Elevation of Serum Total Prostate-Specific Antigen (PSA) Level as Predictor of Prostate Cancer (PCa) of Patient Following Transurethral Resection of Prostate (TURP)

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Abstract

Prostate cancer (PCa) is a significant global health issue, particularly in aging populations. In Indonesia, it is the fifth most common cancer. Diagnosis is often complicated by benign prostatic hyperplasia (BPH), which also elevates Prostate-Specific Antigen (PSA), limiting its specificity. This study aimed to establish an optimal preoperative PSA cutoff and assess the predictive utility of PSA, Neutrophil-Lymphocyte Ratio (NLR), and PSA Density (PSAD) for detecting PCa in patients undergoing Transurethral Resection of the Prostate (TURP). A retrospective cohort study analyzed 152 patients undergoing TURP at Gadjah Mada University Hospital (May 2018–July 2024) using a consecutive sampling method. Preoperative serum Total PSA, NLR, and PSAD were evaluated against postoperative histopathology. Bivariate and multivariate logistic regression were used to analyze relationships, while Receiver Operating Characteristic (ROC) curve analysis determined the optimal PSA cutoff. Prostate cancer was diagnosed in 19.1% of patients (n=29). ROC analysis identified a preoperative PSA cutoff of >19.95 ng/mL for predicting PCa, yielding an Area Under the Curve (AUC) of 0.863, with 75.9% sensitivity and 75.6% specificity. The multivariate analysis confirmed that elevated preoperative PSA (Odds Ratio [OR] 3.648), NLR (OR 3.868), and PSAD (OR 9.553) were all significant independent predictors of a PCa diagnosis. Among these, PSAD emerged as the strongest predictive marker. Preoperative serum PSA, NLR, and PSAD are valuable independent predictors for PCa in patients undergoing TURP for symptomatic BPH. A PSA cutoff of >19.95 ng/mL is a clinically relevant diagnostic threshold for this specific population. Employing a multi-marker panel, with particular emphasis on PSAD, can enhance risk stratification and help clinicians identify high-risk patients warranting further investigation for PCa when planning a TURP procedure.

Keywords: Prostate Specific Antigen (PSA), Prostate Cancer (PCa), Benign Prostate Hyperplasia (BPH), Transurethral Resection of The Prostate (TURP)

INTRODUCTION

Prostate cancer (PCa) represents a significant and escalating global health issue, particularly among aging male populations, alongside a high prevalence of benign prostatic hyperplasia (BPH). As one of the most common malignancies and a leading cause of death in men globally (Rawla, 2019). PCa incidence is projected to rise by 2030 due to aging demographics (Sekhoacha et al., 2022). Concurrently, BPH affected 94 million individuals in 2019, with notable increases in developing nations experiencing rapid epidemiological transitions (Awedew et al., 2022). This dual burden from malignant and benign prostate conditions underscores a growing global health concern, necessitating a clear understanding of their scale for resource allocation and research prioritization.

Within Indonesia, PCa constitutes a notable proportion of diagnosed cancer cases, highlighting its relevance to the nation's public health agenda. GLOBOCAN 2022 data identify PCa as Indonesia's fifth most common cancer, with 13,130 cases (7.05% of all diagnoses) (Ferlay et al., 2021). A study at Sardjito Hospital, Yogyakarta, also indicated a significant number of PCa patients received treatment between 2015 and 2020 (Dany et al., 2021). These figures underscore PCa's burden on the Indonesian healthcare system, demonstrating the need for focused attention on local diagnostic and treatment capacities. Such national and institutional data are vital for informing healthcare policies and guiding research relevant to the Indonesian population.

PSA testing is a central component of initial screening for PCa, credited with reducing mortality and morbidity (Sandhu et al., 2021; Wei et al., 2023). While increased PSA screening has significantly reduced PCa mortality rates (Sandhu et al., 2021), elevated levels are not exclusive to malignancy and can indicate conditions like BPH or prostatitis (Sekhoacha et al., 2022). Studies have noted associations between PCa and PSA levels above certain thresholds, such as 10 ng/dL or 20 ng/dL (Nnabugwu et al., 2014; Wadgaonkar et al., 2013). Although valuable for early detection, PSA's lack of specificity for PCa complicates interpretation and necessitates ongoing research to optimize its use for more precise risk stratification.

Evaluations of PSA performance by organizations like the American Cancer Society (ACS) highlight varying sensitivities and specificities at different cutoffs; for example, a 4.0 ng/mL cutoff showed 21% sensitivity for any PC) and 51% for high-grade PCa, with 91% specificity, while a 3.0 ng/mL cutoff increased sensitivities but reduced specificity. Other bodies, such as the U.S. Preventive Services Task Force (USPSTF), also provide evolving guidelines, often emphasizing shared decision-making due to the balance of benefits and harms. This complexity arises because PSA is organ-specific rather than disease-specific, limiting its ability to differentiate PCa from conditions like symptomatic BPH (Neeli et al., 2021). This limitation, leading to debates on optimal PSA use and risks of overdiagnosis, underscores the need for supplementary diagnostic tools to enhance detection accuracy.

Given the recognized limitations in PSA specificity, this study aimed to evaluate the relationship between preoperative PSA levels and histopathological findings in patients undergoing Transurethral Resection of the Prostate (TURP), and to estimate an optimal PSA cutoff for detecting PCa in this cohort. The rationale stems from the clinical need to improve PCa risk stratification, particularly for symptomatic patients requiring TURP for prostate enlargement. By analyzing the correlation between pre-TURP PSA and post-TURP histopathology, this research seeks to provide data for better risk stratification and treatment

guidance, potentially optimizing management and improving diagnostic accuracy for PCa within this patient group.

METHODS

This retrospective cohort study utilized a consecutive sampling method, including all patients who underwent TURP at the Academic Hospital of Gadjah Mada University (UGM), Yogyakarta, Indonesia, from May 2018 to July 2024 and met the study criteria. A total of 152 such patients formed the study cohort as visualized in Figure 1. Patients included in this study had undergone TURP for absolute or relative indications. TURP is a surgical procedure used to treat BPH by removing obstructing prostate tissue, with the decision to perform it depending on symptom severity and complications. Inclusion criteria required available data on preoperative serum total PSA levels, urological ultrasound, and histopathological examination results from the TURP specimens. Patients who underwent repeated TURP procedures were excluded from this study. All records for the consecutively sampled patients who met inclusion criteria were complete; thus, no patients were excluded due to incomplete data from this cohort of 152.

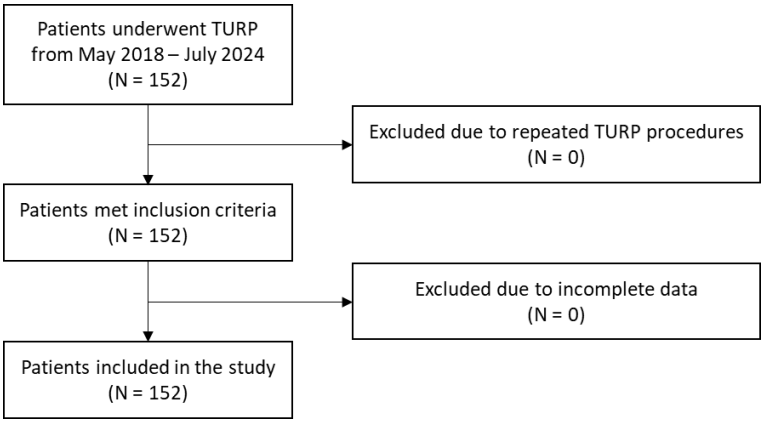

Figure 1. Sampling flowchart

Preoperative serum total PSA levels were measured 3 to 7 days before surgery using the Enzyme-Linked Immunosorbent Assay (ELISA) method. Urological ultrasound examinations were also performed 3 to 7 days pre-surgery. Histopathological results from TURP specimens were reported 7 days after surgery. Gleason scoring was not systematically applied in this study, as the primary histopathological assessment focused on differentiating benign (e.g., BPH) from malignant conditions in tissue obtained from TURP, rather than detailed staging of pre-diagnosed prostate cancer, for which the Gleason score is typically utilized. NLR data were classified as <3.1 and ≥3.1 (Luo et al., 2015). PSAD above 0.15 ng/mL² is typically classified as elevated and serves as a potential predictor for prostate cancer (Pellegrino et al., 2023).

Hypertension was defined as a systolic blood pressure of ≥140 mmHg and/or a diastolic blood pressure of≥90 mmHg (Unger et al., 2020). Diabetes was defined as a fasting venous plasma glucose concentration ≥126 mg/dL or a 2-hour post 75g glucose load ≥200 mg/dL (Palestinian Ministry of Health, 2006). The relationships between histopathological results and PSA levels, body mass index, NLR, PSA density, diabetes, and hypertension were analyzed using SPSS with the Mann-Whitney and Chi-Square test.

This study received approval from the patients and their families, and ethical approval was obtained from the Ethics Committee of the Faculty of Medicine, Gadjah Mada University, with the ethical clearance number KE/FK/1376/EC/2024. The study's objectives, procedures, benefits, and risks were thoroughly explained to each eligible patient and/or their family member. If the patient or their family comprehended the information and agreed to participate, they were required to sign a written consent form.

RESULTS

In our study, 152 patients who underwent TURP were included. The demographic and clinical characteristics of the patients are shown in Table 1.

Table 1. The demographic and clinical characteristics of the patient conducted TURP in Gadjah Mada University Hospital Yogyakarta Indonesia, from 2018 to 2024

Characteristics	Measurement Result			
	Median (Min-Max)	Mean (±SD)	N	%
Age (year	68.5 (44-89)			
Surgical Indication				
Urinary Retention			112	73.7
Vesicolithiasis			14	9.2
Bilateral Hydronephrosis			6	3.9
Hematuria			20	13.2
Additional Procedure				
None			110	72.4
Prostate Biopsy			29	19.1
TURBT (transurethral resection of bladder tumor)			2	1.3
Vesicolithotripsy + Prostate Biopsy			1	0.7
Vesicolithotripsy			10	6.6
Preop PSA				
USG Volume (ml)	10.26 (0.65-100)			
PSAD (ng/ml²/cm³)	52.32 (5-196)			
PSAD group				
>0.15	91 (59.9)			
<0.15	61 (40.1)			
Weight (kg)		63.8 (± 9.17)		
Height (cm)	165 (140-180)			
BMI (kg/m^2)		23.6 (± 3.06)		
Hypertension				
Yes	81 (53.3)			
No	71 (46.7)			

Characteristics	Measurement Result			
	Median (Min-Max)	Mean (±SD)	N	%
Diabetes				
Yes	18 (11.8)			
No	134 (88.2)			
NLR	3.25 (1.13-28.89)			
NLR group				
>3.1	81 (53.3)			
<3.1	71 (46.7)			
Histopatology				
BPH	123 (80.9)			
Pca	29 (19.1)			

Table 2. displays the comparison of preoperative PSA levels between BPH and PCa. PCa patients had higher median PSA levels compared to BPH (40.9 vs 8.1, p<0.001). A significant association was found between preoperative PSA and pathological results by the Mann-Whitney test.

Table 2. Preoperative PSA level according to Pathological result

		Preoperative PSA			p-*value*
		Median	Min	Max	
Pathological result	BPH	8.16	0.65	66.15	<0.001
	Ca	40.90	2.92	100.00	

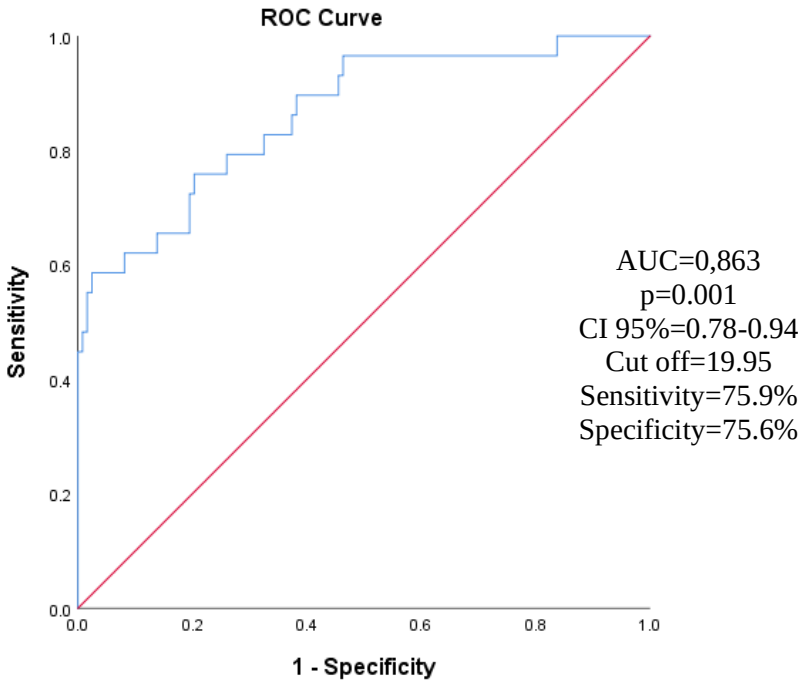

Figure 2. ROC analysis of preoperative PSA to pathological

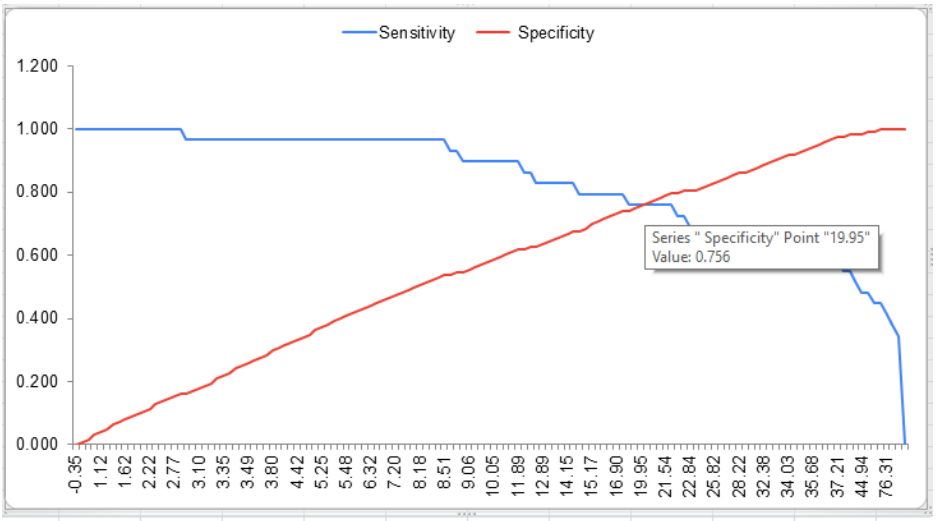

Figure 3. Determination of preoperative PSA cut-off to pathological

ROC analysis showed preoperative PSA statistically significant to pathological results by p=0.001. AUC 0.863 showed the quality of pre-operative PSA discrimination in differentiating pathological results between BPH and PCa in the high category, which is AUC>0.8. The determination of the cutoff for high sensitivity and specificity values is obtained at a pre-operative PSA level of 19.95, with a sensitivity of 75.9% and specificity of 75.6%.

Table 3. Diagnostic test

		Pathological result		Sensitivity (Sn)	Specificity (Sp)	Positive predictive value (PPV)	Negative predictive value (NPV)	Positive likelihood ratio (LR+)	Negative likelihood ratio (LR-)	Accuracy
		Pca	BPH							
PSA	≥19.95	22	30	75.86%	75.61%	42.31%	93.00%	3.11	0.32	75.66%
	<19.95	7	93							

Several independent variables were assessed to examine their relationship with pathological results, and the results can be seen in Table 4 below.

Table 4. Bivariate analysis

		Pathological Result						
		PCa		BPH		p-*value*	OR	CI 95%
		f	%	f	%			
Age (year)		69 (44-89)		68 (53-87)		0.809#		
USG Volume		51.7 (15-196)		52.4 (5-159.2)		0.603#		
Surgery Indication	Urinary retention	21	18.8	91	81.3	0.797#		
	Vesicolithiasis	2	14.3	12	85.7			
	Bilateral hydronephrosis	2	33.3	4	66.7			
	Hematuria	4	20.0	16	80.0			
PSAD (ng/ml^2)	>0.15	28	30.8	63	69.2	0.001*x	26.67	3.52-202.18
	<0.15	1	1.6	60	98.4			

		Pathological Result						
		PCa		BPH		p-*value*	OR	CI 95%
		f	%	f	%			
Hypertension	Yes	15	18.5	66	81.5	0.851[x]	0.93	0.41-2.08
	No	14	19.7	57	80.3			
Diabetes	Yes	6	33.3	12	66.7	0.115[x]	2.41	0.82-7.09
	No	23	17.2	111	82.8			
NLR	>3.1	24	29.6	57	70.4	0.001*[x]	5.56	1.99-15.52
	<3.1	5	7.0	66	93.0			
PSA Level	>19.95	22	42.3	30	57.7	0.001*[x]	9.74	3.78-25.06
	<19.95	7	7.0	93	93.0			

*) statistically significant p<0,05, #) Mann Whitney, x) Chi-Square

Based on the bivariate analysis, PSAD, NLR, and PSA levels are statistically associated with pathological outcomes. Patients with PSAD >0.15 experienced PCa in 28 cases (30.8%), whereas patients with PSAD <0.15 had only 1 case, with a significant difference (p=0.001). The OR value of 26.67 means that patients with PSAD >0.15 are 26.67 times more likely to experience PCa compared to those with PSAD <0.15 (p=0.001, OR 26.67, CI 3.52-202.18). Patients with NLR >3.1 are 5.56 times more likely to experience PCa compared to those with NLR <3.1 (p=0.001, OR 5.56, CI 1.99-15.52). Patients with PSA levels >19.95 are 9.74 times more likely to experience PCa compared to those with PSA <19.95 (p=0.001, OR 9.74, CI 3.78-25.06).

Table 5. Multivariate analysis

	p-*value*	OR	95% CI	
			Lower	Upper
PSAD	.042	9.553	1.086	84.068
NLR	.016	3.868	1.287	11.627
PSA Level	.017	3.648	1.265	10.521

DISCUSSION

The current study established a notably high preoperative prostate-specific antigen (PSA) cutoff of >19.95 ng/dL for prostate cancer (PCa) detection in patients undergoing transurethral resection of the prostate (TURP). This finding contrasts with the lower thresholds commonly used in general screening populations. The median PSA level among PCa cases in the TURP cohort was 40.90 ng/dL, forming the basis for this derived cutoff. These results underscore the necessity of context-specific PSA interpretation for symptomatic patients undergoing TURP.

Our study's elevated PSA cutoff finds resonance in other research focusing on similar patient cohorts. Investigations into symptomatic patients or those undergoing TURP also report

higher PSA thresholds for accurate PCa diagnosis. For example, Daryanto et al. (2024) identified a PSA cutoff >19.71 ng/dL, and the literature discusses findings by Deshpande et al. (2020) where PSA >20 ng/ml was common in PCa cases (Anand et al., 2024; Daryanto et al., 2024). Such consistency suggests that elevated PSA values in TURP candidates warrant careful, nuanced evaluation rather than immediate alarm based on general screening norms.

The elevated baseline PSA levels observed in TURP cohorts are likely influenced by patient-specific factors inherent to this group. Conditions such as benign prostatic hyperplasia (BPH) and preoperative interventions, including urinary catheterization, can contribute to PSA elevation independent of malignancy. In this study, a significant majority of patients (112 individuals) had undergone prior catheterization due to urinary retention. This clinical scenario is known to affect PSA levels, as Anand and Gupta (2021) confirm that urinary tract infections and any form of urinary tract instrumentation can lead to increased PSA measurements. Therefore, clinicians must carefully distinguish between BPH-related or procedure-induced PSA elevations and those that are genuinely indicative of prostate cancer in this patient population.

Furthermore, the TURP procedure itself significantly impacts PSA dynamics, which complicates pre-operative interpretation if based on general population norms. TURP often leads to a marked reduction in PSA levels in patients with BPH, implying that high pre-TURP values might largely reflect benign prostatic enlargement rather than cancer. Cho et al. (2014) demonstrated this by showing that TURP substantially normalized initially elevated PSA levels (≥4 ng/mL) in BPH patients with previous negative biopsies, with mean post-TURP PSA decreasing to approximately 1.26 ng/mL. This highlights that a distinct diagnostic approach for pre-TURP PSA is warranted, differing from asymptomatic screening contexts.

This study also identified an elevated NLR as significantly associated with PCa. This finding suggests the involvement of systemic inflammation in PCa within the TURP patient cohort. This concurs with research by Adhyatma et al. (2019), who stated that NLR is highly promising for predicting PCa in patients with PSA levels above 4 ng/dL (OR = 3.2; 95% CI: 1.96-5.11), and Kawahara et al. (2015) who showed NLR as an independent prognostic factor in PCa. The practical implication is that NLR, an accessible and cost-effective marker, could offer additional diagnostic insight alongside other parameters.

PSAD >0.15 ng/mL² also emerged as a significant predictor for PCa in our analyses. This supports PSAD's role in refining PCa detection by adjusting PSA for prostate volume, a concept introduced by Benson et al. (1992). Our PSAD findings are comparable to those of Yusim et al. (2020), where a PSAD cutoff of 0.20 ng/ml² showed good sensitivity and specificity for

clinically significant cancer. The review by Abedi et al. (2020) further notes the utility of post-TURP PSAD (≤0.08 ng/mL/cc) for active surveillance decisions in incidental PCa, highlighting PSAD's value across the diagnostic and management pathway. Therefore, routine calculation of pre-operative PSAD could improve the accuracy of PCa risk assessment in men scheduled for TURP.

Comparing the predictive strengths of the markers investigated, PSAD demonstrated notable capabilities in this study. PSAD >0.15 ng/mL² exhibited the highest odds ratio (OR 26.67) in bivariate analysis and remained a strong independent predictor in multivariate analysis (OR 9.553), outperforming PSA (OR 3.648) and NLR (OR 3.868) in the latter. This robust performance suggests PSAD's key role in differentiating PCa in TURP patients, likely by effectively adjusting for BPH-related prostate volume increases that can confound PSA interpretation. This finding advocates for a combined marker assessment, potentially prioritizing PSAD, to enhance risk stratification in clinical practice.

The study's single-center design and sample size (152 patients) warrant caution in generalizing these specific cutoffs. The inherent limitations of PSA as a standalone diagnostic emphasize the continued need for additional tools (Farha & Salami, 2022). Our study contributes by showing that preoperative PSA, NLR, and PSAD together can act as useful auxiliary PCa predictors in TURP patients. This aligns with the broader goal of improved risk stratification seen in other research, such as Wu et al. (2022), who used post-TURP PSA dynamics and pathology to guide the management of localized PCa. While our study focuses on pre-TURP diagnosis, it complements work like that of Wu et al. (2022) and the review by Abedi et al. (2020) by identifying at-risk patients earlier. Cho et al. (2014) also highlighted TURP's diagnostic yield (6.5% PCa detection) in a select BPH group. The integration of these preoperative markers into clinical assessment for TURP candidates could refine diagnostic precision and support more informed management discussions.

CONCLUSIONS

This study aimed to establish an optimal preoperative PSA cutoff for identifying PCa in patients undergoing TURP and to investigate the associations between preoperative serum PSA, NLR, and PSAD with PCa histopathological outcomes. The investigation successfully identified a distinct PSA level that served as a predictive threshold for PCa within this specific patient group. Furthermore, the findings consistently demonstrated that elevated preoperative levels of serum Total PSA, alongside increased NLR and PSAD, were significantly linked to the presence of PCa. These three markers, with PSAD showing particular strength, emerged as

independent indicators for PCa in patients undergoing TURP. These results suggest the potential clinical utility of these biomarkers in enhancing risk assessment for PCa in this population; however, further multicenter research is warranted to validate these findings and to explore the integration of these markers into routine clinical practice for improved patient management.

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