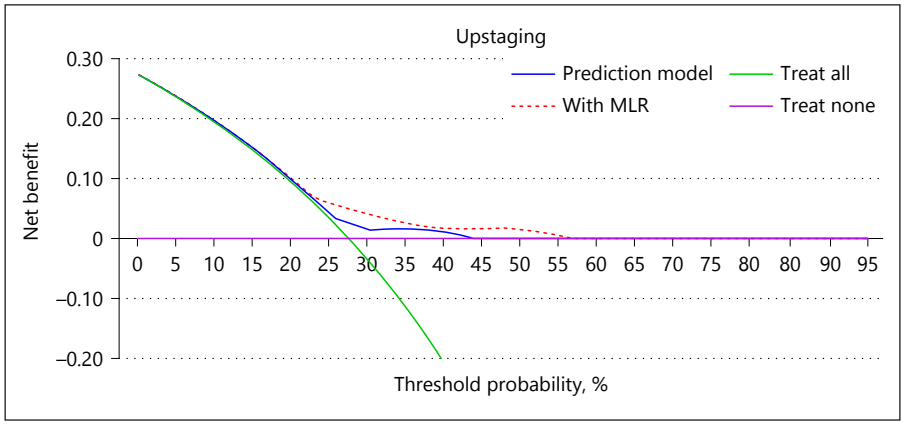

Fig. 2. Violet line: assume no patients have upstaging. Green line: assume all patients have upstaging. Blue line: base prediction model with age, PSA, prostate volume and clinical stage. Dotted red line: prediction model adding MLR. The graph gives the expected net benefit per patient relative to base model with age, PSA, prostate volume, and clinical stage ("treat none"). The unit is the benefit associated with one upstaged patient evaluated with a predicted model including MLR. PSA, prostate-specific antigen; MLR, monocyte to lymphocyte.

in CRPC patients. More recently, it has been reported that [19] NLR is a predictor of GS upgrading and biochemical recurrence in patients with low-risk PCa. Other authors showed that high PLR is a predictor of poor prognosis in PCa patients treated with radiotherapy [36] or ADT [37]. Moreover, some studies indicated that platelets are able to promote cancer aggressive features such as metastasis, angiogenesis, and invasiveness [38–40].

Recently, the association between subpopulations of WBCs and high GS has been studied, and it was found that serum monocyte fraction of WBCs was significantly increased in patients with GS ≥7 [41]. So, to the best of our knowledge, our report is the first indicating that ELR is a predictor of Gleason upgrading.

Interestingly, it has been suggested that eosinophils secrete cytokines involved in cancer progression such as interleukin-6 and tumor necrosis factor-α [42]. Michalaki

et al. [43] showed that serum levels of interleukin-6 and tumor necrosis factor-α correlate with aggressiveness and clinical outcome of prostate cancer patients.

Hypothetically, NLR, PLR, and ELR likely reflect a favorable immune microenvironment for tumor development and metastasis. Tumor-infiltrating inflammatory cells produce cytokines and growth factors able to promote angiogenesis, proliferation, migration, and invasion [44–46].

In low-risk PCa patients, the use of these hematological markers could be useful to identify subjects harboring aggressive tumors. Therefore, these tests may be applied in the clinical management of low-risk PCa patients to identify who may benefit from delayed surgical treatment. Further studies on larger population should investigate the effect of each specific circulating immune-cells index on clinical-decision choice.

Our study had several limitations. First, the retrospective nature of the study, second the lack of other systemic inflammatory index such as C-reactive protein. Third, the current study involved Italian men and thus cannot be extended to other ethnic groups.

In conclusion, our results suggest that an increased pretreatment NLR, PLR, and ELR may be associated with GS upgrading in PCa patients undergoing RP. So, these hematological tests, which are cost-effective and easily measurable, warrant further validation in larger study population.

Disclosure Statement

The authors declare that they have no affiliation with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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