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Prostate-Specific Antigen Density as a Predictor of Biochemical Failure Among Prostate Cancer Patients Who Underwent Open Radical Prostatectomy

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ABSTRACT

In patients with prostate cancer undergoing open radical prostatectomy, early identification of those at risk for biochemical failure (persistence or recurrence) is crucial to guide timely treatment. The aim of this study was to identify clinical, biochemical, and histopathological factors associated with biochemical failure during a 2-year postoperative follow-up and to assess their predictive value. A retrospective, cross-sectional study was conducted on patients who underwent open radical prostatectomy at a tertiary care hospital between 2008 and 2021 to evaluate patient clinical, biochemical, and histopathological characteristics. Descriptive statistics were calculated, and comparisons (Mann–Whitney U tests) or associations (chi-square tests) among the characteristics were performed and compared between patients grouped according to the absence or presence of biochemical failure. Receiver operating characteristic curves were used to evaluate predictive performance. $\alpha = 0.05$ was used in all tests. A total of 163 patients were considered, 117 of which (age range, 50–77 years) met the inclusion criteria. Biochemical failure occurred in 48.70% of patients (24.80% persistence and 23.90% recurrence). A total of 29.06% of patients presented with extracapsular extension, which was significantly associated with biochemical failure ($p = 0.027$). Prostate-specific antigen density (PSAD) shows predictive value ($AUC = 0.617$, $p = 0.029$), with a cutoff point of $PSAD \geq 0.25$, yielding 54.40% sensitivity and 65.00% specificity. The 2-year odds ratio for biochemical failure was 2.06 ($p = 0.05$). Overall, 48.70% of the patients experienced biochemical failure during the first 2 years of follow-up. Extracapsular extension was associated with higher risk of biochemical failure. Our findings suggest that $PSAD \geq 0.25$ is a predictive factor for the occurrence of biochemical failure. It is important to conduct multicenter studies with larger sample sizes to validate these findings and strengthen prediction and follow-up strategies.

Edel Rafael Rodea-Montero and Jorge Luis Hernández-Azuara contributed equally to this work.

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1 | Introduction

Prostate cancer (PCa) is the most common type of cancer in men, with an incidence of one in six in developed countries [1]. In 2020, approximately 1.4 million new cases of PCa were diagnosed, representing 7.3% of all new cancer cases that year; PCa is the third most diagnosed type of cancer worldwide [2]. Generally, PCa is asymptomatic and is typically detected by a PCa-positive biopsy that is performed because of elevated levels of prostate-specific antigen (PSA) [3] or incidentally as a result of prostate surgery [4].

Treatment for PCa can range from conservative management with active surveillance [5, 6] or watchful waiting [7] to hormonal therapy [8], focal therapies [9], radiation therapy [10], or even radical prostatectomy [11]. Radical prostatectomy can be performed as open-approach [12], laparoscopic [13], or robot-assisted [14] surgery. After prostatectomy for PCa, patient follow-up involves PSA monitoring, including the determination of undetectable PSA levels (PSA < 0.2 ng/mL) and the occurrence of biochemical failure (persistence or recurrence).

Biochemical persistence is defined as the continuous presence of detectable PSA levels 6 weeks after surgery, indicating that PSA never reached undetectable levels despite complete removal of the prostate gland [15]. Persistence has been reported to occur in approximately 3.1%–12% of patients undergoing radical prostatectomy [16, 17]. Biochemical recurrence is defined as at least two measurements of PSA $\geq$ 0.2 ng/mL after achieving undetectable PSA levels 6 weeks after surgery [18, 19]. Recurrence has been reported in approximately 10%–40% of patients following radical prostatectomy [20, 21].

PSA monitoring after radical prostatectomy is crucial for providing early treatment and improving survival outcomes. Various studies have evaluated PSA levels over follow-up periods ranging from 1 year [22] to 2 years [23], 4 years [24], 5 years [25], and up to 20 years after surgery [26]. These studies used various monitoring schemes, including quarterly [27] or semiannual [28] intervals, with the aim of detecting biochemical failure effectively.

Multiple risk factors have been associated with biochemical persistence, including lymph node involvement [29], elevated Gleason score [30], and advanced TNM tumor stage [31]. On the other hand, biochemical recurrence has been linked to pathological features such as perineural invasion [32], positive surgical margins [33], extraprostatic extension [34], and seminal vesicle invasion [35].

One notable parameter that has garnered attention is prostate-specific antigen density (PSAD), defined as the ratio of serum PSA level (ng/mL) to prostate volume (cm³) [36]. Several studies have also explored its prognostic value for biochemical recurrence following radical prostatectomy. Proposed PSAD cutoff values for predicting recurrence vary widely, with thresholds such as $\geq$ 0.22, $>$ 0.3, $\geq$ 0.4, and $>$ 0.5 being reported [37–40].

Early detection of biochemical failure is crucial from an oncological standpoint, as it enables timely initiation of salvage treatments, such as radiotherapy or adjuvant hormonal therapy, with the potential to improve long-term outcomes and overall survival [41]. In this context, identifying clinical and pathological factors associated with biochemical persistence or recurrence

becomes essential for risk stratification and individualized follow-up strategies. Therefore, the aim of this study was to describe the clinical and histopathological characteristics of PCa and to evaluate their association with, and predictive value for, biochemical failure (defined as persistence or recurrence based on PSA levels) during a 2-year postoperative follow-up in adult patients who underwent open radical prostatectomy.

2 | Materials and Methods

2.1 | Patients

This cross-sectional study included a total of 163 patients of Mexican ethnicity with PCa who underwent radical open prostatectomy in the Urology Oncology Department of a tertiary care hospital from January 1, 2008, to December 31, 2021. Of these, only 117 adult patients (between 50 and 77 years of age) met the inclusion criteria and were included in the analysis. The selection of patients was carried out retrospectively using a consecutive sampling method on the basis of availability. The exclusion criteria were as follows: PSA levels $>$ 20 ng/mL before surgery (as these patients are more likely to have advanced disease, potentially confounding biochemical failure outcomes), PCa diagnosis after transurethral resection of the prostate, other concomitant cancer, history of orchiectomy (due to its impact on androgen levels and PSA kinetics), use of luteinizing hormone-releasing hormone (LHRH) antagonists during the 3 months before prostatectomy, use of antiandrogens during the 3 months before prostatectomy, use of 5 α -reductase inhibitors during the 6 months before prostatectomy, and inadequate monitoring of PSA levels during the 2-year follow-up.

2.2 | Statement of Ethics

The study protocol was reviewed and approved by Research and Research-Ethics Committees of the HRAEB (protocol codes and dates of approval: CI-HRAEB 038-2024, 24 July 2024, and CEI-043-2024, 22 July 2024). All methods were performed in accordance with the relevant guidelines and regulations. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin given the retrospective nature of the study.

2.3 | Clinical Patient Characteristics

The clinical characteristics of the patients, including age at surgery, weight, height, body mass index (BMI), nutritional status based on BMI, diabetes status, hypertension status, International Society of Urological Pathology (ISUP) index, NCCN risk group, D'Amico risk group, number of total and positive biopsies, CAPRA-S risk group, American Society of Anesthesiologists (ASA) scale score, and Goldman scale score, were obtained from the clinical records.

2.4 | Histological Prostate Characteristics

The histological prostate characteristics, including Gleason score, pathological TNM stage, extracapsular extension (defined as tumor extension reaching the prostatic capsule without implying resection of tissue beyond the prostate), surgical margins, lymph nodes, perineural invasion, and invasion of the seminal

vesicles, lymphadenectomy, and prostate size (g, obtained from the weight of the resected prostate specimen), were obtained from the clinical records of the patients.

2.5 | PSA Monitoring and Further Treatment

The PSA follow-up data, including PSA levels at diagnosis, 1 month after surgery, and quarterly (1st to 8th trimesters) after lavage; PSA nadir and whether the nadir was reached; time to PSA nadir from open radical prostatectomy; and occurrence of biochemical failure (recurrence or persistence according to PSA level) in 2 years after open radical prostatectomy, were obtained from the clinical records of the patients. Additionally, PSAD was determined as the ratio of serum PSA level (ng/mL) to prostate size (g), considering only the weight of the resected prostate gland and not including tumor extension beyond the capsule.

2.6 | Statistical Analysis

All the data were analyzed using the R programming language (Version 3.6.0, R Core Team, Vienna, Austria) [42]. Missing values for the study variables were not substituted; instead, that individual was not included in the analysis for that variable. Descriptive statistics were calculated for the patient clinical characteristics, histological prostate characteristics, and PSA follow-up characteristics. The patients were divided into two groups according to the presence or absence of biochemical failure at the 2-year follow-up, and associations between biochemical failure and each of the characteristics were determined via nonparametric tests. The assumption of normality could not be verified on the basis of the results of Kolmogorov–Smirnov tests ($p < 0.001$) in all the cases. Therefore, all analyses were performed using the Mann–Whitney U test or chi-square test.

In addition, the predictive capacity of each of the significantly different variables was evaluated via univariate logistic models. Crude odds ratios (ORs) and receiver operating characteristic (ROC) curves were generated to determine the cutoff points that best predict the presence or absence of biochemical failure during the 2-year postoperative follow-up. A similar analytical framework using nonparametric tests, logistic regression, and ROC analysis has been previously reported by our group [43]. For all tests, $\alpha = 0.05$.

3 | Results

A total of 163 patients who underwent open radical prostatectomy during the study period were considered for inclusion in the study. Only 117 adult patients (men between 50 and 77 years of age) met the inclusion criteria and were included in the analysis (Figure 1).

The mean age ($\pm$ SD) of the 117 included patients was 64.95 ± 6.05 years. Among them, 60/117 patients (51.30%) did not present biochemical failure, while 57/117 patients (48.70%) did. Of those with biochemical failure, 29/117 patients (24.80%) had biochemical persistence and 28/117 patients (23.90%) experienced biochemical recurrence.

The patients were divided into two groups according to the absence or presence of biochemical failure. Table 1 shows the comparisons of clinical characteristics between these groups via the Mann–Whitney U test; no significant differences were

identified. Using the chi-square test, no associations between the presence or absence of biochemical failure and the clinical characteristics were identified, except for an apparent association with the CAPRA-S risk group ($p = 0.100$).

Furthermore, Table 2 shows the associations between the absence or presence of biochemical failure and both histopathological and follow-up biochemical characteristics. The chi-square test revealed an association between the absence or presence of biochemical failure and the presence of extracapsular extension ($p = 0.027$). Among the 60 patients who did not exhibit biochemical failure, 12 had extracapsular extension (20.00%). In addition, of the 57 patients who exhibited biochemical failure, 22 had extracapsular extension (38.60%). The crude OR was 2.51 (95% confidence interval [CI], 1.10–5.75; $p = 0.029$). Notably, when the follow-up characteristics were compared via the Mann–Whitney U test, the PSAD was significantly greater (0.29 vs. 0.24) in patients who experienced biochemical failure ($p = 0.029$).

Additionally, Figure 2 shows the ROC curve for PSAD as a predictor of the presence of biochemical failure with an area under the curve of 0.617 (95% CI, 0.516–0.719; $p = 0.029$). To explore whether PSAD predicts persistence and recurrence separately, we performed ROC analyses for each outcome. Biochemical persistence (29/89) and recurrence (28/88) showed AUCs of 0.623 ($p = 0.062$) and 0.612 ($p = 0.093$), respectively. Although not statistically significant, likely due to the limited sample size, these results are similar to the overall biochemical failure AUC, suggesting that PSAD predicts both persistence and recurrence comparably.

Building on the overall ROC analysis, Table 3 shows the sensitivity, specificity, and their average (balanced accuracy) for PSAD across different cutoff points for predicting biochemical failure. The optimal cutoff was defined as the value that maximized balanced accuracy (mean of sensitivity and specificity), prioritizing a trade-off between both measures. Higher cutoff points improved specificity at the cost of sensitivity, while lower cutoff points showed the opposite pattern. Accordingly, a PSAD ≥ 0.25 was identified as the optimal cutoff for the presence of biochemical failure, with a sensitivity of 54.40%, a specificity of 65.00%, and a balanced accuracy of 59.70%.

Finally, 26 of the 64 patients (40.63%) who had a PSAD less than 0.25 presented with biochemical failure. In addition, 31 of the 53 patients (58.49%) who had a PSAD greater than or equal to 0.25 presented with biochemical failure. The crude OR was 2.06 (95% CI, 1.00–4.32; $p = 0.05$).

4 | Discussion

In adult patients with PCa undergoing open radical prostatectomy, the identification of patients likely to develop biochemical failure (persistence or recurrence) is essential for deciding on the management of PCa, including additional treatments such as rescue radiotherapy or adjuvant hormonal therapy. Various authors have identified individual factors to predict persistence [29–31] and recurrence [32–35]. Furthermore, studies have developed multifactorial risk scales for biochemical failure that play crucial roles in optimizing the clinical management of PCa according to its prognosis [44–46]. However, these individual factors and scales have not been validated in all populations. One

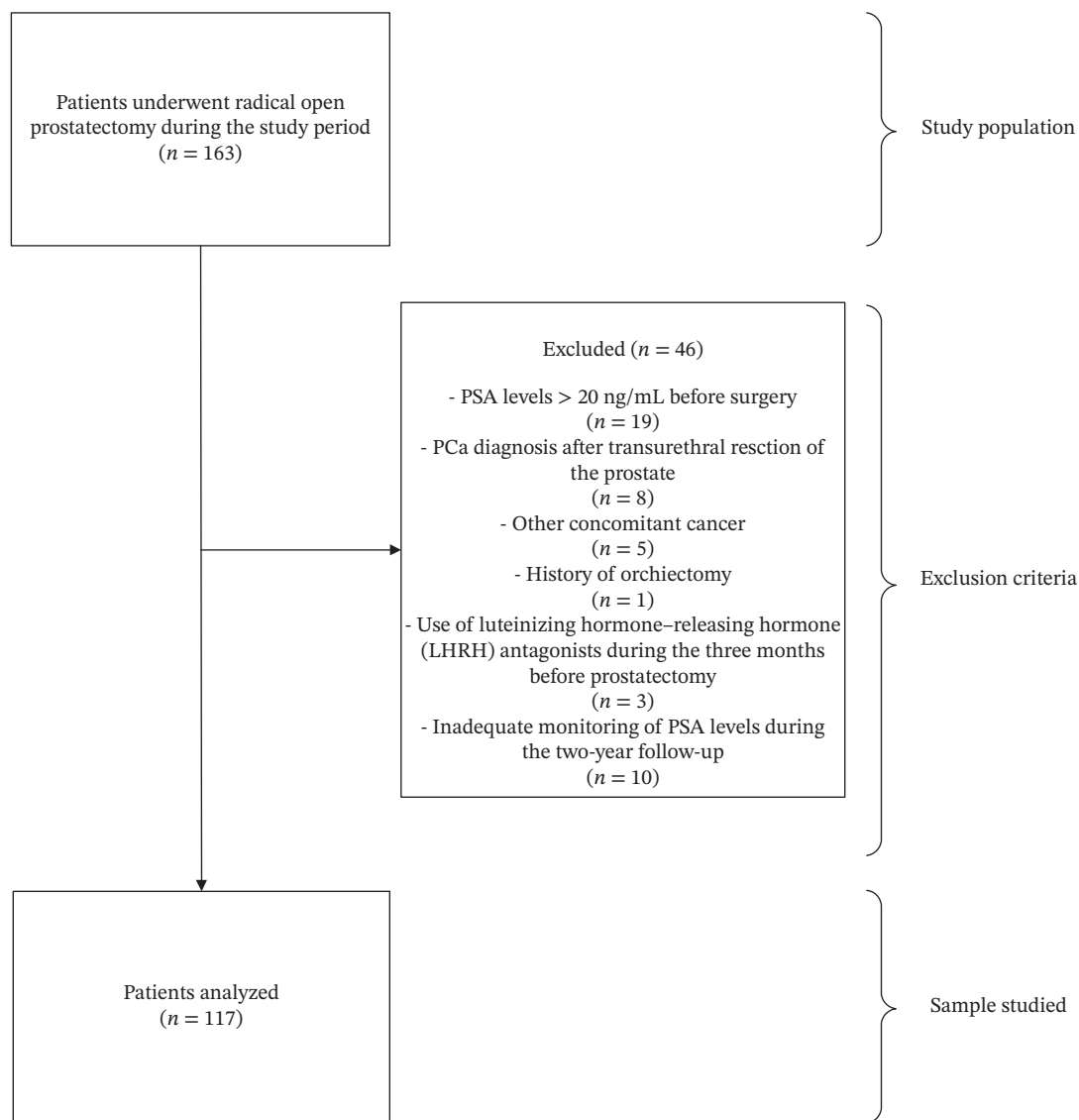


FIGURE 1 | Patient selection flowchart.

notable parameter that has garnered attention is PSAD [36]. The aim of this study was to describe the clinical and histopathological characteristics of PCa and to evaluate their association with, and predictive value for, biochemical failure (defined as persistence or recurrence based on PSA levels) during a 2-year postoperative follow-up in adult patients who underwent open radical prostatectomy.

In our study, which included 117 patients who underwent open radical prostatectomy, 48.70% (57/117) presented with biochemical failure. Of these, 24.80% (29/117) showed persistence, similar to the study by Ün et al. [47], in which a persistence prevalence of 25.00% was reported in a cohort of 152 patients who underwent radical prostatectomy as a treatment for low-risk PCa (according to the NCCN criteria). In contrast, 23.90% (28/117) of patients in our study exhibited recurrence, which was a greater percentage than that reported by Cooperberg et al. [44], with a recurrence prevalence of 14.59% in a cohort of 1439 patients who underwent open radical prostatectomy.

In our study, 29.06% (34/117) of the patients exhibited extracapsular extension confirmed by histopathological analysis, which

was a greater percentage than that reported by Radebe and Claassen [48], with extracapsular extension observed in 17.5% of 200 patients who underwent radical prostatectomy. Furthermore, we identified an association between extracapsular extension and the presence of biochemical failure (persistence or recurrence) ($p = 0.027$), which is consistent with the findings of Gómez-Iturriaga et al. [49], who also reported an association between the presence of biochemical failure and extracapsular invasion; notably, in their study, magnetic resonance imaging was used to determine extracapsular extension.

On the other hand, extracapsular extension is one of the six variables included in the CAPRA-S scale for recurrence risk after prostatectomy [44]. Some studies have validated the CAPRA-S scale as a predictor of biochemical failure [50, 51]. In our analysis, although an apparent association was observed between the CAPRA-S score and the presence of biochemical failure, the association was not statistically significant ($p = 0.100$).

Additionally, when evaluating the weight of the excised prostates, we found an average PSAD of 0.26 ± 0.13 , which exceeds the value reported by Radwan et al. [52], who described a mean

TABLE 1 | Clinical characteristics of prostate cancer patients undergoing radical prostatectomy, overall and grouped by the absence or presence of biochemical failure.

Variable	Overall <i>n</i> = 117	Biochemical failure		Comparison
		Absent <i>n</i> = 60	Present <i>n</i> = 57	
Age (years)	64.95 (6.05)	64.82 (6.40)	65.09 (5.70)	<i>p</i> = 0.812 ^a
Weight	73.98 (10.84)	73.22 (11.06)	74.79 (10.65)	<i>p</i> = 0.432 ^a
Height	1.65 (0.07)	1.65 (0.07)	1.65 (0.07)	<i>p</i> = 0.561 ^a
BMI (kg/m ²)	27.04 (3.49)	26.78 (3.44)	27.32 (3.56)	<i>p</i> = 0.339 ^a
Nutritional status				<i>p</i> = 0.877 ^b
Normal weight (18.5 ≤ BMI < 25), <i>n</i> (%)	32 (27.35%)	17 (28.33%)	15 (26.32%)	
Overweight (25 ≤ BMI < 30), <i>n</i> (%)	65 (55.56%)	32 (53.33%)	33 (57.89%)	
Obese (BMI ≥ 30), <i>n</i> (%)	20 (17.09%)	11 (18.33%)	9 (15.79%)	
Diabetes, <i>n</i> (%)	24 (20.51%)	11 (18.33%)	13 (22.81%)	<i>p</i> = 0.549 ^b
Hypertension, <i>n</i> (%)	35 (29.91%)	15 (25.00%)	20 (35.09%)	<i>p</i> = 0.234 ^b
Alcoholism, <i>n</i> (%)	51 (43.59%)	26 (43.33%)	25 (43.86%)	<i>p</i> = 0.954 ^b
Smoking, <i>n</i> (%)	54 (46.15%)	28 (46.67%)	26 (45.61%)	<i>p</i> = 0.909 ^b
ISUP index				<i>p</i> = 0.496 ^b
1, <i>n</i> (%)	74 (63.25%)	40 (66.67%)	34 (59.65%)	
2, <i>n</i> (%)	28 (23.93%)	11 (18.33%)	17 (29.82%)	
3, <i>n</i> (%)	13 (11.11%)	8 (13.33%)	5 (8.77%)	
4, <i>n</i> (%)	2 (1.71%)	1 (1.67%)	1 (1.75%)	
NCCN risk group				<i>p</i> = 0.331 ^b
Very low, <i>n</i> (%)	11 (9.40%)	8 (13.33%)	3 (5.26%)	
Low, <i>n</i> (%)	28 (23.93%)	16 (26.67%)	12 (21.05%)	
Favorable intermediate, <i>n</i> (%)	49 (41.88%)	26 (43.33%)	23 (40.35%)	
Unfavorable intermediate, <i>n</i> (%)	20 (17.09%)	7 (11.67%)	13 (22.81%)	
High, <i>n</i> (%)	6 (5.13%)	2 (3.33%)	4 (7.02%)	
Very high, <i>n</i> (%)	3 (2.56%)	1 (1.67%)	2 (3.51%)	
D'Amico risk group				<i>p</i> = 0.209 ^b
Low, <i>n</i> (%)	39 (33.33%)	24 (40.00%)	15 (26.32%)	
Intermediate, <i>n</i> (%)	69 (58.97%)	33 (55.00%)	36 (63.16%)	
High, <i>n</i> (%)	9 (7.69%)	3 (5.00%)	6 (10.53%)	
Number of positive biopsies	3.32 (2.06)	3.15 (1.86)	3.51 (2.26)	<i>p</i> = 0.431 ^a
Number of total biopsies	10.72 (1.98)	10.73 (1.97)	10.70 (2.01)	<i>p</i> = 0.881 ^a
% of positive biopsies	31.47% (18.41%)	30.12% (18.37%)	32.89 (18.49)	<i>p</i> = 0.295 ^a
CAPRA-S risk group				<i>p</i> = 0.100 ^b
1, <i>n</i> (%)	10 (8.55%)	8 (13.33%)	2 (3.51%)	
2, <i>n</i> (%)	22 (18.80%)	15 (25.00%)	7 (12.28%)	
3, <i>n</i> (%)	34 (29.06%)	14 (23.33%)	20 (35.09%)	
4, <i>n</i> (%)	23 (19.66%)	12 (20.00%)	11 (19.30%)	
5, <i>n</i> (%)	12 (10.26%)	5 (8.33%)	7 (12.28%)	
6, <i>n</i> (%)	8 (6.84%)	3 (5.00%)	5 (8.77%)	
7, <i>n</i> (%)	3 (2.56%)	0 (0.00%)	3 (5.26%)	
8, <i>n</i> (%)	4 (3.42%)	3 (5.00%)	1 (1.75%)	
9, <i>n</i> (%)	1 (0.85%)	0 (0.00%)	1 (1.75%)	
ASA-PS score				<i>p</i> = 0.139 ^b
I, <i>n</i> (%)	39 (33.33%)	24 (40.00%)	15 (26.32%)	
II, <i>n</i> (%)	65 (55.56%)	32 (53.33%)	33 (57.89%)	

(Continues)

TABLE 1 | (Continued)

Variable	Overall <i>n</i> = 117	Biochemical failure		Comparison
		Absent <i>n</i> = 60	Present <i>n</i> = 57	
III, <i>n</i> (%)	13 (11.11%)	4 (6.67%)	9 (15.79%)	<i>p</i> = 0.637 ^b
Goldman scale				
I, <i>n</i> (%)	47 (40.17%)	26 (43.33%)	21 (36.84%)	
II, <i>n</i> (%)	51 (43.59%)	26 (43.33%)	25 (43.86%)	
III, <i>n</i> (%)	18 (15.38%)	8 (13.33%)	10 (17.54%)	
IV, <i>n</i> (%)	1 (0.85%)	0 (0.00%)	1 (1.75%)	

Note: Unless otherwise indicated, all values are shown as the mean (standard deviation).

^aMann—Whitney U test.

^bChi-square test.

TABLE 2 | Histopathological and follow-up biochemical characteristics, overall and grouped by the absence or presence of biochemical failure.

Variable	Overall <i>n</i> = 69	Biochemical failure		Comparison
		Absent <i>n</i> = 60	Present <i>n</i> = 57	
Histopathological				
Gleason score				<i>p</i> = 0.364 ^b
6 (3 + 3), <i>n</i> (%)	50 (42.74%)	27 (45.00%)	23 (40.35%)	
7 (3 + 4), <i>n</i> (%)	38 (32.48%)	15 (25.00%)	23 (40.35%)	
7 (4 + 3), <i>n</i> (%)	16 (13.68%)	11 (18.33%)	5 (8.77%)	
8 (3 + 5), <i>n</i> (%)	1 (0.85%)	1 (1.67%)	0 (0.00%)	
8 (4 + 4), <i>n</i> (%)	7 (5.98%)	3 (5.00%)	4 (7.02%)	
9 (4 + 5), <i>n</i> (%)	3 (2.56%)	1 (1.67%)	2 (3.51%)	
9 (5 + 4), <i>n</i> (%)	1 (0.85%)	1 (1.67%)	0 (0.00%)	
10 (5 + 5), <i>n</i> (%)	1 (0.85%)	1 (1.67%)	0 (0.00%)	
Pathological TNM stage				<i>p</i> = 0.212 ^b
pT2N0M0, <i>n</i> (%)	83 (70.94%)	48 (80.00%)	35 (61.40%)	
pT3aN0M0, <i>n</i> (%)	18 (15.38%)	6 (10.00%)	12 (21.05%)	
pT3aN1M0, <i>n</i> (%)	3 (2.56%)	2 (3.33%)	1 (1.75%)	
pT3bN0M0, <i>n</i> (%)	11 (9.40%)	4 (6.67%)	7 (12.28%)	
pT3bN1M0, <i>n</i> (%)	1 (0.85%)	0 (0.00%)	1 (1.75%)	
pT4N0M0, <i>n</i> (%)	1 (0.85%)	0 (0.00%)	1 (1.75%)	
Extracapsular extension, <i>n</i> (%)	34 (29.06%)	12 (20.00%)	22 (38.60%)	<i>p</i> = 0.027 ^{b,*}
Surgical margins, <i>n</i> (%)	32 (27.35%)	15 (25.00%)	17 (29.82%)	<i>p</i> = 0.558 ^b
Lymph nodes, <i>n</i> (%)	5 (4.27%)	3 (5.00%)	2 (3.51%)	<i>p</i> = 0.690 ^b
Perineural invasion, <i>n</i> (%)	71 (60.68%)	35 (58.33%)	36 (63.16%)	<i>p</i> = 0.593 ^b
Invasion of seminal vesicles, <i>n</i> (%)	15 (12.82%)	6 (10.00%)	9 (15.79%)	<i>p</i> = 0.349 ^b
Lymphadenectomy, <i>n</i> (%)	43 (36.75%)	25 (41.67%)	18 (31.58%)	<i>p</i> = 0.258 ^b
Prostate size (g)	43.59 (21.63)	46.1 (26.34)	40.94 (14.99)	<i>p</i> = 0.507 ^a
Biochemical				
PSA at diagnosis (ng/mL)	10.33 (4.31)	9.71 (4.07)	10.98 (4.49)	<i>p</i> = 0.131 ^a
PSA density	0.26 (0.13)	0.24 (0.13)	0.29 (0.13)	<i>p</i> = 0.029 ^{a,*}
PSA nadir reached, <i>n</i> (%)	90 (76.07%)	60 (10.00%)	30 (52.63%)	<i>p</i> < 0.001 ^{b,*}
PSA nadir (ng/mL)	0.04 (0.03)	0.03 (0.03)	0.04 (0.04)	<i>p</i> = 0.562 ^a
Time to PSA nadir (months)	6.07 (6.75)	5.92 (6.97)	6.38 (6.39)	<i>p</i> = 0.304 ^a

Note: Unless otherwise indicated, all values are shown as the mean (standard deviation).

^aMann—Whitney U test.

^bChi-square test.

*Significant *p* value.

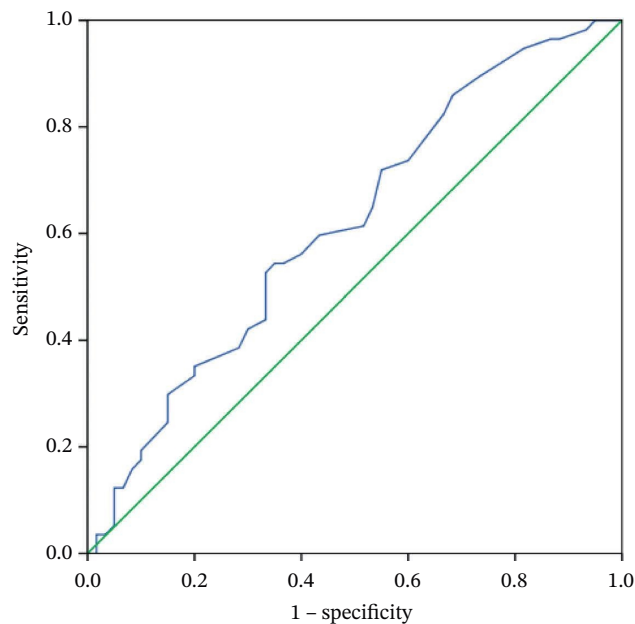


FIGURE 2 | ROC curve of PSA density as a predictor of the presence of biochemical failure ($n = 117$).

TABLE 3 | Cutoff points and effectiveness of PSA density as a predictor of the presence of biochemical failure ($n = 117$).

Positive prediction of biochemical failure if the PSA density is greater than or equal to:	Sensitivity	Specificity	Balanced accuracy (sensitivity + specificity)/2
0.00	1.000	0.000	0.500
0.10	0.982	0.067	0.525
0.15	0.895	0.267	0.581
0.20	0.649	0.467	0.558
0.21	0.614	0.483	0.549
0.22	0.596	0.567	0.582
0.23	0.561	0.600	0.581
0.24	0.544	0.633	0.589
0.25	0.544	0.650	0.597*
0.26	0.526	0.667	0.596
0.27	0.439	0.667	0.553
0.28	0.421	0.700	0.561
0.29	0.386	0.717	0.551
0.30	0.351	0.800	0.575
0.40	0.193	0.900	0.546
0.50	0.088	0.950	0.519
1.00	0.000	1.000	0.500

*Maximum value of the balanced accuracy criterion.

PSAD of 0.15 ± 0.14 in a cohort of 1327 patients who undergoing radical prostatectomy. In our study, PSAD was significantly higher in patients who experienced biochemical failure compared to those who did not (0.29 vs. 0.24, $p = 0.029$). This finding is consistent with the findings of Sfoungaristos and Perimenis [53], who observed a higher PSAD among patients with

biochemical failure (0.46 vs. 0.29) in a study involving 244 radical prostatectomy cases.

Furthermore, we identified PSAD as a potential predictor of biochemical failure. A threshold value of ≥ 0.25 yielded a sensitivity of 54.40% and a specificity of 65.00%, with an OR of 2.06 (95% CI, 1.00–4.32; $p = 0.05$). This is aligned with the findings of

Peng et al. [38], who reported a OR of 3.07 (95% CI, 1.38–6.82; $p = 0.006$) for a PSAD cutoff > 0.30 in patients with intermediate-risk PCa undergoing radical prostatectomy. Similarly, Shida et al. [40] found a significant association in high-risk patients undergoing robot assisted radical prostatectomy, reporting an OR of 2.48 (95% CI, 1.15–5.35; $p = 0.021$) using PSAD cutoff > 0.5 for predicting biochemical recurrence. Collectively, these findings reinforce the potential role of PSAD as a stratification tool for predicting biochemical failure following radical prostatectomy, with varying thresholds potentially reflecting differences in patient risk profiles and disease aggressiveness. However, in patients with extracapsular extension, PSAD may not fully reflect total tumor burden, as it is based solely on the weight of the resected prostate gland and does not account for tumor extension beyond the capsule. PSAD has shown variable performance across clinical settings and may not reliably predict incidental PCa in patients undergoing surgery for benign prostatic hyperplasia [54].

This study has several limitations. First, the cross-sectional design does not allow us to infer causality. Second, the results are based on a small sample ($n = 117$) from a single center, and the long study period may have also limited subgroup homogeneity. Third, no detailed characterization of the patients using new generation images (MRI, PET/CT, and PET/MRI) was performed, which would have allowed us to explore the potential associations between radiomic biomarkers and the presence of biochemical failure [55]. In this context, prostate-specific membrane antigen positron emission tomography/computed tomography (PSMA-PET/CT) has emerged as a valuable tool in the postoperative setting, particularly for identifying patients with biochemical recurrence and guiding salvage therapies [56, 57]. It may also complement clinical markers such as PSAD, providing a more comprehensive evaluation of patients at risk of biochemical failure. Fourth, the retrospective nature of our study limited the evaluation of some variables that have been previously associated with biochemical failure, such as the degree of invasion of the seminal vesicles [58], serum markers (fibronectin 1, galectin-binding protein-3, lumican, and matrix metalloproteinase 9) [59], and/or transcriptomic markers (9 mRNA signatures) [60, 61]. Fifth, although statistically significant, the predictive performance of PSAD was modest and should be interpreted in conjunction with other clinical variables rather than as a standalone predictor.

However, our study has important strengths, such as the evaluation of various clinical characteristics of patients, the histological prostate characteristics, and the follow-up of PSA levels for 2 years in the Mexican population.

Given the limitations, a multicenter study with a larger sample size would be valuable for fully identifying the most relevant characteristics to predict the presence of biochemical failure after radical prostatectomy in the Mexican population. This study should ideally include radiomic biomarkers obtained from new generation images and serum and/or transcriptomic markers to build a multivariate model using logistic regression and evaluate its performance in the prediction of biochemical failure through a wide variety of clinical, histological, biochemical, and imaging characteristics.

5 | Conclusion

This study increases our understanding of PCa in the Mexican population and allows us to identify variables that can be used to predict the risk of biochemical failure (persistence or recurrence) after open radical prostatectomy. A total of 48.70% of the patients developed biochemical failure; 24.80% of patients exhibited persistence, and 23.90% exhibited recurrence. Furthermore, 29.06% of the patients presented with extracapsular extension confirmed by histopathology, which was significantly associated with the presence of biochemical failure ($p = 0.027$).

Our findings suggest that PSAD is a relevant predictor for the occurrence of biochemical failure, with an AUC = 0.617 ($p = 0.029$) and an optimal cutoff point of PSA ≥ 0.25 , which offers a sensitivity of 54.40% and a specificity of 65.00%. These results highlight the importance of conducting multicenter studies with a sufficient sample size that allows the validation of these findings and strengthens prediction and follow-up strategies. This study could improve the clinical decision-making process and response time in the management of PCa, especially in patients at high risk of biochemical failure.

Author Contributions

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Disclosure

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

All data underlying the findings are available on request to corresponding author (edel.rodea@hraeb.gob.mx).

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