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Serum (-2)proPSA/freePSAratio, (-2)proPSA/freePSA density, prostate health index, and prostate health index density as clues to reveal postoperative clinically significant prostate cancer in men with prostate-specific antigen 2–10 ng/mL

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Abstract

Background: There is a strong clinical need to fill the gap of identifying clinically significant prostate cancer (csPCa) in men with prostate-specific antigen (PSA) gray zone values. Promising, but not definitive results have been obtained using PSA derivatives such as prostate health index (PHI) and PHI density (PHID) and the percentage (-2)proPSA/free PSA (%p2PSA/fPSA). Thus, this study aimed to compare the diagnostic value of PHI, PHID, %proPSA/fPSA, and (-2)proPSA/freePSA density (-2pPSA/fPSAD) for csPCa in the patients with PSA within 2–10 ng/mL.

Methods: Serum samples and clinicopathological features were prospectively collected from 142 patients who underwent robot-assisted radical prostatectomy between September 2021 and December 2023. According to the inclusion criteria, the patients with total PSA within 2 and 10 ng/mL and negative or suspicious digital rectal examination were enrolled. We used two different classifications for csPCa: 1) patients with Gleason score (GS) ≥ 7(4 + 3) and 2) patients with GS ≥ 7(3 + 4). The receiver operating characteristic curves and the area under the curve (AUC) values were used to assess the diagnostic performance.

Results: Of the 142 men included, 116 (82%) patients were diagnosed with csPCa as GS ≥ 3 + 4 and 107 (75%) defined as csPCa as GS ≥ 7(4 + 3), respectively. We found that p2PSA/fPSA, p2PSA/fPSAD, PHI, and PHID were significantly higher in csPCa classified as GS ≥ 7(3 + 4) as well as GS ≥ 7(4 + 3), with *p*-values 0.027, 0.054, 0.0016, and 0.0027, respectively. AUCs of the analyzed variables were higher when used to predict csPCa as GS ≥ 6 compared to csPCa as GS ≥7(4 + 3), with an AUC equal, respectively, to 0.679 (95% CI: 0.571–0.786), 0.685 (95% CI: 0.571–0.799), 0.737 (95% CI: 0.639–0.836), and 0.736 (95% CI: 0.630–0.841) in the first subgroup and with an AUC equal, respectively, to 0.653 (95% CI: 0.552–0.754), 0.665 (95%

CI: 0.560–0.770), 0.668 (95% CI: 0.568–0.769), and 0.670 (95% CI: 0.567–0.773) in the second, respectively. Both PHID and p2PSA/fPSAD allowed improvement in the diagnostic accuracy with respect to PHI and p2PSA/fPSA ratio, however the differences were not statistically significant ($p = 0.409$, 0.180 for csPCa as G ≥ Gleason grade (GG) 2 and 0.558 and 0.087 for csPCa as G ≥ GG3, respectively). We found that PHI, PHID, p2PSA/fPSA ratio, and p2PSA/fPSAD showed higher sensitivity, specificity, and positive predictive value when used to predict csPCa as GG ≥ 2, whereas negative predictive value of all four parameters was higher when used to predict GG ≥ 3.

Conclusions: In men with a PSA level between 2 and 10 ng/mL, PHI and PHID, p2PSA/fPSA, and p2PSA/fPSAD showed good diagnostic performance for postoperative csPCa. However, PHID and p2PSA/fPSAD had a small advantage over PHI which needs to be further investigated for the reduction of unnecessary surgical interventions. This finding suggests that it could be a promising biomarker for making the treatment-decision strategy.

KEYWORDS

PHI density, prostate cancer, prostate health index (PHI), radical prostatectomy

1 | INTRODUCTION

In the last decades, prostate-specific antigen (PSA) widespread use caused a significant rate of overdiagnosis and overtreatment which not only deplete national health system resources, but also are detrimental for patients' quality of life due to radical prostatectomy side effects as erectile disfunction and incontinence.[1] Thus, there is an urgent clinical need to identify novel tools to help urologists to choose the best therapeutic option for each patient. To address this aim it is important to have tools to stratify the risk category of the patient at initial diagnosis to match cancer aggressiveness with treatment invasiveness.

The isoform (-2)proPSA (p2PSA), which is one of the truncated isoform of proPSA, is a widely studied serum marker for the early diagnosis of prostate cancer (PCa).[2] p2PSA derivatives, such as percentage of p2PSA (%p2PSA) and prostate health index (PHI), are superior to percentage free PSA (%fPSA) in the identification of clinically significant PCa (csPCa).[3] In addition, several authors showed that the use of PHI density (PHID) further improve the accuracy of patients' stratification.[4] However, the conclusions from published studies remain debated.[5] In a single-center study including a large Caucasian cohort of 1446 men PHID showed only a small improvement compared with PHI alone in predicting csPCa at biopsy in patients with PSA in the gray zone.[6]

One large study with more than 1600 biopsied patients reported no additional clinical net benefit using prostate volume (PV) in addition to PHI.[7]

Thus, further studies are encouraged to investigate the diagnostic performance of PHID compared to PHI and p2PSA/%fPSA in predicting csPCa, especially in patients with PSA in the gray zone. To address this issue, we compared the ability of PHI, PHID, %p2PSA/fPSA, and p2PSA/fPSA density (fPSAD) to discriminate between indolent and csPCa classified both as Gleason grade (GG) ≥ 2 and GG ≥ 3.

2 | MATERIALS AND METHODS

2.1 | Study population

This study was a prospective, observational single-centre study in a radical prostatectomy cohort at the University Hospital Federico II in Naples between September 2021 and December 2023.

Serum samples and clinicopathological features were prospectively collected from each patient who underwent robot-assisted radical prostatectomy.

The inclusion criteria were patients with PSA values between 2 and 10 ng/mL and negative or suspicious digital rectal examination (DRE).

The exclusion criteria were: 1) history of other cancers, 2) factors affecting PSA levels (surgical interventions, use of 5α-reductase inhibitors, acute urinary tract infection in the previous 3 months), and 3) patients with missing diagnostic data.

A total of 142 patients were finally enrolled in this study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The protocol for this study was approved by the Ethics Committee of the University Hospital Federico II in Naples (approval No. 118/20). All the participants gave informed consent before taking part in this study. Preoperative PV was measured by transrectal ultrasound (TRUS) of the prostate using an ellipsoid formula.

The surgical specimens were reviewed by a pathologist with 15 years of experience specializing in uro-oncology and reported according to the guidelines of the 2014 International Society of Urological Pathology Consensus Conference.[8] GG1 is equivalent to a Gleason score (GS) of 3 + 3 = 6, GG2 is equivalent to GS 3 + 4 = 7, GG3 is equivalent to GS 4 + 3 = 7, GG4 is equivalent to GS 4 + 4 = 8, and GG5 is equivalent to GS 9–10. In our study, csPCa was defined as GG ≥ 2 or GG ≥ 3.

2.2 | Blood collection and PSA molecular forms measurements

Blood samples were collected immediately before robot-assisted radical prostatectomy (RARP), processed within 3 h, and serum were stored at −80°C. Sera were analyzed using the Access 2 immunoassay system (DxI 800; Beckman Coulter). Total PSA (tPSA), fPSA, and p2PSA were measured according to Hybritech standards. PHI was calculated according to the following formula PHI = p2PSA/fPSA × √tPSA, PHID was calculated as PHID = PHI/PV, p2PSA/fPSAD (p2/fPSAD) as (p2PSA/fPSA)/PV.

2.3 | Statistical analysis

Continuous variables were reported as median (interquartile range [IQR]) and mean (standard deviation [SD]). Statistical differences were assessed using an independent Student's *t*-test. Univariate analysis was used to determine the association between measured variables and csPCa. The diagnostic performance was evaluated using the area under the receiver operating characteristic (ROC) curve, and the DeLong test was used to examine the differences between area under the curves (AUCs). The sensitivity, specificity, and positive and negative predictive values (PPV and NPV) of the evaluated variables were calculated at different cutoff values for the detection of csPCa. Statistical analyses were performed using IBM SPSS Statistics (version 23.0; IBM Corp.) and R studio. Statistical significance was set at a two-sided *p*-value < 0.05. Statistical analysis were reported according to Assel et al. guidelines.[9]

3 | RESULTS

3.1 | Study population

The overall cohort consisted of 142 patients with a mean age of 67 ± 6.5 years (y), median 68 (IQR 62–73 y). Mean PSA was equal to 5.82 ± 1.92 ng/mL (range: 2–10 ng/mL). Mean %fPSA was equal to 15.42 % ± 0.6. Median PHI was equal to 53.7 (range: 40.2–74.1).

Among these, we analyzed 109 patients (77%) with pT2, 116 (82%) patients with GS ≥7(3 + 4). We classified patients as non-csPCa versus csPCa using two different criteria: GG ≥ 2 and GG ≥ 3.

All the characteristics of the study population are shown in Table 1.

TABLE 1 Characteristics of the study population.

Patients	
N	142
Age (y) median (IQR)	68 (62.52–72.67)
Age (y) mean (SD)	67 (±6.51)
Biomarkers	Values
PSA (ng/mL)	
Median (IQR)	5.62 (4.38–7.30)
Mean (SD)	5.82 (±1.92)
%freePSA	
Median (IQR)	14.71 (10.76–19.42)
Mean (SD)	15.42 (±0.06)
ProPSA (pg/mL)	
Median (IQR)	16.86 (12.55–27.82)
Mean (SD)	22.29 (±23.49)
PSA density (ng/mL^2)	
Median (IQR)	0.14 (0.08–0.19)
Mean (SD)	0.17 (±0.12)
PHI	
Median (IQR)	53.74 (40.18–74.11)
Mean (SD)	61.54 (±33.19)
%ProPSA/freePSA	
Median (IQR)	2.31 (1.82–2.95)
Mean (SD)	2.55 (±1.18)
PHI density	
Median (IQR)	1.35 (0.80–2.64)
Mean (SD)	1.84 (±1.53)
ProPSA/freePSA density ×10^3	
Median (IQR)	1.36×10^3 (0.34–1.02)
Mean (SD)	0.76×10^3 (±0.59)
Grading	
GG	***N* (%)**
GG1	26 (18)
GS2	9 (6)
GG3	14 (10)
GG4	79 (56)
GG5	14 (10)
Pathologic stage	
pT	***N* (%)**
1c	0 (0)
2	109 (76.76)
3×	3 (2.11)

(Continues)

TABLE 1 (Continued)

Pathologic stage	
pT	***N* (%)**
3a	22 (15.49)
3b	5 (3.52)
3c	0 (0)
4	3 (2.81)
Total	142 (100)

Abbreviations: GG, Gleason grade; GS, Gleason score; IQR, interquartile range; PSA, prostate-specific antigen; SD, standard deviation.

TABLE 2 %p2PSA/fPSA, p2PSA/PSAD, PHI, and PHID mean values in clinically significant PCa defined as GG ≥ 2.

Test	GG ≤ 2 (mean ± SD)	GG ≥ 2 (mean ± SD)	*p*-Value
%P2PSA/fPSA	2.15% (±1.22)	2.64% (±1.16)	0.0540
P2PSA/fPSAD	0.45 (±0.34)	0.83 (±0.61)	0.0027*
PHI	48.49 (±22.89)	64.46 (±34.47)	0.0266*
PHID	1.00 (±0.66)	2.04 (±1.60)	0.0016*

Abbreviations: GG, Gleason grade; fPSA, free prostate-specific antigen; p2PSA, (-2)proPSA; p2PSA/fPSAD, p2PSA/fPSA density; PCa, prostate cancer; PHID, PHI density; SD, standard deviation.
*$p < 0.05$.

3.2 | Diagnostic performance of p2PSA/fPSA, p2PSA/fPSAD, PHI, and PHID to discriminate csPCa as GG ≥ 2

A clinically significant PCa defined as GG ≥ 2 was observed in 116 patients (82%).

PHI, the ratio between p2PSA and fPSA, PHID, and p2PSA/fPSAD mean values were significantly higher in csPCa with *p*-values 0.027, 0.054, 0.0016, and 0.0027, respectively (Table 2).

PHI as well as the ratio between p2PSA and fPSA, PHID, and p2PSA/fPSAD presented a significant association with the presence of csPCa at surgery with an AUC equal, respectively, to 0.679 (95% CI: 0.571–0.786), 0.685 (95% CI: 0.571–0.799), 0.737 (95% CI: 0.639–0.836), and 0.736 (95% CI: 0.630–0.841) (Figure 1). However, the difference between PHI, PHID, the ratio between p2PSA and fPSA and p2PSA/fPSAD *p* score was no longer statistically significant ($p = 0.4092$ and 0.5581, respectively).

Table 3 shows cutoff, PPV and NPV of PHI, PHID, the ratio between p2PSA and fPSA and p2PSA/fPSAD based on the postoperative GS to define csPCa defined as GG ≥ c2. PHI cutoff was 51 with a sensitivity of 64%, a specificity of 73%, a PPV of 91% and a NPV of 31%; PHID cutoff was 0.81 with a sensitivity of 80%, a specificity of 61%, a PPV of 90% and a NPV of 41%; the ratio between p2PSA and fPSA cutoff was 2.1 with a sensitivity of 68%, a specificity of 73%, a PPV of 92% and a NPV of 34%; p2PSA/fPSAD cutoff was 0.36 with a sensitivity of 80%, a specificity of 61%, a PPV of 90% and a NPV of 41%.

3.3 | Diagnostic performance of p2PSA/fPSA, p2PSA/fPSAD, PHI, and PHID to discriminate csPCa as GG ≥ 3

A clinically significant PCa defined as GG ≥ 3 was observed in 107 patients (75%).

PHI, the ratio between p2PSA and fPSA, PHID, and p2PSA/fPSAD mean values were significantly higher in csPCa with *p*-values 0.0171, 0.0342, 0.0049, and 0.0076, respectively (Table 4).

PHI as well as the ratio between p2PSA and fPSA, PHID, and p2PSA/fPSAD showed a significant association with the presence of csPCa at surgery with an AUC equal, respectively, to 0.653 (95% CI: 0.552–0.754), 0.665 (95% CI: 0.560–0.770), 0.668 (95% CI: 0.568–0.769), and 0.670 (95% CI: 0.567–0.773) (Figure 2). However, the difference between PHI, PHID, the ratio between p2PSA and fPSA and p2PSA/fPSAD was no longer statistically significant ($p = 0.1801$ and 0.0871, respectively).

PHI cutoff was 51 with a sensitivity and a specificity of 63%, a PPV of 84% and NPV of 36%, PHID cutoff was 0.82 with a sensitivity of 79% and a specificity of 51%, a PPV of 83% and a NPV of 45%, the ratio between p2PSA and fPSA cutoff was 2.1 with a sensitivity of 69% and a specificity of 66%, a PPV of 86% and NPV of 41%, and p2PSA/fPSAD cutoff was 0.36 with a sensitivity of 79% and a specificity of 48%, a PPV of 82% and a NPV of 43% to discriminate between GG ≥ 3 (Table 5).

4 | DISCUSSION

Patients with indolent PCa have therapeutic options other than surgery, including watchful waiting and active surveillance. These noninvasive approaches are very impactful treatment alternatives as associated with no side effects detrimental to quality of life and high 5 and 10 years overall and cancer-specific survival rates.[10]

Thus, early detection of csPCa is extremely relevant to choose treatment strategy.[11]

In this study, we analyzed the diagnostic performance of p2PSA/fPSA, p2PSA/fPSAD, PHI, and PHID in the detection of csPCa.

Of the 142 men included, 116 (82%) patients were diagnosed with csPCa as GG ≥ 2 and 107 (75%) defined as csPCa as GG ≥ 3, respectively. We found that p2PSA/fPSA, p2PSA/fPSAD, PHI, and PHID were significantly higher in csPCa classified as GG ≥ 2 as well as GG ≥ 3.

AUCs of the analyzed variables were higher when used to predict csPCa as GG ≥ 2 compared to csPCa as GG ≥ 3. Both PHID and p2PSA/fPSAD allowed improvement in the diagnostic accuracy with respect to PHI and p2PSA/fPSA ratio, however the differences were not statistically significant. We found that PHI, PHID, p2PSA/fPSA ratio, and p2PSA/fPSAD showed higher sensitivity, specificity, and PPV when used to predict csPCa as GG ≥ 2, whereas NPVs of all four parameters were higher when used to predict GG ≥ 3.

Our findings confirmed that p2PSA/fPSA ratio and PHI, it could be used at initial diagnosis as one of the tools useful to stratify the risk category of PCa and choose the best therapeutic option for each patient.

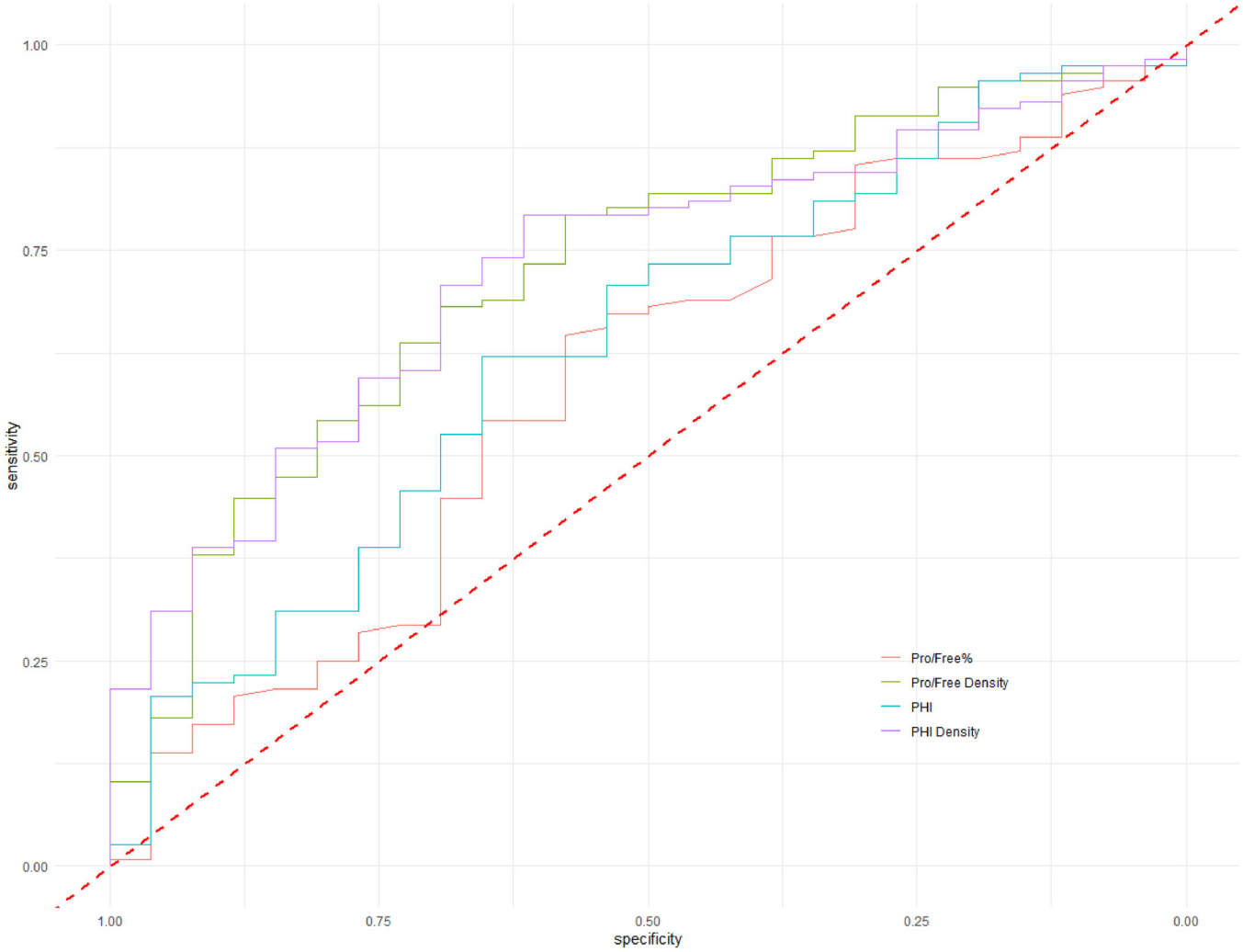

FIGURE 1 Receiver operating characteristic curve analysis for prostate health index (PHI), PHI density, (-2)proPSA/free prostate-specific antigen (p2PSA/fPSA) ratio, p2PSA/fPSA density to predict clinically significant prostate cancer at radical prostatectomy as G ≥ GG2. Red dotted line refers to the useless classifier in which the false positive rate (1—specificity) equals the true positive rate (sensitivity). GG2, Gleason grade 2. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Cutoff, sensitivity, specificity, PPV, and NPV of p2PSA/fPSA %, p2PSA/fPSAD, PHI, and PHID in csPCa as GG ≥ 2.

Test	Cut off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
%P2PSA/fPSA	>2.07%	68.10	73.08	91.86	33.93
P2PSA/fPSAD	>0.36	80.17	61.54	90.29	41.02
PHI	>51.14	63.79	73.08	91.36	31.15
PHID	>0.81	80.17	61.54	90.29	41.02

Abbreviations: csPCa, clinically significant prostate cancer; fPSA, free prostate-specific antigen; NPV, negative predictive value; p2PSA, (-2)proPSA; p2PSA/fPSAD, p2PSA/fPSA density; PHI, prostate health index; PHID, PHI density; PPV, positive predictive value.

PHI combines the ratio p2PSA/fPSA and √PSA, it was developed to improve the specificity of PSA and was approved by the FDA for PCa in 2012[12]. Several authors reported the clinical benefit of p2PSA/fPSA ratio and PHI to discriminate PCa from benign prostatic hyperplasia in the clinical setting of men with PSA levels between 2 and 10 ng/mL and a negative DRE.[13] More recently, some authors showed that these PSA derivatives were significantly higher in csPCa defined based on postoperative grading.[14,15]

PV is a relevant factor in the interpretation of PSA and PSA derivatives. Filella et al. demonstrated that ROC-AUC of PHI for PCa diagnosis was 0.818 when the PV was lower than 35 cc, but when

the PV was within 36 and 50 cc and more than 50 cc, AUC decreased to 0.716 and 0.654, respectively.[16]

For the first time in 2014, by analogy with PSA density, PHID was introduced.[17] Tosoian et al.[18] evaluated the ability of PHID in 118 men underwent first biopsy showing that PHID had the highest ability to identify csPCa (AUC 0.84), allowing to avoid 38% of unnecessary biopsies and missing only 2% of csPCa.[19]

However, contrasting findings have been reported on the ability of PHI and PHID to detect csPCa defined after radical prostatectomy.[20]

In our study, PHID and p2PSA/fPSAD showed the highest AUC for csPCa defined with both classification (for csPCa as GG ≥ 2, AUC 0.737, 0.736; for csPCa as GG ≥ 3, AUC 0.668, 0.670, respectively), but did not significantly differ from that of PHI and p2PSA/fPSAratio (for csPCa as GG ≥ 2, $p = 0.409$, 0.180 and for csPCa as GG ≥ 3, $p = 0.558$, 0.087, respectively). Further studies on larger population are needed to better address this issue. Notably, the diagnostic performance of all parameters was better when used to discriminate between non-csPCa versus csPCa stratified as GG ≥ 2 than GG ≥ 3, with higher sensitivity, specificity, and PPV.

Furthermore, there is still no consensus on the optimal p2PSA/fPSA, p2PSA/fPSAD, PHI, and PHID cutoff value. We found optimal

TABLE 4 Ratio between %p2PSA/fPSA, p2PSA/PSAD, PHI, and PHID mean values in clinically significant PCa defined as GG ≥ 3

Test	GG ≤ 3 (mean ± SD)	GS ≥ G3 (mean ± SD)	*p*-Value
%P2PSA/fPSA	2.19 (±1.12)	2.67 (±1.18)	0.0342*
P2PSA/fPSAD	0.53 (±0.38)	0.84 (±0.62)	0.0076*
PHI	49.94 (±22.07)	65.33 (±35.33)	0.0171*
PHID	1.22 (±0.85)	2.05 (±1.64)	0.0049*

Abbreviations: fPSA, free prostate-specific antigen; GG, Gleason grade; p2PSA, (-2)proPSA; p2PSA/fPSAD, p2PSA/fPSA density; PCa, prostate cancer; PHID, PHI density.

*$p < 0.05$.

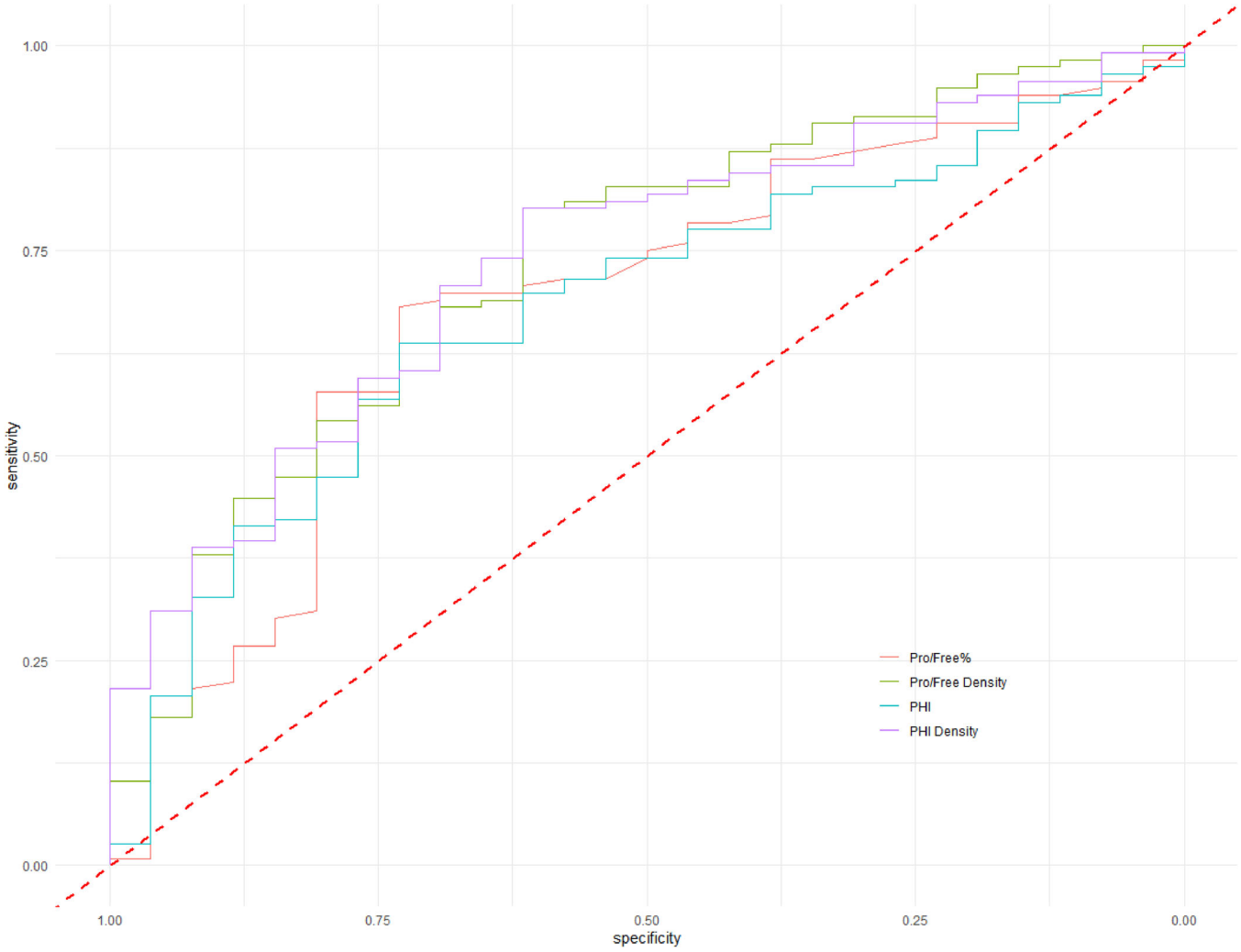

FIGURE 2 Receiver operating characteristic curve analysis for prostate health index (PHI), PHI density -2proPSA/free prostate-specific antigen (p2PSA/fPSA) ratio, p2PSA/fPSA density to predict clinically significant prostate cancer at radical prostatectomy as G ≥ GG3. Red dotted line refers to the useless classifier in which the false positive rate (1−specificity) equals the true positive rate (sensitivity). [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 5 Cutoff, sensitivity, specificity, PPV, and NPV of p2PSA/fPSA %, p2PSA/fPSAD, PHIand PHID in csPCa as GG ≥ 3.

Test	Cutoff	Sensitivity (%)	Specificity (%)	PPV(%)	NPV (%)
%P2PSA/fPSA	>2.07%	69.16	65.71	86.05	41.07
P2PSA/fPSAD	>0.36	79.44	48.57	82.52	43.59
PHI	>51.14	63.55	62.86	83.95	36.07
PHID	>0.82	79.44	51.43	83.33	45.00

Abbreviations: csPCa, clinically significant prostate cancer; fPSA, free prostate-specific antigen; GG, Gleason grade; NPV, negative predictive value; p2PSA, (-2)proPSA; p2PSA/fPSAD, p2PSA/fPSA density; PHID, prostate health index density; PPV, positive predictive value.

cutoff to detect csPCa in a cohort of radical prostatectomy patients, which could be used to stratify patients for risk category at initial diagnosis, avoiding unnecessary biopsies without missing aggressive cancers.

Comparable results were obtained in 144 Asian patients who underwent radical prostatectomy.[21] Accordingly, Garrido et al. showed that when applying the biomarker cutoff that allowed for approximately 90% of diagnostic sensitivity for csPCa, 26.3% of unnecessary biopsies could be avoided at PHID ≥ 0.49.[22] In a study by Chiu et al., at 90% sensitivity, 43.7% of unnecessary biopsies could be avoided when the PHID was >0.67.[23] Boo et al.[19] showed that with a cutoff of PHID ≥ 0.91, PHID had a 56.2% specificity, and 49.3% of unnecessary biopsies could be avoided at the cost of 8.3% of csPCa. In this study, when applying the optimal biomarkers cutoffs, the PPV of PHI, PHID, p2PSA/fPSA, p2PSA/fPSAD was 91%, 90%, 92%, and 90% for csPCa, respectively. This is probably due to the high incidence of csPCa in our study population with both classifications. However, the NPV was relatively low at approximately 31%–45% for csPCa. These real descriptors of the diagnostic test performance are expected to improve through machine learning approach on large population in the future.

To the best of our knowledge this is the first report on the ability of p2PSA/fPSA ratio density to detect csPCa. We found that it can increase diagnostic performance of p2PSA/fPSA ratio, suggesting it is worth of further investigation as tool to risk stratification in PCa patients.

This study had several limitations. First, an inherent selection bias may be due to the retrospective design of a study involving a single hospital, even if we analyzed a prospectively collected database that mirrored real-world clinical practices. Second, the sample size of the cohort was limited; therefore, the diagnostic performances need further validation with a larger cohort to confirm the findings. Third, in our study, the PV was estimated using an ellipsoid formula via TRUS, since prostate weight of the radical prostatectomy specimen and measured volume from the MRI were not available. This point is important, since some differences may occur depending on the method used to measure PV and this must be considered when interpreting the diagnostic performance of the four variables. Despite these limitations, our study has an intrinsic strength due to the availability of a cohort including more than 100 patients undergone radical prostatectomy, allowing the analysis of the postoperative outcomes.

5 | CONCLUSIONS

In men with a PSA level between 2 and 10 ng/mL, PHI and PHID, p2PSA/fPSA, and p2PSA/fPSAD showed good diagnostic performance for postoperative csPCa. However, PHID and p2PSA/fPSAD had a small advantage over PHI which needs to be further investigated for the reduction of unnecessary surgical interventions. This is particularly supported by the evidence that the four analyzed PSA derivatives performed slightly better when used to discriminate between non-csPCa versus csPCa stratified as GG ≥ 2. Therefore, they can be used as a triaging test in a clinical setting to preselect the risk of csPCa and reduce the number of unnecessary radical prostatectomies and the associated detrimental side-effects. Based on this preliminary findings, further studies should be conducted to investigate whether a combination of serum biomarkers and the result of multiparametric MRI can more clearly predict the risk of postoperative csPCa.

AUTHOR CONTRIBUTIONS

Matteo Ferro: Supervision; manuscript writing/editing. **Felice Crocetto**: Data collection and management. **Evelina La Civita**: Data collection and management. **Mariano Fiorenza**: Data collection and management. **Giuseppe Jannuzzi**: Data analysis. **Gianluigi Carbone**: Data collection and management. **Rosa Sirica**: Data collection and management. **Enrico Sicignano**: Data collection and management. **Giovanni Pagano**: Data collection and management. **Ciro Imbimbo**: Supervision. **Daniela Terracciano**: Supervision; protocol/project development; manuscript writing/editing. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request. The data set used and/or analyzed during the current study is available from the corresponding author upon reasonable request.

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