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The 2012 Briganti nomogram predicts disease progression after surgery in high-risk prostate cancer patients

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ABSTRACT

Objectives: We tested whether the 2012 Briganti nomogram for the risk of pelvic lymph node invasion (PLNI) may represent a predictor of disease progression after surgical management in high-risk (HR) prostate cancer (PCa) patients according to the European Association of Urology.

Methods: Between January 2013 and December 2021, HR PCa patients treated with robot-assisted radical prostatectomy (RARP) and extended pelvic lymph node dissection (ePLND) were identified. The 2012 Briganti nomogram was evaluated as a continuous and categorical variable, which was dichotomized using the median. The risk of disease progression, defined as the event of biochemical recurrence and/or local recurrence/distant metastases was assessed by Cox regression models.

Results: Overall, 204 patients were identified. The median 2012 Briganti nomogram score resulted 12.0% (IQR: 6.0–22.0%). PLNI was detected in 57 (27.9%) cases. Compared to patients who had preoperatively a 2012 Briganti nomogram score ≤12%, those with a score >12% were more likely to present with higher percentage of biopsy positive cores, palpable tumors at digital rectal examination, high-grade cancers at prostate biopsies, and unfavorable pathology in the surgical specimen. At multivariable Cox regression analyses, disease progression, which occurred in 85 (41.7%) patients, was predicted by the 2012 Briganti nomogram score (HR: 1.02; 95%CI: 1.00–1.03; $p = 0.012$), independently by tumors presenting as palpable (HR: 1.78; 95%CI: 1.10.2.88; $p = 0.020$) or the presence of PLNI in the surgical specimen (HR: 3.73; 95%CI: 2.10–5.13; $p = 0.012$).

Conclusions: The 2012 Briganti nomogram represented an independent predictor of adverse prognosis in HR PCa patients treated with RARP and ePLND. As the score increased, so patients were more likely to experience disease progression, independently by the occurrence of PLNI. The association between the nomogram, unfavorable pathology and tumor behavior might turn out to be useful for selecting a subset of patients needing different treatment paradigms in HR disease.

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Introduction

Actually, prostate cancer (PCa) is an epidemic issue, as stated by the European Association of Urology (EAU) and the National Comprehensive Cancer Network (NCCN) whose task is to continuously update guidelines in order to address best treatment options thus avoiding overtreatments and regret of patients [1–4]. Accordingly, patients are classified into prognostic risk groups that are heterogenous and often not equivalent for the two systems, which consider management options varying from monitoring to active treatment strategies including radical prostatectomy (RP), eventually associated with extended pelvic lymph node dissection (ePLND), and radiation therapy (RT) [1,2].

Approximately from 17 to 31% of newly-diagnosed PCa patients have a high-risk (HR) localized or locally advanced disease at clinical presentation [5,6]. This risk class represents one of the most challenging for being heterogeneous and not equivalent among inclusion criteria for the EAU and the NCCN [1,2]. Additionally, despite these patients require active treatments, according to life expectancy issues, there is still no consensus regarding the optimal management, and

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currently different strategies, including both local and systemic treatments as a part of a multi-modal therapy seem to provide better cancer control outcomes [7]. In this context, more prognostic factors might turn useful in order to further stratify this group of patients to identify the most appropriate management.

In HR PCa patients candidates to RP, ePLND is strongly recommended by international guidelines due to the risk of pelvic lymph node invasion (PLNI) which ranges from 15 to 40% according to reports [1,2,7,8]. Several validated nomograms assessing the risk of PLNI are available [9–14]. Of these, the 2012 Briganti nomogram is one of the most used for its facility to compute [9]. Nevertheless, its role as a potential prognostic risk factor in this subset of patients, after surgery, has not yet been evaluated [1,2,5]. Accordingly, the aim of the present study was to test whether the 2012 Briganti nomogram score may also predict disease progression after surgery in a selected cohort of EAU HR PCa patients.

Materials and methods

Selection and evaluation of the EAU high-risk population

The present study was approved by internal Institutional Review Board. From January 2013 to December 2021, data on 204 EAU HR PCa patients treated with robot-assisted radical prostatectomy (RARP) and ePLND at the Department of Urology of the Integrated University Hospital of Verona were retrospectively evaluated. All patients were not under androgen blockade, did not undergo previous active treatments and had available follow-up data.

Patients were clinically evaluated for age (years), body mass index (BMI; kg/m^2), physical status according to the American Society of Anesthesiologist classification system [15], prostate specific antigen (PSA; ng/mL), prostate volume (PV, mL), biopsy positive cores (BPC; percentage), International Society of Urological Pathology (ISUP) grade group at prostate biopsy [16], and tumor stage according to the Tumor Node Metastasis (TNM) system (8th edition, 2017 version) [17]. Surgery, which was performed by five skilled surgeons, included RARP and ePLND with a template including external iliac, obturator, Cloquet's and Marcille's regions [18,19]. Two dedicated uropathologists assessed surgical specimens for tumor grade, stage, as well as for cancer invasion of surgical margins [20] and of counted pelvic lymph nodes; accordingly, tumors were graded according to the ISUP system and staged by the TNM system [16,17].

After surgery, patients were followed up according to guidelines and decisions of further treatments (adjuvant or at disease progression) were discussed in a multidisciplinary setting including urologists, radiation oncologists, and medical oncologists to optimize recommendations with patients' personal issues.

The outcome of interest was disease progression that was defined as the event of biochemical recurrence and/or PSA persistence and/or local recurrence and/or distant metastases.

Statistical analysis

Descriptive statistics included frequencies and proportions for categorical variables. Medians and interquartile ranges (IQR) were used for continuous variables. The 2012 Briganti nomogram score (%) was evaluated both as a continuous and categorical variable, which was dichotomized at the median. Associations of categorized 2012 Briganti nomogram with clinical and pathological factors were assessed by the logistic regression model (univariable and multivariable analysis).

The length of time between surgery and PCa progression or the last available follow-up was measured as time to event occurrence. Accordingly, non-adjusted Kaplan–Meier estimator curves were generated. The association of clinical and pathological factors with the risk of PCa progression was evaluated by the Cox proportional hazard regression models including univariable and multivariable analysis, which was performed according to the Wald's forward method for collinearity of the nomogram. Odds ratios (ORs), hazard ratios (HRs), and relative 95% confidence intervals (CIs) were computed. IBM-SPSS version 26.0 (IBM Corp., Armonk, NY, USA) was used for all analyses. All tests were two-sided with $p < 0.05$ considered to indicate statistical significance.

Results

Characteristics of the study population

The main characteristics of 204 HR PCa patients treated with RARP and ePLND are listed in Table 1. Median age was 67 (61–71) years. Preoperative ASA physical status was 1 in 15 (7.4%) patients, 2 in 163 (79.9%) patients, and 3 in 26 (12.7%) patients. Median 2012 Briganti nomogram score was 12.0% (6.0–22.0%). Anatomical staging of pelvic lymph nodes was performed in all cases and the median number of counted lymph nodes was 25 (19–32). PLNI was detected in 57 (27.9%) cases. Compared to patients who had preoperatively a 2012 Briganti nomogram score ≤12%, those who had a score >12% were more likely to present with higher percentage of BPC (58.8% vs. 28.5%), palpable tumors at digital rectal examination (78.8% vs. 54.3%), and high-grade cancers at prostate biopsies (70.7% vs. 51.4%). Furthermore, they were also more likely to harbor unfavorable pathology in the surgical specimen including tumors with ISUP grade group 4–5

Table 1. Descriptive statistics of the study population stratified according to the 2102 Briganti nomogram score (≤12% vs. >12%) and logistic regression models testing the association of clinical and pathological factors with the 2012 Briganti nomogram score.

	Overall $n = 204$	2012 Briganti nomogram score ≤ 12% $n = 105$ (51.5%)	2012 Briganti nomogram score > 12% $n = 99$ (48.5%)	Univariable analysis		Multivariable analysis	
				OR (95% CI)	P-value	OR (95% CI)	P-value
Clinical factors							
Age (years)	67 (61–71)	65 (60–70)	67 (62–71)	1.03 (0.99–1.08)	0.1	1.01 (0.96–1.09)	0.4
BMI (kg/m^2)	25.7 (24.2–28.4)	25.7 (24.0–28.4)	25.7 (23.8–28.4)	1.03 (0.95–1.12)	0.4	1.01 (0.89–1.15)	0.9
PV (mL)	40.0 (30.0–56.0)	40.0 (30.0–56.5)	40.0 (30.0–53.0)	1.00 (0.98–1.01)	0.6	1.00 (0.98–1.02)	0.9
PSA (ng/mL)							
≤20	159 (77.9)	86 (81.9)	73 (73.3)	Ref.	-	Ref.	-
>20	45 (22.1)	19 (18.1)	26 (26.3)	1.61 (0.83–3.15)	0.2	3.09 (0.94–10.17)	0.06
BPC (%)	42.8 (26.6–64.2)	28.5 (20.0–38.7)	58.8 (46.6–85.7)	1.09 (1.06–1.11)	**<0.001**	1.09 (1.06–1.12)	**<0.001**
Clinical tumor stage							
cT1c	69 (33.8)	48 (45.7)	21 (21.2)	Ref.	-	Ref.	-
cT2	135 (66.2)	57 (54.3)	78 (78.8)	3.13 (1.69–5.79)	**<0.001**	4.09 (1.66–10.08)	**0.002**
ISUP grade group at PBx							
ISUP ≤3	80 (39.2)	51 (48.6)	29 (29.3)	Ref.	-	Ref.	-
ISUP >3	124 (60.8)	54 (51.4)	70 (70.7)	2.28 (1.28–4.06)	**0.005**	6.40 (2.29–17.92)	**<0.001**
Clinical node stage							
cN0	152 (54.5)	75 (45.7)	77 (77.8)	Ref.	-	Ref.	-
cN1	52 (25.5)	30 (54.3)	22 (22.2)	0.71 (0.38–1.35)	0.3	1.59 (0.56–4.52)	0.4
Pathological factors							
ISUP grade group at RP							
ISUP ≤3	83 (40.7)	57 (54.3)	26 (26.3)	Ref.	-	Ref.	-
ISUP >3	121 (59.3)	48 (45.7)	73 (73.7)	3.33 (1.85–6.01)	**<0.001**	2.28 (1.20–4.34)	**0.012**
Pathological tumor stage							
pT2 (OC)	114 (55.9)	76 (72.4)	29 (27.3)	Ref.	-	Ref.	-
pT3a (ECE)	30 (14.7)	12 (11.4)	18 (18.2)	3.00 (1.31–6.87)	**0.009**	2.33 (0.98–5.53)	0.056
pT3b (SVI)	60 (29.4)	17 (16.2)	43 (43.4)	5.06 (2.54–10.02)	**<0.001**	3.41 (1.60–7.27)	**0.001**
Pathological node stage							
pN0	147 (72.1)	87 (82.9)	60 (60.6)	Ref.	-	Ref.	-
pN1	57 (27.9)	18 (17.1)	39 (39.4)	3.14 (1.64–6.01)	**0.001**	1.45 (0.68–3.10)	0.3
Surgical margins status							
Negative (R0)	136 (66.7)	78 (74.3)	58 (58.6)	Ref.	-	Ref.	-
Positive (R1)	68 (33.3)	27 (25.7)	41 (41.4)	2.04 (1.13–3.69)	**0.018**	1.50 (0.78–2.89)	0.2

Continuous variables are reported as medians (interquartile range), categorical factors as frequencies (percentages).

Abbreviations: OR, odds ratio; CI, confidence interval; BMI, body mass index; PV, prostate volume; PSA, prostate-specific antigen; BPC, biopsy positive cores; ISUP, International Society of Urological Pathology; PBx, prostate biopsies; RP, radical prostatectomy; OC, organ-confined; ECE, extra capsular extension; SVI, seminal vesicle invasion.

Values in bold indicate statistical significance set at $p < 0.05$.

(73.7% vs. 45.7%), extracapsular extension (18.2% vs. 11.4%), seminal vesicle invasion (43.4% vs. 16.2%), as well as PLNI (39.4% vs. 17.1%).

The prognostic impact of the 2012 Briganti nomogram on disease progression

Median follow-up was 61.0 (54.0–67.9) months. Disease progression occurred in 85 (41.7%) patients (Table 2). Patients who did experience disease progression presented a higher median 2012 Briganti nomogram score compared to those who did not experience progression (16.0% vs. 10.0%; Figure 1). Kaplan–Meier plots depicted PCa progression free-survival according to the 2012 Briganti nomogram score; here, median progression free survival was higher in patients with a nomogram score ≤12% compared to those with a nomogram score >12% (67.0 vs 52.0 months, $p < 0.001$; Figure 2). At multivariable Cox proportional hazards regression analysis, PCa progression was independently predicted by the 2012 Briganti nomogram (HR: 1.02; 95%CI: 1.00–1.03; $p = 0.012$), independently by tumors presenting as palpable (HR: 1.78; 95%CI: 1.10.2.88; $p = 0.020$) or by the presence of PLNI in the surgical specimen (HR: 3.73; 95%CI: 2.10–5.13; $p = 0.012$; Table 2). The distribution of the median 2012 Briganti nomogram score according to clinical tumor stage (palpable vs. not palpable tumors) and stratified by the occurrence of disease progression is shown in Figure 3.

The prognostic impact of the 2012 Briganti nomogram on PCa progression is summarized in Table 3. Accordingly, as the nomogram score increased, so patients were more likely to experience progression independently by presenting with unfavorable clinical factors, as well as harboring unfavorable pathology in the surgical specimen.

Discussion

The EAU HR PCa class is a heterogenous and controversial category requiring primary and often secondary treatments for the risk of disease recurrence and progression [5,7,21]. Likewise, surgically treated HR PCa patients have mortality rates that vary from 5.8% to 13.5% at 10 years, according to class 4 and 5 of the Cambridge Prognostic Group Classification, respectively [22,23]. However, not all HR PCa patients will experience disease progression, thus stressing the issue of identifying more prognostic factors. Accordingly, it has been shown that factors associated with disease progression include early biochemical

Table 2. Cox regression models testing the 2012 Briganti nomogram as a predictor of disease progression after surgery in 204 EAU high-risk prostate cancer (PCa) patients treated with robot-assisted radical prostatectomy and extended pelvic lymph node dissection.

	No PCa progression $n = 119$ (58.3)	PCa progression $n = 85$ (41.7)	Univariable analysis		Multivariable analysis (*)	
			HR (95% CI)	p-value	HR (95% CI)	p-value
Age (years)	65 (60–70)	67 (62–71)	1.05 (1.01–1.08)	**0.016**		
BMI (kg/m^2)	25.7 (24.4–28.1)	25.8 (24.0–29.2)	1.03 (0.97–1.09)	0.3		
PV (mL)	40.0 (30.0–55.0)	40.0 (31.2–56.0)	1.01 (1.00–1.03)	0.09		
PSA (ng/mL)						
≤20	104 (77.4)	55 (64.7)	Ref.	-		
>20	15 (12.6)	30 (35.3)	1.46 (0.93–2.30)	0.1		
BPC (%)	35.7 (25.0–58.3)	50.8 (44.0–65.0)	1.02 (1.01–1.03)	**<0.001**		
ISUP grade group at PBx						
ISUP ≤3	51 (42.9)	29 (34.1)	Ref.	-		
ISUP >3	68 (57.1)	56 (65.9)	1.08 (0.69–1.70)	0.7		
Clinical tumor stage						
cT1c	42 (35.3)	27 (31.8)	Ref.	-	Ref.	-
cT2	77 (64.7)	58 (68.2)	1.86 (1.16–2.96)	**0.010**	1.78 (1.10–2.88)	**0.020**
Clinical node stage						
cN0	86 (72.3)	64 (77.6)	Ref.	-		
cN1	33 (27.7)	19 (22.4)	0.90 (0.54–1.50)	0.7		
ISUP grade group at RP						
ISUP ≤3	66 (55.5)	17 (20.0)	Ref.	-		
ISUP >3	53 (44.5)	68 (80.0)	2.65 (1.56–4.53)	**<0.001**		
Pathological tumor stage						
pT2 (OC)	82 (68.9)	32 (37.6)	Ref.	-		
pT3a (ECE)	20 (16.8)	10 (11.8)	1.39 (0.68–2.83)	0.4		
pT3b (SVI)	17 (14.3)	43 (50.6)	2.61 (1.65–4.14)	**<0.001**		
Pathological node stage						
pN0	105 (88.2)	42 (49.4)	Ref.	-	Ref.	-
pN1	14 (11.8)	43 (50.6)	3.61 (2.33–5.57)	**<0.001**	3.73 (2.10–5.13)	**0.012**
Surgical margins status						
Negative (R0)	88 (73.9)	48 (56.5)	Ref.	-		
Positive (R1)	31 (26.1)	37 (43.5)	1.77 (1.14–2.73)	**0.010**		
2012 Briganti nomogram (%)	10.0 (5.0–19.0)	16.0 (7.0–29.5)	1.03 (1.01–1.04)	**<0.001**	1.02 (1.00–1.03)	**0.012**

(*) by Wald's forward method.

Abbreviations: EAU, European Association of Urology; HR, hazard ratio; CI, confidence interval; BMI, body mass index; PV, prostate volume; PSA, prostate-specific antigen; BPC, biopsy positive cores; ISUP, International Society of Urological Pathology; PBx, prostate biopsies; RP, radical prostatectomy; OC, organ-confined; ECE, extra capsular extension; SVI, seminal vesicle invasion.

Values in bold indicate statistical significance set at $p < 0.05$.

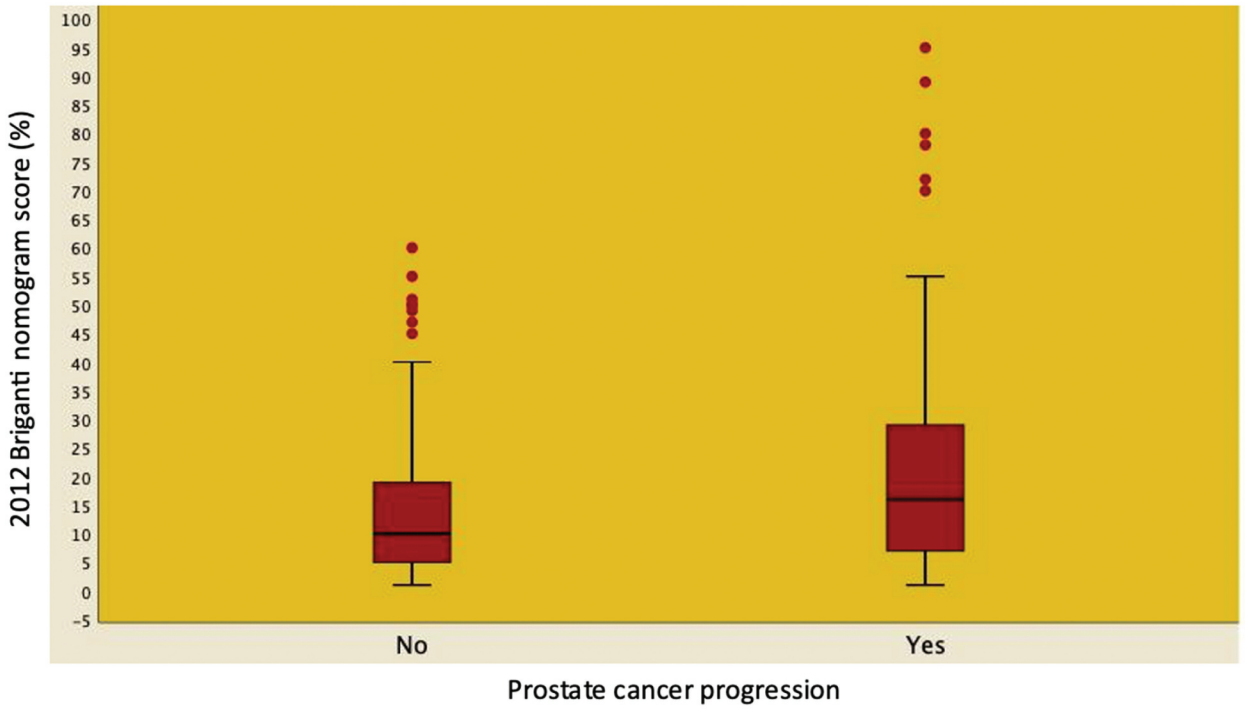

Figure 1. Box and whisker plots illustrating the distribution of the 2012 Briganti nomogram score predicting lymph node invasion stratified according to the occurrence of disease progression in 204 EAU high-risk patients treated with radical prostatectomy and extended pelvic lymph node dissection. Median risk score was significantly higher in patients experiencing disease progression compared to those who did not progress (16.0, IQR: 7.0–29.5 vs. 10.0, IQR 5.0–19.0; OR: 1.03; 95%CI: 1.01–1.04; *p <0.001*).

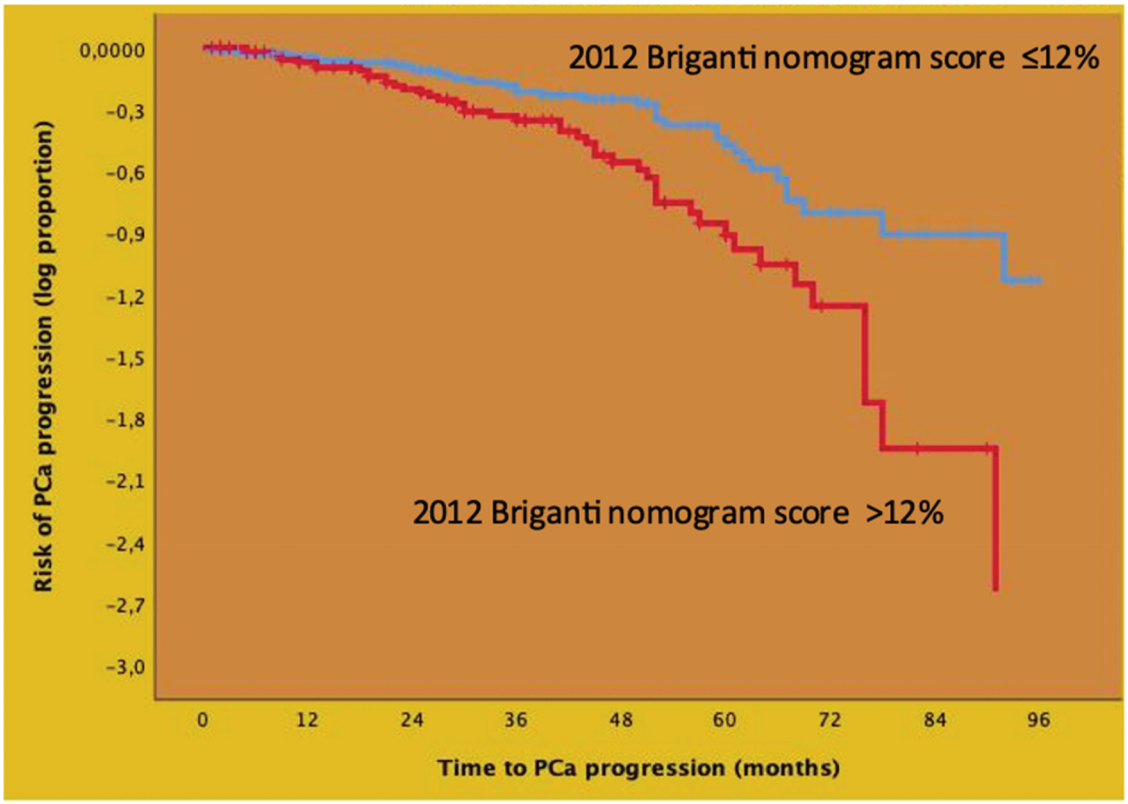

Figure 2. Kaplan-Meier plots depicting prostate cancer (PCa) progression – free survival in 204 EAU high – risk patients treated with robot-assisted radical prostatectomy and extended pelvic lymph node dissection according to the 2012 Briganti nomogram score (up to the median vs. above the median). Median PCa progression free survival was higher in patients exhibiting a score ≤ 12% (67.0, IQR: 59.1–4.3 months) compared to those exhibiting a score > 12% (52.0, IQR: 44.6–59.3 months) with the difference being statistically significant (Mantel-Cox log rank test: $p < 0.001$; univariable hazard ratio: 1.87, 95% CI: 1.21–2.87; $p = 0.005$).

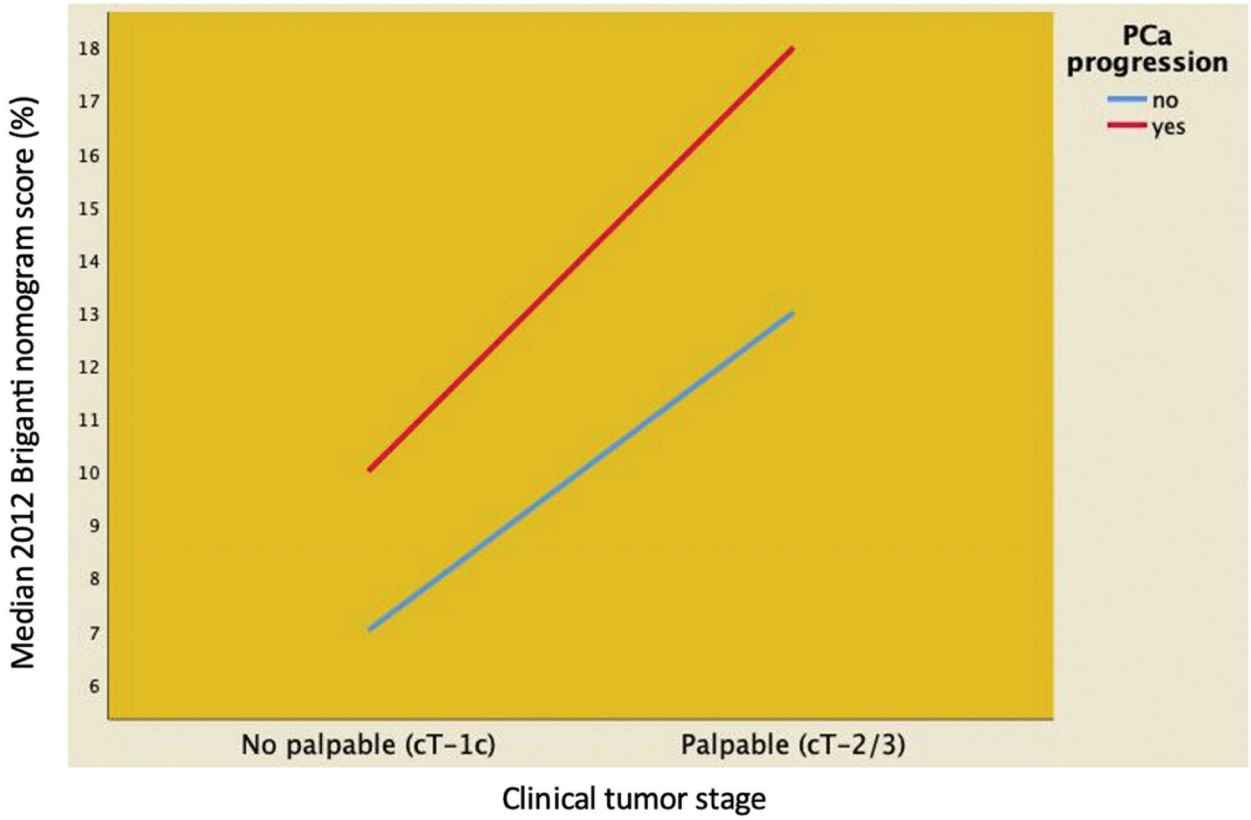

Figure 3. Distribution of median 2012 Briganti nomogram score predicting pelvic lymph node invasion stratified according to clinical tumor stage (palpable vs. not palpable tumors) and disease progression in 204 EAU high-risk prostate cancer patients treated with robot-assisted radical prostatectomy and extended pelvic lymph node invasion. Median 2012 Briganti nomogram score was higher in progressing patients, independently by clinical tumor stage.

Table 3. Summary of the prognostic impact of the 2012 Briganti nomogram score on prostate cancer progression in 204 EAU high-risk prostate cancer patients treated with robot-assisted radical prostatectomy and extended pelvic lymph node.

	HR (95% CI)	*P – value*
After adjustment for clinical factors	1.03 (1.01–1.04)	0.005
After adjustment for pathological factors	1.02 (1.01–1.03)	<0.001
After adjustment for all factors	1.02 (1.10–2.88)	0.020

Abbreviations: EAU, European Association of Urology; HR, hazard ratio; CI, confidence interval. See also Tables 1 and 2.

recurrence, unfavorable tumor grades, and PSA doubling time; nevertheless, multilevel nomograms could improve the accuracy of such prognostic factors [24,25]. The 2012 Briganti nomogram, which accounts for PSA, clinical tumor stage, primary and secondary Gleason Grade Group at prostate biopsies, and percentage of BPC, still stand as one of the most effective tools for predicting PLNI [9], for those including multiparametric magnetic resonance imaging (mpMRI) findings are not always reproducible [11,26].

In our study, we have shown that the 2012 Briganti nomogram score was an independent predictor of PCa progression in a cohort of patients presenting with EAU HR disease treated at a tertiary referral center. Accordingly, as the nomogram score increased, so patients were more likely to experience disease progression; conversely, patients presenting with unfavorable tumor stage and/or harboring PLNI but having a lower median nomogram score were less likely to undergo disease progression.

The findings of the present study are a novelty and may have important clinical implications. In HR PCa including both localized and locally advanced disease, although surgery is one of the main primary treatments, appropriate selection of patients still remains a challenging task because of implications on paradigm treatments, which include local and systemic treatments within a multidisciplinary integrated approach [7,21,27]. Although blood and tissue novel biomarkers can help for selecting patients, they are still far from everyday clinical practice [28]. Accordingly, our results have shown that EAU HR PCa patients can be stratified according to the 2012 Briganti nomogram score, which was higher in patients who were more likely to experience progression, independently by presenting with palpable tumors and/or harboring PLNI. Specifically, a nomogram score above 12% predicted adverse prognosis after associating with unfavorable pathology in the surgical specimen. However, confirmatory studies are required. Likewise, our results showed that it is possible to cluster EAU HR PCa patients at clinical presentation according to the score of the nomogram.

In our study, we showed that 2012 Briganti nomogram predicted the natural history of PCa after tracing patterns of unfavorable pathology in the surgical specimen. Accordingly, as the risk score increased, so patients not only were more likely to have undifferentiated cancers invading seminal vesicle and metastasizing to pelvic lymph nodes but also to experience disease progression. In our opinion, these findings might be explained by the fact that the nomogram includes several clinical variables, which interact and integrate with each other at a high-dimensional level, thus allowing the identification of cancers that will show a malignant behavior because of the dynamic genetic instability structuring these cancers, as well. Nevertheless, these hypotheses need to be tested by controlled studies.

Despite its novelty, the present study is not devoid of limitations. First, it is a retrospective study. Second, surgical procedures were performed by different surgeons, thus reflecting real-world practice but possibly affecting outcomes assessment. Third, MRI findings were not evaluated for not being available in all cases; therefore, we did not use the updated version of the nomogram, which specifically accounts for clinical stage and Gleason Grade Group based on MRI data, as well as for maximum diameter of the targeted index lesion at MRI, demonstrating higher accuracy compared to other existing tools [11]. Nevertheless, our study has strengths such as anatomical staging of pelvic lymph nodes that was extensive and appropriate for evaluating oncological results of the EAU HR category [29,30].

Conclusions

The 2012 Briganti nomogram represented an independent predictor of disease progression in EAU HR PCa patients treated with RARP and ePLND at a tertiary referral center. Accordingly, as the risk score increased, so patients were more likely to experience disease progression, independently by the occurrence of PLNI. The association of the nomogram with unfavorable pathology and tumor behavior turns out to be useful for selecting subset of patients needing different treatment paradigms in high-risk disease.

Disclosure statement

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All authors read and approved the final version of the manuscript.

Data availability statement

All data generated or analyzed during this study are included in this article. Further enquires can be directed to the corresponding author.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by our Institutional Review Board. Data were collected prospectively but evaluated retrospectively; as such, Ethical Committee Approval was not required.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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