Central European Journal of Urology

ORIGINAL PAPER

UROLOGICAL ONCOLOGY

Differential prognostic impact of favourable prostate cancer pathology risk score patterns predicted by Briganti's 2012 nomogram across EAU risk groups: Analysis of 757 cases treated with robotic surgery

Antonio Benito Porcaro[1], Sonia Costantino[1], Francesca Montanaro[1], Alberto Baielli[1], Francesco Artoni[1], Emanuele Serafin[1], Luca Roggero[1], Claudio Brancelli[1], Andrea Franceschini[1], Alessandro Princiotta[1], Michele Boldini[1], Lorenzo Treccani[1], Lorenzo De Bon[1], Alberto Bianchi[1], Alessandro Veccia[1], Riccardo Rizzetto[1], Matteo Brunelli[2], Vincenzo De Marco[1], Salvatore Siracusano[1], Maria Angela Cerruto[1], Riccardo Giuseppe Bertolo[1], Alessandro Antonelli[1]

[1]*Department of Urology, University of Verona, Azienda Ospedaliera Universitaria Integrata, Verona, Italy*
[2]*Department of Pathology, University of Verona, Azienda Ospedaliera Universitaria Integrata, Verona, Italy*

Citation: Porcaro AB, Costantino S, Montanaro F, et al. Differential prognostic impact of favourable prostate cancer pathology risk score patterns predicted by Briganti's 2012 nomogram across EAU risk groups: Analysis of 757 cases treated with robotic surgery. Cent European J Urol. 2025; 78: 109-115.

Article history
Submitted: Aug. 11, 2024
Accepted: Feb. 1, 2025
Published online: May 27, 2025

Corresponding author
Antonio Benito Porcaro
Department of Urology,
Azienda Ospedaliera Universitaria Integrata Verona,
Piazzale Stefani 1 – 37126,
Verona, Italy
drporcaro@yahoo.com
drporcaro61@gmail.com

Introduction The aim of this study was to evaluate the prognostic impact of favourable prostate cancer (PCa) pathology patterns through Briganti's 2012 nomogram and beyond EAU risk classes in patients treated with robotic surgery.

Material and methods We analysed 757 patients from January 2013 to December 2021 with favourable pathology features (ISUP 1-3, pT2/pT3a, and pN0/x) and available follow-up. Pathologic features were scored from zero (ISUP 1 + pT2) to three (ISUP 3 + pT3a). Associations with Briganti's 2012 nomogram by EAU risk class were evaluated to determine the prognostic impact on PCa progression, defined as biochemical persistence/recurrence or loco-regional/metastatic recurrence.

Results Favourable pathology risk scores were most commonly grades one (49%) and two (30.95%), followed by zero (15.2%) and three (4.9%). After adjusting for EAU prognostic groups, higher nomogram scores were associated with increased risk scores of two and three. PCa progression occurred in 12.7% of cases after a mean follow-up of 92.1 months. Patients with recurrence had a worse prognosis as risk scores increased from one to three, even after adjustment for Briganti's 2012 nomogram by EAU class.

Conclusions Favourable pathology risk scores, grouped by Briganti's 2012 and EAU nomograms, impact prognosis. As scores increase, the likelihood of disease progression rises, potentially influencing treatment strategies.

Key Words: prostate cancer ‹› EAU risk classes ‹› prostate cancer nomograms ‹› robot assisted radical prostatectomy ‹› favorable prostate cancer pathology ‹› prostate cancer progression

INTRODUCTION

The increasing incidence of clinical prostate cancer (PCa) has prompted the European Association of Urology (EAU) and the National Comprehensive Cancer Network (NCCN) to update guidelines to reduce overtreatment and prevent treatment-related patient regret [1, 2]. Treatment options include monitoring strategies like active surveillance (AS) and watchful waiting (WW), surgery (robotic-assisted radical prostatectomy [RARP] with or without extended pelvic lymph node dissection [ePLND]), radiation therapy, and combination therapies tailored to prognostic risk categories (low to high) [3, 4].

Prognostic risk classes differ between classification systems and remain heterogeneous due to a mix of favourable and unfavourable pathology features. Reliable predictors are lacking, as molecular biology is not yet part of routine practice and multiparametric magnetic resonance imaging (MRI) is not consistently reproducible in multicentre studies.
Preoperative nomograms, such as Briganti's 2012 model, estimate the risk of pelvic lymph node invasion (PLNI) by integrating multiple clinical variables [5, 6]. Among these tools, Briganti's 2012 nomogram is one of the most effective and widely used. This study aimed to evaluate the impact of favourable pathology patterns on PCa progression after assessing associations with the Briganti's 2012 nomogram using EAU risk stratification in patients treated with robotic surgery.

MATERIAL AND METHODS

Evaluation of parameters in the investigated prostate cancer patient population

We analysed 757 patients (January 2013–December 2021) with no prior PCa treatment, including androgen blockade. Robotic surgery, with or without ePLND, was performed by five experienced surgeons following a standardised template. Data were collected prospectively and analysed retrospectively. Clinical factors included age, body mass index (BMI), physical status, prostate-specific antigen (PSA), prostate volume (PV), biopsy positive cores percentage (BPC), and tumour grade and stage. Surgical specimens included the resected prostate and any sampled lymph nodes. Tumours were graded according to the International Society of Urological Pathology (ISUP) system and staged according to the TNM system. The samples were evaluated according to the pathological guidelines in force at the time of surgery. Patient follow-up adhered to guidelines, and a multidisciplinary team reviewed decisions regarding disease progression to optimise and personalise recommendations.

Model assumptions with evaluation of endpoints

The study focused on identifying favourable pathological features in surgical specimens, such as ISUP 1/3, pT2/3a, and pN0/x. These features were categorised into grades (0–3) based on different combinations. The study then assessed the relationship between these grades, Briganti's 2012 nomogram, and EAU classes. The goal was to determine the impact of these combined patterns on PCa progression, including biochemical recurrence, local recurrence, or metastases. Individual cancer factor scores were not calculated for Briganti's 2012 nomogram and EAU prognostic classes.

Statistical methods

Continuous variables were evaluated as medians with interquartile ranges (IQR), and categorical variables were evaluated as frequencies (percentages). Associations of risk score patterns were tested using the Kruskal-Wallis test for continuous variables and the χ^2 test for categorical variables. The multinomial logistic regression model evaluated the associations between Briganti's 2012 nomogram, EAU classes, and the risk of combined patterns. Time to event occurrence was censored as the time between surgery and PCa progression or the last follow-up. Cox's proportional model was used to evaluate the risk of disease progression by examined patterns adjusted for Briganti's 2012 nomogram beyond EAU classes. Unadjusted Kaplan-Meier related curves were also generated. IBM-SPSS version 26 was used for the analysis. All tests were two-tailed, and $p < 0.05$ was considered statistically significant.

Bioethical standards

The Institutional Review Board of Univeristy of Verona approved the study, and all patients provided informed consent.

RESULTS

Associations of favourable pathology risk score patterns

Grades one and two were the most frequent favourable pathologic risk score patterns (49% and 30.95%, respectively), followed by grades zero (15.2%) and three (4.9%). Increasing risk score patterns were associated with older age, unfavourable cancer features, higher nomogram scores, and unfavourable EAU prognostic classes. Extended pelvic lymph node dissection (ePLND) was performed in 54.8% of cases, with a median of 26 lymph nodes counted (Table 1).

Favourable pathology risk score patterns predicted by Briganti's 2012 nomogram through EAU risk classes

As the nomogram score increased, patients were more likely to have less favourable patterns. This included risk scores two (OR = 1.088; 95% CI: 1.010–1.171; p = 0.025) and three (1.096; 95% CI: 1.096; 1.010–1.189; p = 0.028) compared to pattern zero. It also included risk scores two (OR = 1.075;

95% CI: 1.038–1.114; p <0.0001) and three (OR = 1.084; 95% CI: 1.032–1.139; p = 0.001) compared to pattern one. Risk score one showed no significant association with pattern zero on multivariate analysis (Table 2).

Prognostic impact of favourable pathology risk score patterns

Prostate cancer (PCa) progression occurred in 12.7% (Table 3) of cases after a mean follow-up of 92.1 months. Patients with higher risk scores were more likely to have a worse prognosis. Compared to score zero, the hazard ratios were 2.478 for score one, 4.361 for score two, and 7.227 for score three, after adjusting for Briganti's 2012 and EAU classes. Kaplan-Meier survival risk curves for PCa progression are shown in Figure 1. There were 19 (2.5%) patient deaths, of which 4 (0.5%) were related to PCa. Androgen deprivation therapy was administered in 9.2% of patients and radiation therapy in 10.6%, with 4.9% receiving salvage therapy.

Table 1. *Associations of factors with favorable pathology risk cores patterns in 757 patients treated with robotic surgery*

	Favorable pathology risk score pattern in the surgical specimen				p
	Zero	One	Two	Three	
Cases, n (%)	15 (15.2)	371 (49.0)	234 (30.9)	37 (4.9)	
Physical features					
Age (years)	63 (58–68)	64 (58–69)	65 (61–71)	66 (60.5–70.5)	0.005
BMI [kg/m^2]	25.6 (23.7–28.0)	25.8 (24.0–27.8)	26.0 (23.9–28.1)	26.1 (22.8–28.5)	0.729
ASA score 1	13 (4.3)	36 (9.7)	17 (7.3)	5 (13.5)	0.266
ASA score 2	96 (83.5)	304 (81.9)	189 (80.8)	27 (73.0)	
ASA score 3	6 (5.2)	31 (8.4)	28 (12.0)	5 (13.5)	
PV [ml]	42 (32–53)	40 (30–50)	36.7 (28.7–47.2)	34 (30–47)	0.054
Clinical cancer features					
PSA [ng/ml]	6.1 (4.6–7.9)	6.2 (4.7–8.1)	6.4 (5.0–8.6)	8.1 (5.6–10.1)	0.007
BPC (%)	21.4 (14.2–35.7)	28.5 (16.6–42.8)	30 (20–50)	30 (21.8–51.6)	<0.0001
ISUP 1	96 (83.5)	156 (42.0)	62 (26.5)	7 (18.9)	<0.0001
ISUP 2/3	19 (16.5)	209 (56.3)	160 (68.4)	30 (81.1)	
ISUP 4/5	0 (0.0)	6 (1.6)	12 (5.1)	0 (0.0)	
cT1	90 (78.3)	232 (62.5)	138 (59.0)	16 (43.2)	<0.0001
cT2/3	25 (21.7)	139 (37.5)	96 (41.0)	21 (56.8)	
EAU risk class					
Low-risk	92 (80)	122 (32.9)	51 (21.8)	4 (10.8)	<0.0001
Intermediate-risk	19 (16.5)	219 (59.0)	149 (63.7)	25 (67.6)	
High-risk	4 (3.5)	30 (8.1)	34 (14.5)	8 (21.6)	
Nomogram for PLNI					
Briganti 2012 (%)	2 (1–3)	2 (1–4)	4 (2–8)	4 (2.5–8.5)	<0.0001
PLND	32 (27.8)	199 (53.6)	157 (67.1)	27 (73.0)	<0.0001
Pathology features					
ISUP 1	115 (100)	1 (0.3)			<0.0001
ISUP 2		370 (99.7)	20 (8.5)		
ISUP 3		214 (91.5)	37 (100)		
pT2	115 (100)	370 (99.7)	214 (91.5)		<0.0001
pT3a		1 (0.3)	20 (8.5)	37 (100)	
R1	12 (10.4)	74 (19.9)	42 (17.9)	20 (54.1)	<0.0001

Continuous variables are reported as medians (interquartile ranges) while categorical factors as frequencies (percentages); and methods; for further details see sections relative to material

ASA – American Society of Anesthesiologists; BMI – body mass index; EAU – European Association of Urology

DISCUSSION

Managing PCa is challenging due to the heterogeneity of prognostic risk groups, which differ between the two main systems [1, 2, 9–12]. Treated PCa can become life-threatening, with progression occurring in about 35% of cases and mortality affecting about 16% of patients [1, 2, 7–12].

Table 2. *Impact of Briganti's 2012 nomogram through EAU risk classes for predicting favourable pathology risk score patterns*

	Univariate analysis		Multivariate analysis	
Statistics	OR (95% CI)	p	OR (95% CI)	p
a) Risk score one vs zero				
Briganti 2012 nomogram	1.119 (1.030–1.217)	0.008	1.011 (0.939–1.089)	0.768
EAU intermediate vs low risk	8.692 (5.059–14.934)	<0.0001	8.524 (4.890–14.860)	<0.001
EAU high vs low risk	5.656 (1.925–16.618)	0.002	5.435 (1.795–15.458)	0.003
b) Risk score two vs zero				
Briganti 2012 nomogram	1.216 (1.119–1.322)	<0.0001	1.088 (1.010–1.171)	0.025
EAU Intermediate vs low risk	14.147 (7.862–25.454)	<0.0001	11.733 (6.428–21.417)	<0.0001
EAU high vs low risk	15.333 (5.150–45.654)	<0.0001	10.042 (3.244–31.086)	<0.0001
c) Risk score three vs zero				
Briganti 2012 nomogram	1.236 (1.131–1.352)	<0.0001	1.096 (1.010–1.189)	0.028
EAU Intermediate vs low risk	30.263 (9.437–97.052)	<0.0001	24.478 (7.532–79.544)	<0.0001
EAU high vs low risk	46.000 (9.638–219.542)	<0.0001	28.264 (5.603–142.579)	<0.0001
d) Risk score two vs one				
Briganti 2012 nomogram	1.086 (1.050–1.124)	<0.0001	1.075 (1.038–1.114)	<0.0001
EAU Intermediate vs low risk	1.628 (1.105–2.398)	0.014	1.376 (0.925–2.049)	0.115
EAU high vs low risk	2.711 (1.503–4.890)	0.001	1.848 (0.990–3.451)	0.054
e) Risk score three vs one				
Briganti 2012 nomogram	1.104 (1.050–1.124)	<0.0001	1.084 (1.032–1.139)	0.001
EAU Intermediate vs low risk	3.482 (1.184–10.237)	0.023	2.872 (0.967–8.531)	0.058
EAU high vs low risk	8.133 (2.296–28.816)	0.001	5.201 (1.395–19.389)	0.014

CI – confidence interval; EAU – European Associan of Urology risk classes; see also materials, methods and results for further details; OR – odds ratio

Table 3. *Impact of favourable pathology risk score patterns on prostate cancer progression through EAU risk classes and by Briganti's 2012 nomogram in 757 cases treated with robotic surgery*

	Total cases	Cases progressing	Univariate analysis		Multivariate analysis	
Statistics	757	96 (12.7)	HR (95% CI)	P	HR (95% CI)	P
Briganti's 2012 nomogram						
one-two	385	37 (9.6)	Ref.		Ref.	0.03
> two	372	59 (15.9)	2.455 (1.616–3.693)	<0.0001	1.595 (1.030–2.470)	
EAU prognostic risk class						
Low risk	269	25 (9.3)	Ref.		Ref.	
Intermediate risk	412	59 (14.3)	3.152 (1.962–5.063)	<0.0001	2.035 (1.234–3.355)	0.005
High risk	76	12 (15.8)	3.997 (1.990–8.030)	<0.0001	2.050 (0.971–4.330)	0.06
Favourable pathology pattern						
Risk score zero	115	6 (5.2)	Ref.		Ref.	
Risk score one	371	37 (10.0)	3.307 (1.393–7.850)	0.007	2.478 (1.027–5.981)	0.044
Risk score two	234	42 (17.9)	6.901 (2.925–16.283)	<0.0001	4.361 (1.793–10.612)	0.001
Risk score three	37	11 (2.97)	13.063 (4.803–35.526)	<0.0001	7.227 (2.520–20.724)	<0.0001

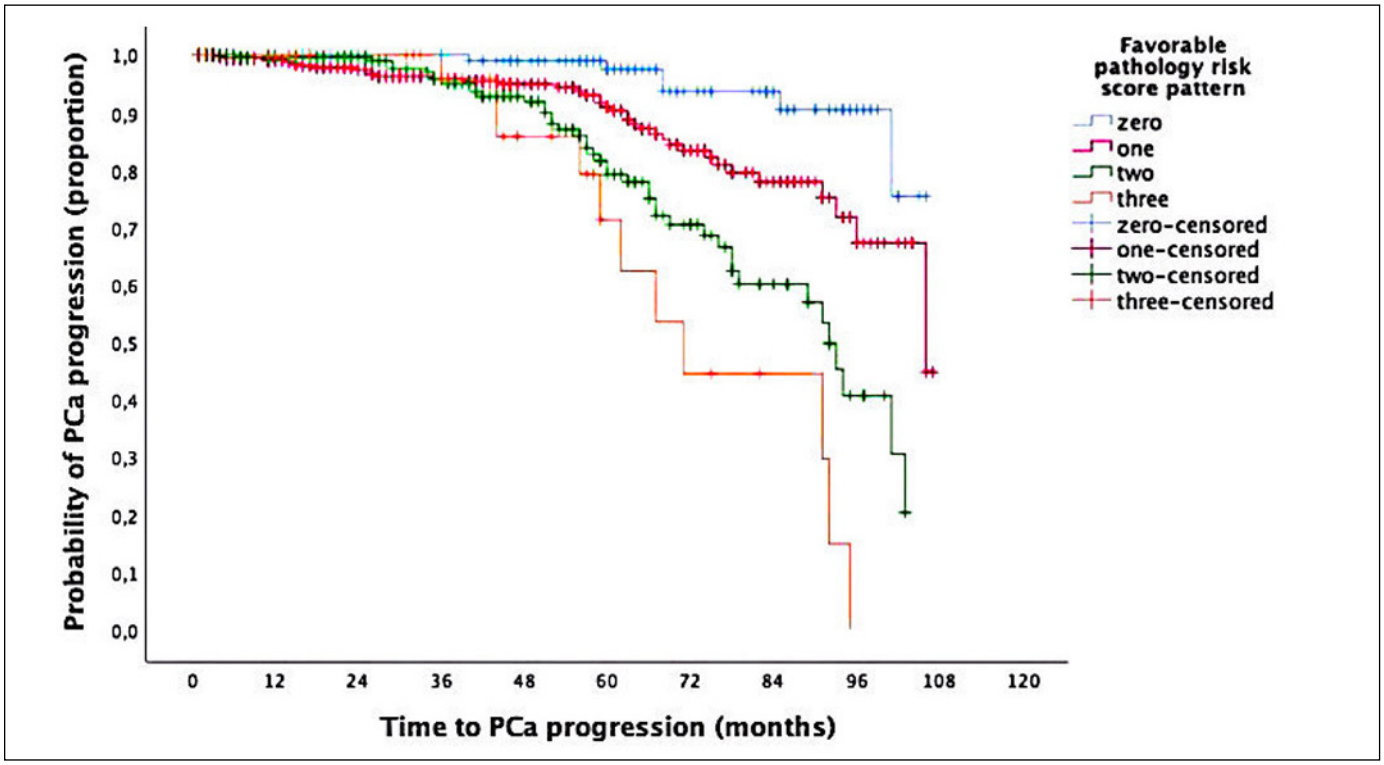

Figure 1. *Kaplan-Meyer survival risk curves of prostate cancer (PCa) progression in 757 patients treated with robotic surgery and stratified through favourable pathology risk score patterns in the surgical specimen. Accordingly, mean survival time of PCa progression decreased from favourable pathology pattern risk score zero (101.7 months; 95% CI: 98.6–104.9 months), one (94.5 months, 95% CI: 90.9–98.1 months), two (83.3 months; 95% CI: 78.6–87.9 months), and three (73.4 months; 95% CI: 63.3–83.5 months) with the difference being significant (Mantel-Cox log rank test: p <0.0001).*

The Cambridge Prognostic Group Classification reports mortality rates between 1.2% and 13.7% [1, 2, 9–12]. Surgically treated PCa may present with various pathological features, categorised as unfavourable (e.g. high-grade tumours with seminal vesicle invasion or lymph node invasion) or favourable [13–20]. Molecular biology and mpMRI are not yet reliable tools for resolving this issue in daily practice [1, 2, 5, 6, 9–20].

This study highlights new considerations for evaluating surgically treated PCa patients with favourable pathological features.

Higher pathology risk scores were associated with increased disease progression, regardless of EAU risk classes or Briganti's 2012 nomogram [21–24]. These findings require further confirmation.

Given these results, it is crucial to consider whether patients with favourable pathology should undergo more intensive follow-up or alternative management strategies. While current protocols primarily focus on high-risk features, our findings suggest that patients with intermediate favourable pathology risk scores may benefit from a more tailored surveillance approach. For example, patients with a pathology risk score of 2 or 3 could undergo closer PSA monitoring, earlier imaging assessment, or discussions about adjuvant therapy options, particularly in those with additional risk factors such as high PSA levels or adverse molecular markers. However, prospective studies are needed to validate these recommendations before modifying current standard protocols.

Grouping favourable pathology features into risk scores, as predicted by Briganti's 2012 nomogram and EAU classifications, may help improve patient counselling [1, 2, 21–24]. This study shows that patients with favourable features may have different prognostic risk patterns predictable preoperatively.

Although Briganti's 2012 nomogram independently predicted prognosis, it did not significantly differentiate between risk scores zero and one in multivariate analysis. This suggests that, for very low-risk patients, additional factors may be required to refine prognostic accuracy.

Briganti's 2012 nomogram is associated with the risk of several favourable pathologic prognostic patterns and disease progression. This may be because it combines several clinical variables into a risk score associated with an aggressive cancer biology phenotype.

However, the role of preoperative nomograms in risk stratification is evolving, particularly with the widespread use of mpMRI and targeted biopsies. These modern imaging techniques improve tumour localisation and risk assessment, potentially reducing the reliance on traditional nomograms. Despite this, our study demonstrates that Briganti's 2012 nomogram retains prognostic value, particularly in settings where mpMRI access remains variable or where additional risk stratification is needed beyond imaging findings.

Managing PCa is complex because EAU prognostic groups are not homogeneous [1, 2, 9–12]. Unrecognised aggressive cancers classified as indolent and vice-versa can lead to undertreatment or overtreatment [1, 2, 9–12].

The natural history of PCa is influenced by a combination of favourable and adverse pathology features that combine into patterns with varying prognostic impacts. This study showed that favourable pathology risk score zero had the best prognosis, while pattern risk score three (ISUP grade group 3 with extracapsular extension) had the worst. Briganti's 2012 nomogram predicted this outcome through EAU risk classes. These results have implications for clinical practice. These findings suggest that integrating pathology risk scores with existing nomograms may refine risk stratification and potentially influence postoperative management strategies.

This study has limitations, as it was retrospective, included several surgeons, and did not evaluate the extent of cancer invasion in each biopsy core or mpMRI findings. However, its strengths include the cohort size, the adequate number of lymph nodes counted when ePLND was performed, and its reflection of daily practice in urologic units.

CONCLUSIONS

Favourable pathology risk score characteristics clustered into risk score groups predicted by Briganti's 2012 nomogram by EAU risk classes showed prognostic impact. As the favourable pathology risk score increased, patients were more likely to progress, regardless of Briganti's 2012 nomogram and/or EAU risk class. Different patterns of favourable pathology risk scores impact prognosis and may alter treatment paradigms.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

FUNDING

This research received no external funding.

ETHICS APPROV AL STATEMENT

The Institutional Review Board of Univeristy of Verona approved the study.

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