ADDIS ABABA UNIVERSITY

COLLEGE OF HEALTH SCIENCES

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DEPARTMENT OF PATHOLOGY

Correlation between Serum Prostate-Specific Antigen Levels and Histopathological Pattern of Prostate Lesions at Tikur Anbessa Specialized Hospital, Ethiopia: A Five-Year Retrospective Cross-sectional Study

Principal investigator: Dr. Biruk Legesse (MD, Final Year Pathology Resident)

A Research Thesis to be Submitted to the Department of Pathology, Tikur Anbessa Specialized Hospital, School of Medicine, College of Health Sciences, Addis Ababa University for Partial Fulfillment of the Requirements for Post-Graduate Diploma in Pathology.

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Abstract

Introduction: *Prostate cancer is a major health concern in males, emphasizing the need for early detection and precise diagnosis. Serum Prostate-Specific Antigen (PSA) is a crucial biomarker for assessing prostate health. Elevated PSA levels may signal potential abnormalities, prompting further diagnostic evaluation. This study aims to correlate Serum PSA Levels with histopathological patterns of prostatic lesions, enhancing diagnostic precision for early identification of malignancies.*

Objectives: *This study aims to assess correlation between Serum PSA Levels and histopathological Pattern of Prostatic Lesions.*

Methodology: *Institution-based Retrospective Cross-sectional descriptive study was conducted at the Pathology Department of Tikur Anbessa Specialized Hospital (TASH) to review all the prostate biopsy histopathology reports and their corresponding serum PSA level laboratory result. Data was retrieved from the archive of department of pathology and hospital i-care system that were seen at TASH from year January 2019 to December 2023 G.C.*

Result*: Benign prostatic hyperplasia/Prostatic nodular hyperplasia (BPH) emerged as the predominant lesion in our study, constituting 78.9% (340) of cases, followed by adenocarcinoma at 20%(86) and, intraepithelial proliferative lesions was identified in 1.2%(5) of cases. Within the subset of BPH, 9.1% (31/340) showed concomitant prostatitis. Mean age was 65.5±9.1years for BPH cases and 68.98±9.2 for adenocarcinoma cases. Serum PSA levels were above 4ng/ml in 65.3% of BPH cases and 97.7% of adenocarcinoma cases. Mean PSA values were 8.5±8.9 ng/ml for BPH and 84.7±61.5 ng/ml for adenocarcinoma cases.*

Conclusion: *On statistical analysis serum PSA is found to be a sensitive and early marker for the diagnosis of prostate cancer. With a cut off value of 4ng/ml sensitivity was found to be 97.7% and specificity was 34.7%. A correlation is found between elevated PSA values and advancing age, and prostatic adenocarcinoma (p-value <0.05).*

Acronyms And Abbreviations

AAU - Addis Ababa University

SPSS - Statistical Package for Social Sciences

TASH -Tikur Anbessa Specialized Hospital

BPH - benign prostatic hyperplasia

PNH - Prostatic nodular hyperplasia

PCa - Prostate Cancer

PIN - prostate intraepithelial neoplasia

IPLs - Intraepithelial proliferative lesions

HGPIN - high-grade prostatic intraepithelial neoplasia

PSA - prostate-specific antigen

LUTS – Lower urinary tract symptoms

TURP - transurethral resection of the prostate

CNB - Core Needle Biopsy

RP – Radical prostatectomy

DRE - digital rectal examination

ISUP - International Society of Urological Pathology

GS - Gleason's Score

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Tables and figures

Acknowledgment

I wish to extend my sincere gratitude to the TASH, Department of Pathology, for granting me the opportunity to conduct this study in a field where data is insufficient.

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1 Introduction

1.1 Background

The prostate gland, which weighs about 20 gms in normal adult, is the largest secondary male reproductive organ. It is a retroperitoneal organ that surrounds the urethra and bladder neck. As an exocrine gland, the prostate contributes significantly to seminal fluid. Histologically, it consists of glands separated by abundant fibromuscular stroma. The glands are lined by two layers of cells: a basal layer of low cuboidal basal epithelium covered by a layer of columnar secretory cells, and it is dependent on testicular androgen to function normally. Inflammation, benign nodular enlargement, and tumors are significant causes of prostatic morbidity and mortality, affecting mainly older males.[1]

Notably, prostate cancer ranks as the second most commonly diagnosed cancer in men and holds the fifth position in global cancer prevalence[2]. In Ethiopia prostate cancer is the third most common cancer among men[3]. According to Globocan, 2020, Prostate Cancer prevalence in Ethiopia was 3775 an incidence of 2720 with 1600 deaths[4]. With advancing age, the incidence of both benign prostatic hyperplasia (BPH) and prostate cancer increases simultaneously[5].

Pioneering the understanding of prostatic tumor histological architecture, Gleason introduced a seminal grading system for prostate carcinoma[6]. Since then, numerous improvements have been made. The 2005, 2014 and 2019 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma, conducted on to standardize the score, endorsed the current widely used Gleason's score (GS) method. The result of this consensus acknowledged the important added value of Gleason pattern quantity, minor Gleason patterns, invasive cribriform carcinoma, and intraductal carcinoma (IDC), and provided recommendations for their reporting.[7–9]

The assessment of serum prostate-specific antigen (PSA) levels, supported by digital rectal examination (DRE), remains crucial for the first screening of prostate cancer[10,11]. Randomized clinical trials reveal that PSA-based screening in men aged 55 to 69 may prevent around 1.3 prostate cancer deaths and approximately 3 cases of metastatic prostate cancer per 1000 men screened over about 13 years[12]. Serum PSA's upper normal threshold is commonly defined as 4.0 ng/mL, with values between 4 and 10 ng/mL categorized as borderline, and values

exceeding 10 ng/mL classified as high[13]. The significance of the 4 ng/mL cutoff is its dual embodiment of high sensitivity in detecting prostate cancers and high specificity in excluding malignancy-free cases[13]. Indisputably, the Gleason score and serum PSA level claim the role of chief prognostic factors in prostate cancer, yet the definitive Gleason score necessitates post-radical prostatectomy validation.[14]

1.2 Statement of the problem

Inadequate understanding of the intricate relationship between Serum PSA Levels and Histopathological Patterns of Prostatic Lesions presents a notable challenge. This study endeavors to bridge this gap by comprehensively exploring the correlation, unveiling inherent complexities. Motivated by the need to examine clinicopathological attributes in benign and malignant prostatic lesions, it aims to establish a crucial correlation between pre-operative serum PSA levels and histological findings. This correlation enhances diagnostic certainty, especially in perplexing scenarios.

1.3 Significance of the study

In concordance with the escalating incidence of prostate cancer and BPH or PNH (Prostatic nodular hyperplasia), oftentimes aligned with advancing age [15], and amidst the array of diagnostic tools—ranging from digital rectal examinations to transrectal ultrasonography—serum PSA levels have consistently demonstrated their indispensability since their introduction in 1988[16] [13].

The study aims to create a unified framework for understanding the intricate interactions between serum PSA levels and histopathological patterns in prostate lesions. It also endeavors to establish the significance of serum PSA levels in differentiating various prostate lesions, such as prostatitis, BPH or PNH, and prostate adenocarcinoma. The examination of clinicopathological characteristics in both benign and malignant prostatic lesions, alongside establishing a crucial link between pre-operative serum PSA levels and histological findings, enhances diagnostic certainty, especially in challenging scenarios.

This research holds paramount significance in addressing the identified knowledge gap. By unraveling the complex relationship between serum PSA levels and diverse histopathological patterns, particularly across sociodemographic and clinical characteristics, the study provides invaluable insights. These insights align with the US Preventive Services Task Force's push for a

more personalized approach to prostate cancer screening, enriching the understanding of this complex interplay and paving the way for tailored screening and management strategies[12].

2 Literature Review

2.1 Incidence of various prostatic lesion, Histopathological Patterns, and Serum Prostate-Specific Antigen (PSA) Levels

Prostatic lesions encompass a wide spectrum of conditions, including BPH, prostatic intraepithelial neoplasia, and adenocarcinoma prostate. Precise diagnosis hinges on histopathological examination. Global studies have meticulously documented the intricate histopathological patterns observed in prostatic lesions, offering valuable insights into their characteristics and clinical implications.

Prostatitis, BPH, and prostate cancer are the most common conditions that affect the prostate[17,18]. In majority males, prostate enlargement occurs with the increase in age [19]. The non-malignant adenomatous enlargement of the prostate gland is known as BPH or PNH[20,21]. It is characterized by prostatic stromal and epithelial cell hyperplasia, which leads to the development of large, distinct nodules in the peri-urethral region of the prostate[19]. It often presents with lower urinary tract symptoms[22]. Symptoms include weak stream, hesitancy, frequency, urgency, nocturia, incomplete emptying, terminal dribbling, overflow or urge incontinence and complete urinary retention[20,21]. Incidence of prostatic cancer is increases proportionally after age of 50 years[18]. In approximately, 70% of cases it arises in the peripheral zone of gland particularly in the posterior location[23]. Adenocarcinoma is its most common histological variant[18]. In most cases, it is asymptomatic and develops slowly. However, it may present with pain, difficulty in urinating and problems during sexual intercourse[24].

Serum PSA is a serine protease in the kallikrein family, produced by the secretory cells in the prostatic ducts and acini. Normal prostate architecture keeps serum PSA confined to the gland while allowing only fraction to be leaked into the circulation which enables its detection in serum. Serum PSA circulates in free and complexed form. Complexed forms are bound to protease inhibitors[25]. Serum PSA levels correlate strongly with the risk of prostate cancer. So along with factors like increasing age, race, family history and digital rectal examination findings, serum PSA is commonly used as a screening tool to determine the need for biopsy. Serum PSA levels also appear elevated in conditions including BPH, prostatitis, or extrinsic manipulations of prostate like bicycling, catheterization, etc. Hence other PSA derivatives like

PSA density (that is the ratio of PSA to gland volume), PSA doubling time, PSA velocity (that is the change of PSA over time), and age and race specific PSA reference ranges are commonly used to improve the specificity.[26–28]

The significance of Serum PSA levels in prostate disease evaluation cannot be overstated. Elevated PSA levels often raise suspicion of malignancy, prompting further investigation. International research has elucidated the multifaceted role of serum PSA, not only as a diagnostic marker but also as a tool for risk stratification and monitoring. These findings underscore the importance of understanding serum PSA dynamics in clinical practice.

2.2 Association of serum PSA level with Histopathological pattern of Prostatic lesions

The correlation between Serum PSA levels and histopathological Patterns of prostate lesions is a pivotal aspect of prostate disease diagnosis and management.

Extensive studies from various regions of the world have explored the correlation between serum PSA levels and histopathological patterns of prostatic lesions. These investigations have revealed a spectrum of associations, ranging from strong correlations in some contexts to more nuanced relationships in others. It is essential to consider the clinical context and patient demographics when interpreting these findings.

A retrospective investigation carried out in India encompassed 63 diagnosed cases of prostatic lesions over a year-long duration, with patients exhibiting a mean age of 67.84 years (range: 48-60) at the point of diagnosis. Predominantly, benign lesions constituted the most prevalent prostatic conditions, constituting a total of 54 cases (85.71%). Among these, 38 cases were identified as BPH, 14 cases comprised BPH with prostatitis, and isolated cases included BPH with granulomatous prostatitis and basal cell hyperplasia. The mean serum PSA value for benign lesions was recorded at 6.57 ng/ml. Malignant cases totaled eight, including 7 cases (11.11%) of Prostate Cancer (PCa) and a single case (1.59%) of metastatic transitional cell carcinoma. The mean PSA value for PCa cases was notably higher, measuring 35.05 ng/ml. Additionally, a singular case (1.59%) of HGPIN was also detected.[29]

Another retrospective descriptive cross-sectional study in India analyzed 75 prostatic specimens, categorizing lesions into benign and malignant. BPH with chronic prostatitis was the most common benign lesion. Serum PSA demonstrated high sensitivity at 4ng/ml but lacked specificity. Malignancies were predominantly adenocarcinomas, primarily Gleason's Grade 2.

The study emphasized PSA as an early and sensitive marker, but with limitations at the conventional 4ng/ml cut-off due to reduced specificity.[30]

Another study analyzed 150 cases presenting as prostatic lesions, correlating serum PSA levels and tissue biopsy. Cases with abnormal digital rectal examination (DRE) were confirmed as malignant on biopsy, establishing a PSA malignancy cut-off at 19.5ng/ml. Median PSA levels for BPH, prostatitis, prostate intraepithelial neoplasia (PIN), and adenocarcinoma were 5ng/ml, 10ng/ml, 14ng/ml, and 81ng/ml, respectively. Interestingly, no significant serum PSA level differences were observed between low-grade and high-grade prostate intraepithelial neoplasms. The study concluded that PSA levels in benign prostatic lesions typically ranged from 0 to 4.0ng/ml. The PSA cut-off value of 19.5ng/ml emerged as the most sensitive and specific for malignant lesion detection. In cases where PSA levels exceeded 4.0ng/ml and were accompanied by abnormal DRE, transurethral resection of the prostate (TURP) biopsy proved to be the most accurate diagnostic method for prostatic lesions, reinforcing the importance of judicious PSA use to minimize patient anxiety.[31]

A retrospective study of 2189 prostatic lesion patients in Pakistan (2007-2017) disclosed BPH in 76.56% of cases. Notably, serum PSA levels exceeding 10 ng/ml were consistent markers for prostate carcinoma and PIN patients. The findings underscored the prevalence of BPH and the significant association between elevated PSA levels and malignant prostatic conditions, reinforcing the diagnostic importance of serum PSA in assessing prostatic lesions.[32]

In the Ethiopian setting, recent studies have started addressing this correlation, but a comprehensive understanding remains to be developed. Our study aims to bridge this gap by focusing on Tikur Anbessa specialized hospital (TASH), aiming to contribute meaningful data to the body of knowledge on this topic.

3 Objectives

3.1 General Objective

-To assess correlation between Serum PSA Levels and Histopathological Pattern of Prostatic Lesions in TASH, pathology department, Addis Ababa, Ethiopia.

3.2 Specific objectives

-To assess the histopathological distribution of prostatic lesions

-To determine correlation between serum PSA levels and histopathological pattern of prostatic lesions

-To identify sociodemographic and clinical characteristics according to histopathological pattern of prostatic lesions

-To determine age distribution of various prostatic lesions

4 Methods and materials

4.1 Study area

The study was conducted at TASH, pathology department which is found in city of Addis Ababa, Ethiopia. It is the one of the largest tertiary teaching hospitals in the country with the vast majority of cases investigated at this department being patients referred from all over the country. The department gives cytopathology, surgical pathology, hematology and neonatal autopsy services. All of the pathologist staff and residents rotate to work through all services.

4.2 Study Design and study period

A five-year institution-based Retrospective Cross-sectional descriptive study was conducted to review all the prostate biopsy histopathology reports and their corresponding serum from November 2023-December 2023. PSA level laboratory result. Data was retrieved from the archive of department of pathology and hospital i-care system that was seen at TASH from January 2019 to December 2023 G.C.

4.3 Population

- **Sources population**: All biopsy diagnosed cases of prostatic lesions over a five-year period at department of pathology, TASH.
- **Study population**: All diagnosed cases of prostatic lesions at department of pathology, TASH (including prostate biopsy specimens referred for histopathology evaluation) over the study period for which serum PSA levels was available recorded.

4.4 Inclusion criteria

- All diagnosed cases of prostatic lesions at TASH (including prostate biopsy specimens referred for histopathology evaluation) during the study period for which serum PSA levels were available recorded.
- All prostate biopsies formalin-fixed and hematoxylin and eosin-stained before microscopic diagnosis.

4.5 Exclusion criteria

- Cases without serum PSA levels

- Cases with inadequate/non-diagnostic biopsies
- Cases without adequate relevant clinical data (incomplete record)

4.6 Sample size determination;

The overall minimum sample size was determined by using single population proportion calculation formula:

$$n = \frac{(Z\ \alpha/2)2 \times P(1-P)}{d\ 2}$$

Where n= minimum sample size required for the study

Z= standard normal distribution (Z=1.96) with confidence interval of 95% and α=0.05

P= Since no study found in our setup regarding correlation of PSA with histopathologic pattern, so - p value- 0.5 will be used

d=is a tolerable margin of error (d=0.05)

$$n = \frac{(1.96)2 \times 0.5(1-0.5)}{0.05\ 2}$$

= 384 By adding 10 % for error gives final sample size of 422 cases.

4.7 Sampling procedures

All the hard copy as well the electronic digital data recording of prostate biopsy histopathology reports and their corresponding serum PSA level laboratory result from year January 2019 GC to December 2023 GC year was reviewed from the archive of pathology department and hospital i-care system.

4.8 Variables

In the study, the following variables were included:

4.8.1 Dependent variable

- Serum PSA level.

4.8.2 Independent variables

- Age
- Histopathologic Diagnosis
- Gleason Score: (for prostate cancer cases)

- Type of Specimen Received at Pathology Department
- Serum PSA value (ng/ml)
- Clinical Diagnosis
- Clinical symptoms

4.9 Operational Definitions

- **Prostatic lesions**: Encompass a wide spectrum of conditions, including BPH/PNH (Benign prostatic hyperplasia or Prostatic nodular hyperplasia), HGPIN, and Prostatic adenocarcinoma.
- **Serum PAS level**: Serum PSA level refers to the concentration of PSA a protein produced by the prostate gland, measured in nanograms per milliliter (ng/ml) of blood serum using standardized laboratory procedures. The serum PSA level is an important biomarker used in the assessment of prostate lesions and can indicate potential benign prostate lesions and prostate cancer. In this study, serum PSA levels was measured through a standardized blood test and a range of 0 to 4ng/ml will be considered as a normal value.
- **BPH/PNH**: Is defined as a benign prostatic tissue with glandular and stromal proliferation confirmed on the histopathological examination[20,21].
- **Histopathology**: Refers to microscopic study of tissue from biopsy or surgical specimen.
- **Histological grading (of prostatic adenocarcinoma)**: The adenocarcinoma cases were graded according to Gleason's grade which is based on evaluation and classification of the degree of glandular architectural differentiation and growth pattern of the tumor in relation to the stroma.[9]
    - **Gleason's grade was as follows:**
        - Grade group 1 = Gleason score 3+3=6
        - Grade group 2 = Gleason score 3+4=7
        - Grade group 3 = Gleason score 4+3=7
        - Grade group 4 = Gleason score 8 (4+4=8, 3+5=8, 5+3=8)
        - Grade group 5 = Gleason score ≥ 9 (4+5=9, 5+4=9, 5+5=10)

4.10 Data collection tools and procedures

The data extraction/collection tool including socio-demographic data, histopathology diagnoses, and corresponding serum PSA level which was extracted from the hard copy/electronic data recording using Kobo Toolbox data collection software.

4.11 Data Quality Control, processing and analysis

A total of 769 prostatic specimens received at TASH pathology department within the study period. Based on the inclusion and exclusion criteria 431 cases were included in this study. All the data was checked for completeness and internal consistency. For further analysis, the data was exported to Statistical Package for Social Science (SPSS) version 26 software. The descriptive analysis of data was indicated using numerical summary measures and presented using frequency tables, figures, and graphs. Manny-Whitney analysis was used to show the presence of statistically significant mean rank difference of age and serum PSA value between benign and malignant prostatic lesions, p-value<0.05 was considered significant. Specificity and sensitivity of the PSA levels at different cut off were calculated by using the formula.

- Sensitivity = TP/ TP+FN (TP=true positive, FN=false negative)
- Specificity =TN/ TN+FP (TN=true negative, FP= false positive)

4.12 Dissemination of the results

The results of the study will be presented to Addis Ababa University, College of health sciences, pathology department. The results of the study will also be sent to reputable journals for publication.

4.13 Ethical consideration

The study proposal was submitted for approval to Institution Review Board (IRB) ethical review committees of the Department of pathology, college of medicine and health sciences, Addis Ababa University.

5 Result

In this study a total of 431 cases were included. The mean age of patients in the study is 66.22±9.1 years. The distribution of biopsy year shows variations with 2019 having 58 cases (13.5%), 2020 with 54 cases (12.5%), 2021 with 99 cases (23.0%), 2022 with 126 cases (29.2%), and 2023 with 94 cases (21.8%). In terms of age groups, the majority falls in the 60-69 years range (156 cases, 36.2%), followed by 70-79 years (146 cases, 33.9%). The histopathologic diagnosis indicates a prevalent occurrence of Benign lesion (340 cases, 78.9%), followed by malignant lesion (86 cases, 20.0%) and intraepithelial proliferative lesions (IPLs) 5 cases (1.2%). In majority of patients 96.8% the presenting symptom was lower urinary tract symptoms (LUTS). Among the total of 431 specimens received during the study period, core needle biopsies (CNB) constituted the major bulk 71.2% (307 cases), followed by radical prostatectomies (RP) 17.2% (74 cases) and TURP chips 11.6% (50 cases). **Table 1** & **Figure 1**

Table 1: characteristics of patients of prostate lesions specimen at TASH, Addis Ababa, January 2019– December 2023.

Variable		Frequency, n	Percentage, %
Biopsy year	2019	58	13.5
	2020	54	12.5
	2021	99	23.0
	2022	126	29.2
	2023	94	21.8
Age group	≤49	13	3.0
	50-59	81	18.8
	60-69	156	36.2
	70-79	146	33.9
	≥80	35	8.1
Histopathologic diagnosis	Benign	340	78.9
	IPLs	5	1.2
	Malignant	86	20.0
Symptoms	LUTS	417	96.8
	Other (Back pain, hematuria etc.)	14	3.2
Specimen type	CNB	307	71.2
	RP	74	17.2
	TURP	50	11.6
	Total	431	100.0

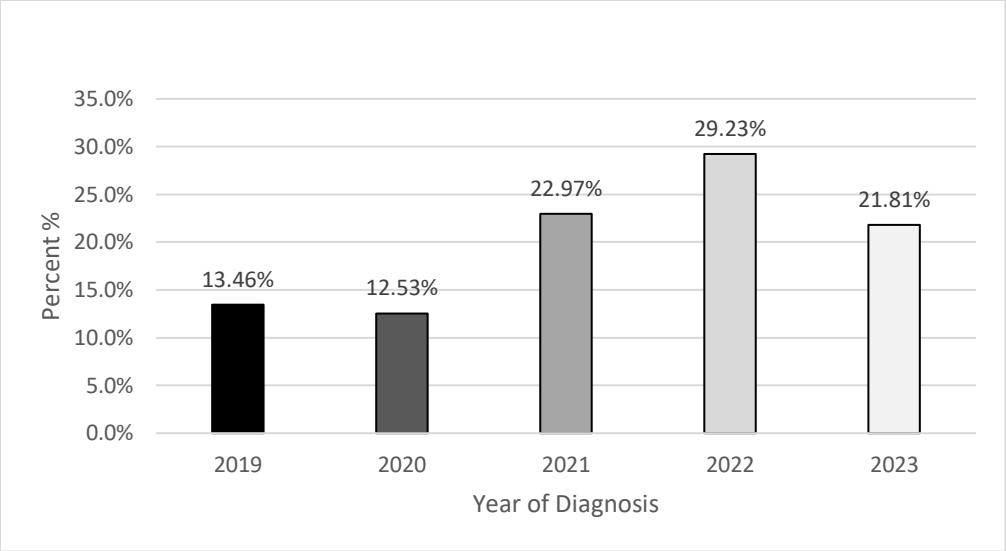

Figure 1 : The five-year pattern of prostate specimens diagnosed (n=431), at TASH, Addis Ababa, January 2019– December 2023.

In the age-wise distribution of specific prostatic lesions from total of 431 cases in the study, the distribution of specific prostatic lesions within each age category is detailed as follows: for patients aged ≤49 years (13 cases), 100% exhibited benign lesions; in the 50-59 years age group (81 cases), the prevalence was primarily benign (84.0%), with a small percentage of malignant lesions (16%); among those aged 60-69 years (156 cases), the distribution included 84% benign, 1.3% IPLs, and 14.7% malignant lesions; patients aged 70-79 years (146 cases) showed 71.2% benign, 2.1% IPLs, and 26.7% malignant lesions; and for individuals aged ≥80 years (35 cases), 68.6% were diagnosed with benign lesions, while 31.4% had malignant lesions. The overall distribution across all age groups revealed 78.9% benign lesions, 1.2% IPLs, and 20% malignant lesions among the total patients. **Table 2**

Table 2: Age wise distribution of Specific prostatic lesion, n=431

Age group (Years)	Total no. patients	Benign	IPLs	Malignant
		n (%)	n (%)	n (%)
≤49	13	13(100)	-	-
50-59	81	68(84.0)	-	13(16)
60-69	156	131(84.0)	2(1.3)	23(14.7)
70-79	146	104(71.2)	3(2.1)	39(26.7)
≥80	35	24(68.6)	-	11(31.4)
Total	431	340(78.9)	5(1.2)	86(20.0)

Overall, the distribution of specific prostatic lesions among 431 cases revealed a predominant occurrence of benign lesions, constituting 78.9% (340 cases) of the total cases. Specifically, the benign lesions were exclusively BPH/PNH with different presentations. BPH/PNH without prostatitis and BPH/PNH with prostatitis accounted for, 306 cases (71.0%) and 25cases (5.8%), respectively. Whereas, BPH/PNH with Tuberculosis/Granulomatous inflammation were identified in 6 cases (1.4%), while BPH/PNH with basal cell hyperplasia was present in 3 cases (0.7%). IPLs, HGPIN, constituted 1.2% (5 cases). Malignant cases, exclusively represented by prostatic acinar adenocarcinoma, accounted for 20.0% (86 cases). **Table 3**

Table 3: Spectrum of specific Prostatic Lesions, n=431

Prostatic lesions	Frequency, n	Percentage, %
Benign		
BPH/PNH	306	71.0%
BPH/PNH with prostatitis	25	5.8%
BPH/PNH with Tuberculosis/Granulomatous inflammation	6	1.4%
BPH/PNH with Basal cell hyperplasia	3	0.7%
IPLs		
HGPIN	5	1.2%
Malignant		
Acinar adenocarcinoma	86	20.0%
Total	431	100.00%

Regarding the serum PSA levels of 431 cases, the findings revealed varying patterns across different PSA ranges. Among the cases, 34.7% with serum PSA levels up to 4 ng/ml and 36.2% in the 4-10 ng/ml range were primarily seen in BPH/PNH. In the higher serum PSA ranges (50-100 ng/ml and >100 ng/ml), the majority of cases were classified as acinar adenocarcinoma, constituting 33.7% and 36.0%, respectively. These findings underscore the correlation between elevated serum PSA levels and an increased likelihood of malignancy within the studied patient population. **Table 4**

Table 4: Serum prostate specific antigens correlation with prostatic lesions, n=431

Serum PSA (ng/ml)	Total no. patients	BPH/PNH	HGPIN	Acinar adenocarcinoma
		n (%)	n (%)	n (%)
Up to 4	121	118(34.7)	1(20.0)	2(2.3)
4-10	124	123 (36.2)	-	1(1.2)
10-20	80	68(20)	3(60.0)	9(10.5)
20-50	43	28(8.2)	1(20.0)	14(16.3)
50-100	32	3(0.9)	-	29(33.7)
>100	31	-	-	31(36.0)
Total	431	340(100.00)	5(100.00)	86(100.00)

When assessing the probability of malignancy in patients, serum PSA levels were utilized, and a cutoff point of 4 ng/ml was adopted. Values below 4 ng/ml were categorized as indicating the absence of malignancy, while values exceeding the threshold were regarded as indicative of malignancy. The test outcomes were subsequently compared with the histopathological diagnosis distinguishing between BPH/PNH and acinar Pca. Sensitivity and specificity, along with positive and negative predictive values, were computed for the analysis. **Table 5**

Table 5: Probability of PSA in detecting malignancy

	%
Sensitivity	97.7%
Specificity	34.7%
Positive predictive value	27.5%
Negative predictive value	98.3%

There is statistically significant difference in the mean rank (median) of serum PSA value and age between BPH/PNH and prostatic acinar adenocarcinoma cases (174.1 Vs 369.5, p-value<0.001 and 203.7 Vs 252.4, p-value=0.001, respectively). This implies that there is direct association between increased age and higher serum PSA value, and prostatic acinar adenocarcinoma. **Table 6**

Table 6: Comparison of mean rank (median) of age and serum PSA value between benign and malignant prostatic lesions. N=426 (Mann-Whitney U test)

Variable	Benign, n=340	Malignant, n=86	P-value
	Mean Rank(median)		

Age	203.7	252.4	0.001
Serum PSA ng/ml	174.1	369.5	<0.001
	Mean±SD		
Age	65.5±9.1	68.98±9.2	-
Serum PSA ng/ml	8.5±8.9	84.7±61.5	-

The distribution of Gleason's grade groups in prostate acinar adenocarcinoma cases (n=86), the study observed varying proportions within distinct grade categories. Remarkably, Gleason's Grade group 5 exhibited the highest prevalence, comprising 57.0% of the total cases. This was followed by Gleason's Grade group 4, 3, 2, and 1, representing 22.1%, 8.1%, 8.1% and 4.7% of the prostatic acinar adenocarcinoma cases respectively. **Figure 2**

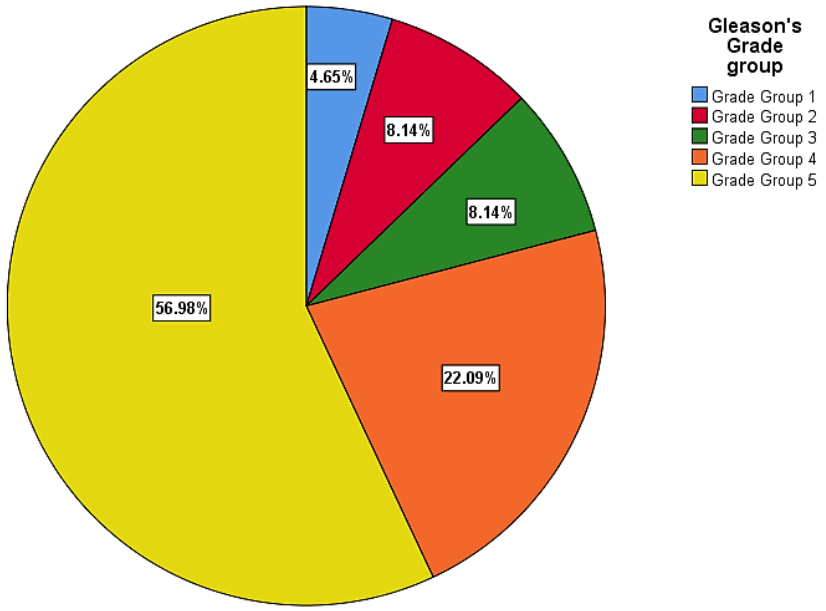

Figure 2: Pie-chart: Percentage of Gleason's grade group among Prostatic adenocarcinoma cases, n=86

Among the prostatic acinar adenocarcinoma cases (86 cases), 38.4% exhibited Perineural invasion (PNI), while 9.3% showed no signs of PNI. Remarkably, the majority (52.3%) did not have PNI status reported. **Figure 3**

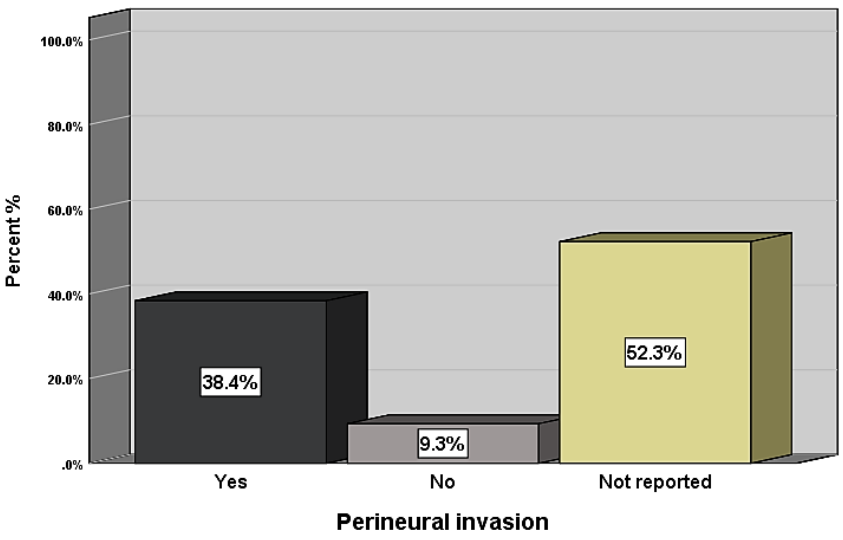

Figure 3: Distribution of Perineural invasion among prostate acinar adenocarcinoma patients, n=86

6 Discussion

This study included 431 patients diagnosed with prostatic lesions at the pathology department of TASH over five years from January2019 to December 2023. Patient ages ranged from 48 to 90 years, with a mean age of 66.22±9.2 years, predominantly in the 7th decade of life. This finding was in line to various studies done in Nepal, India, Saudi Arabia and Nigeria. [30,32–35]

In this study, BPH/PNH constituted 78.9% of histopathological diagnoses, followed by adenocarcinoma at 20%, aligning with mentioned studies. BPH/PNH with prostatitis occurred in 5.8%, akin to an Indian study (7.3%)[5,29,35,36]. However, in contrast to another Indian study reporting 25.31% BPH/PNH with prostatitis, our setup might overlook reporting presence of inflammation[5,29,36]. Prostatic adenocarcinoma constituted 20.0% of our study cases, aligning with rates in a 2003 Nigerian study (22.4%), a 2014 Indian study (23.58%) and other studies[5,29,35–37]. While our findings align with global studies, prostate cancer incidence varies, with lower rates in native Asian men but higher in Asians in Westernized countries[38]. The lower Asian incidence is not fully understood, potentially linked to genetic, environmental factors like Western diets. Limited exposure to prostate-specific antigen (PSA) screening in Asian individuals may significantly contribute[38]. Overall, this study's comprehensive analysis underscores benign lesions, particularly BPH/PNH, dominating prostatic pathology.

In our study, BPH/PNH peaks in the 7th decade, followed by the 8th decade (mean age 65.5±9.1 years). Prostatic intraepithelial neoplasm peaks at 70-79 years (mean 69.2±5.9 years). The age range aligns with a comparable study in India[17,35,36,39].Aging is a crucial demographic factor influencing BPH incidence and severity [21]. Our study identified a cluster of prostatic adenocarcinoma cases above the 7th decade (72.8%, mean age 68.98 ±9.2 years), aligning with a 2020 institution study (73% above the 7th decade)[40]. This aligns with similar findings in other Indian studies[35,36].

In this study, the majority of patients were in Gleason's grade group 4 and grade group 5, comprising 22.09% and 56.98%, respectively—comparable to a 2020 Saudi Arabian study, which documented 15.9% grade group 4 and 52.27% grade group 5 [41]. The Gleason grading system, derived from architectural features of prostate cancer cells, stands as the predominant histological grading method for prostatic adenocarcinoma. It closely correlates with clinical behavior, serving as a crucial prognostic index[5,42]. Additionally, this score, along with stage, age, and PSA, significantly influences treatment decisions[42]. It's the sole system

acknowledging histologic tumor heterogeneity within a single prostate specimen, assigning grades to primary and secondary patterns, amalgamating them into scores and grade groups (ranging from 6-10 and 1-5, respectively)[9]. Patients with a pathological GS of ≤6 exhibit excellent progress-free survival, reaching up to 90%. Conversely, men with GS ≥7 adenocarcinoma face a 29-43% risk of death from prostate cancer[43]. Limited disease awareness contributes to the elevated scores[44].

Perineural invasion is pathognomonic for prostate cancer when tumor cells show circumferential or intraneural invasion[45]. A study conducted in India, Iran, and the USA, PNI was identified in 42.5%, 25.5%, and 20% of prostate cancer cases, respectively[46–48]. These findings align with our study, indicating PNI in 38.4% of prostatic adenocarcinoma cases. Notably, a majority (52.3%) lacked reported PNI status, emphasizing the need for standardized reporting to understand PNI's prevalence and impact in prostate cancer.

In our study, the mean serum PSA value in BPH/PNH cases was 8.5±8.9 ng/ml which is comparable to study done in India which showed 5.02 ± 3.13 ng/ml, 4.86 ± 3.03 ng/ml and 5.05 ± 3.15 ng/ml[35,39,49]. Modest elevation in BPH/PNH cases in our study may be due to associated prostatitis or Tuberculosis/Granulomatous inflammation. Prostatic adenocarcinoma in this study had a mean serum PSA value of 84.7±61.5 ng/ml in line with study in India done in 2017 59.65 ±38.65 ng/ml and in 2016 60.63±38.42 ng/ml [35,49]. Finally, a statistically significant distinction emerged in the median serum PSA values and age between BPH/PNH cases and prostatic acinar adenocarcinoma cases. The medians differed significantly, recording at 174.1 Vs 369.5 ($p<0.001$) for PSA values and 203.7 Vs 252.4 ($p=0.001$) for age, respectively. This highlights an association between higher PSA values and advancing age with prostatic adenocarcinoma.

In this study, out of 340 cases of BPH/PNH 34.7% had serum PSA value below 4 ng/ml, 36.2% between 4ng/ml to 10 ng/ml and 29.1% above 10ng/ml. whereas, almost all 97.7% (84/86) prostatic adenocarcinoma cases had serum PSA value above 4 ng/ml, only 2 cases (2.3%) had below 4 ng/ml and one case of prostatic adenocarcinoma had serum PSA value between 4 to 10 ng/ml range similar to the study done in our institution in 2020 which showed 90.5% of PSA value above 4ng/ml[40].

In a study carried out within the Iranian context, serum PSA threshold of 4 ng/ml is usually an indication for prostate biopsy. Moreover, serum PSA concentrations that reside in the

range of 4 ng/ml to 10 ng/ml, herein termed the 'grey zone,' exhibit a noteworthy but diminished sensitivity. Notably, levels surpassing the 10 ng/ml benchmark demonstrate a high sensitivity for prostate cancer. The sensitivity even reaches 100% if we consider values higher than 15 ng/ml[50].

Table 7: Comparison of sensitivity and specificity of PSA.

	Present study	Souza Pereira et al. 2017,[51]	Ghafoori et al. 2009.,[50]	Catalona WJ et al.,[52]	Morgan et al.,[53]	Sheikh et al.,[54]
Sensitivity	97.7%	96.67 %	93.4%	79%	94.9%	93.4%
Specificity	34.7%	38.57%	15.3%	59%	88.4%	59%

7 Conclusion

Our study found serum PSA, a valid and sensitive marker, is crucial for early prostate cancer screening, with a cut-off value of 4 ng/ml showing 97.7% sensitivity and 34.7% specificity. Although sensitive, screening prostatic lesions with PSA lacks specificity.

Our study concludes nodular prostatic hyperplasia is the most prevalent lesion, with carcinoma and BPH/PNH mainly presenting in the seventh and sixth decades. Gleason's grade group 5 dominates prostatic carcinoma grades, and a correlation is found between elevated PSA values and advancing age, and prostatic adenocarcinoma.

Our study affirms PSA's value as a screening tool for prostatic adenocarcinomas, especially when levels are high. However, it highlights the need for a more specific screening test, as PSA levels lack specificity.

8 Strength and Limitations of the Study

In Ethiopia, no prior studies compare serum Prostate-Specific Antigen (PSA) values across various prostatic lesions. Our study, involving 431 diverse patients with prostatic lesions over five years, offers robust insights. The comprehensive age range (48 to 90 years, mean age 66.22±9.2) enhances representation. The study's focus on lesions diagnosed at TASH's pathology department adds credibility, reinforcing overall reliability.

A significant limitation was the inability to include PSA levels for all subjects, impacting the study's comprehensiveness. The single-center study at TASH may limit the generalizability of findings to broader populations. Additionally, the absence of a follow-up study hinders assessing patients' eventual outcomes.

Moving forward, further research in advanced settings is encouraged to deepen the understanding of clinicopathological correlations in prostatic lesions.

9 Recommendation

Enhanced Reporting Practices: Implement standardized reporting for PNI in prostate cancer cases. This will significantly improve our understanding of PNI prevalence and impact.
Targeted Screening: Prioritize screening and awareness efforts for prostatic lesions in the 6^{th} and 7^{th} decades. This proactive approach aims to enhance early detection, facilitating timely intervention and potentially improving patient outcomes.

Additionally, future research should address study limitations. Including serum PSA levels for all subjects and conducting follow-up studies will offer valuable insights into the long-term outcomes of patients with prostatic lesions, contributing to a more robust knowledge base in this field.

10 References

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11 Annexes

11.1 Annex 1: Data Collection sheet

No.	Questions	Response	Code	Remark
	ID number of the patient	_____		
Q101	Age of the Patients in Year	_____ Years		
Q102	Residence			
Q103	Histopathologic Diagnosis	BPH/PNH		
		Prostatitis		
		Prostate intraepithelial neoplasia (PIN)		
		Adenocarcinoma		
		Other (please specify): _____		
Q103.1	Gleason Score: (for prostate cancer cases)			
Q104	Type of Specimen Received at Pathology Department	please specify: _____		
Q105	Type of Biopsy Procedure	please specify: _____		
Q106	Prostate Volume: (if available)	_____ (in cc)		
Q107	Clinical Diagnosis	please specify: _____		
Q108	Clinical symptoms (Check all that apply)	Urinary frequency		
		Urinary urgency		
		Nocturia		
		Hematuria		
		Lower back pain		
		Erectile dysfunction		
		Other (please specify): ____		
Q109	Digital Rectal Examination (DRE) Results (if available)	Normal		
		Abnormal		
Q110	PSA Levels: (in ng/ml)	_____ ng/ml		
Q111	Medical History related to Prostate	Previous prostate-related surgeries		
		Previous prostate biopsy		

		Others (please specify): _____		