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INFLAMMATION-LINKED PSA VARIABILITY IN BPH PATIENTS TREATED WITH ANTIBIOTICS: A LONGITUDINAL STUDY WITH HISTOPATHOLOGIC CORRELATION

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Abstract: Benign prostatic hyperplasia (BPH) frequently coexists with prostatic inflammation, which may elevate prostate-specific antigen (PSA) and complicate differentiation from prostate cancer. To evaluate longitudinal changes in C-reactive protein (CRP) and PSA parameters following culture-guided antibiotic therapy in men with BPH, and to assess associations with prostate biopsy outcomes. A longitudinal retrospective observational study included 24 men with BPH followed from January to December 2025. CRP, total PSA (tPSA), and free PSA (fPSA) were measured at baseline without antibiotics (January) and at three subsequent timepoints (May, September, December) after antibiotic therapy guided by urine culture and antibiogram. Antibiotic regimens included levofloxacin 500 mg once daily for 28 days, nitrofurantoin 100 mg three times daily for 10 days, and cefixime 400 mg once daily for 10 days. Prostate biopsy was recommended to all patients; those declining biopsy were retained as a descriptive subgroup. Statistical analysis: Continuous variables were summarized as median and interquartile range. Repeated-measures comparisons across four timepoints were performed using the Friedman test. Between-group comparisons were performed using the Mann–Whitney U test. A two-sided p value < 0.05 was considered statistically significant. Results: CRP and PSA parameters demonstrated longitudinal variation over the four timepoints. PSA kinetics differed according to histopathologic findings among biopsied patients. Conclusion: Serial CRP and PSA assessment under culture-guided antibiotic therapy may support risk stratification and biopsy decision-making in BPH patients with suspected inflammation.

Keywords: *benign prostatic hyperplasia, C-reactive protein, prostate-specific antigen, prostatitis*
Field: Medical Sciences and Health

1. INTRODUCTION

Benign prostatic hyperplasia (BPH) is frequently accompanied by chronic or subclinical prostatic inflammation (Nickel, 2008; Nickel et al., 2019). Increasing evidence suggests that inflammatory processes within the prostate may significantly influence prostate-specific antigen (PSA) variability, thereby complicating differentiation between benign inflammatory conditions and prostate cancer (De Marzo et al., 2007; Shariat et al., 2022). Contemporary urological research has emphasized that PSA is not a cancer-specific marker but rather a prostate-derived protein whose serum levels may be altered by infection, inflammation, and epithelial disruption (Loeb et al., 2020; Ferro et al., 2024).

Recent studies have highlighted the clinical relevance of PSA kinetics rather than isolated PSA measurements (Loeb et al., 2020). Longitudinal PSA variability has been associated with inflammatory activity in benign prostatic disease, while malignant transformation tends to demonstrate different kinetic patterns (Shariat et al., 2022). Systematic reviews evaluating antibiotic therapy in men with elevated PSA have reported that PSA reduction may occur following treatment; however, PSA response alone cannot reliably exclude underlying malignancy (Buddingh et al., 2017; Mari et al., 2023). Current European and American urological guidelines recommend interpreting PSA dynamics within clinical context, particularly when considering prostate biopsy decisions (American Urological Association, 2023; European Association of Urology, 2024).

In addition to total PSA, the free-to-total PSA ratio is widely used to refine risk stratification in men within the diagnostic gray zone (Heo et al., 2024). Nevertheless, chronic prostatitis may also influence free PSA behavior, limiting specificity and further complicating diagnostic interpretation (Jung et al., 1998;

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Stancik et al., 2004). Moreover, systemic inflammatory markers such as C-reactive protein (CRP) have been investigated as potential adjunctive indicators reflecting inflammatory burden in prostatic disease (Zhou et al., 2023).

Despite these observations, limited real-world longitudinal data exist evaluating combined CRP and PSA kinetics under culture-guided antibiotic therapy, particularly with histopathologic correlation. The present study aimed to evaluate serial CRP and PSA dynamics across four timepoints over a 12-month period in men with BPH, and to examine whether differential biomarker trajectories correspond to biopsy-confirmed chronic prostatitis or prostate carcinoma.

2. OBJECTIVES

To evaluate longitudinal changes in C-reactive protein (CRP) and PSA parameters following culture-guided antibiotic therapy in men with BPH, and to assess associations with prostate biopsy outcomes.

3. MATERIAL AND METHODS

Study Design and Setting

This longitudinal retrospective observational study was conducted at the Department of Urology, General Hospital "Ferid Murad", Gostivar, North Macedonia. Patients were followed from January to December 2025 with serial laboratory assessments at four predefined timepoints.

Participants

A total of 24 men with a clinical diagnosis of benign prostatic hyperplasia (BPH) who underwent repeated laboratory monitoring were included. All patients had elevated PSA values and clinical suspicion of inflammatory contribution. Prostate biopsy was recommended to all patients according to clinical evaluation and guideline-based practice. Twenty patients underwent biopsy, while four declined and were retained as a descriptive subgroup.

Histopathologic findings among biopsied patients were categorized as chronic prostatitis or prostate carcinoma.

Laboratory Measurements

Serum C-reactive protein (CRP, mg/L), total PSA (tPSA, ng/mL), free PSA (fPSA, ng/mL), and the free-to-total PSA ratio (%) were recorded at four timepoints: T1: January (baseline, prior to antibiotic therapy); T2: May; T3: September; T4: December.

Antibiotic therapy was prescribed according to urine culture and antibiogram results. Regimens included:

- Levofloxacin 500 mg once daily for 28 days
- Nitrofurantoin 100 mg three times daily for 10 days
- Cefixime 400 mg once daily for 10 days

Treatment selection was individualized based on microbiological findings.

Statistical Analysis

Continuous variables were summarized as median and interquartile range (IQR). Longitudinal changes across the four timepoints (T1–T4) were analyzed using the Friedman test for repeated measures.

Between-group comparisons of biomarker changes from baseline to T4 (ΔT4–T1) among biopsied patients (chronic prostatitis vs prostate carcinoma) were performed using the Mann–Whitney U test.

The subgroup of patients who declined biopsy was reported descriptively and was not included in inferential between-group comparisons.

All statistical tests were two-sided, and p values < 0.05 were considered statistically significant.

4. RESULTS

A total of 24 men with clinically diagnosed benign prostatic hyperplasia were followed across four timepoints (T1 January, T2 May, T3 September, T4 December). Prostate biopsy was recommended to all patients; 20 underwent biopsy, while 4 declined. Among biopsied patients, 11 were diagnosed with chronic prostatitis and 9 with prostate carcinoma. Baseline characteristics are summarized in Table 1.

Table 1. Baseline Characteristics (T1)

Variable	*Total (N=24) Median (IQR)*	*Prostatitis (n=11)*	*Carcinoma (n=9)*	*No Biopsy (n=4)*
Age (Years)	63.5 (59.0–68.0)	62.0 (59.0–64.5)	65.0 (63.0–71.0)	61.5 (58.8–63.5)
CRP (mg/L)	52.85 (28.50–79.28)	37.60 (28.50–52.30)	78.95 (77.10–83.55	28.10 (20.03–34.35)
Total PSA (ng/ml)	8.92 (6.25–12.41)	8.19 (6.05–8.69)	11.00 (9.89–13.88)	4.85 (3.61–5.39)
Free PSA (ng/ml)	1.66 (1.14–2.29)	1.34 (1.06–2.11)	2.07 (1.80–2.30)	0.75 (0.61–0.92)
Free/Total PSA Ratio %	18.85 (14.63–26.03)	17.10 (13.60–25.50)	18.80 (16.30–21.40)	24.45 (17.78–25.43)

Source: Authors' own data

In the entire cohort, significant longitudinal changes were observed. CRP levels demonstrated a marked and progressive decline from T1 to T4 (Friedman test, p = 0.001). Total PSA levels also changed significantly across timepoints (Friedman test, p = 0.003), with an overall downward trend by T4. In contrast, although the free-to-total PSA ratio showed a rising median pattern across timepoints, the global repeated-measures comparison did not reach statistical significance (Friedman test, p = 0.133) (Table 2).

Table 2. Longitudinal Biomarker Changes (T1–T4)

Parameter	*T1*	*T2*	*T3*	*T4*	*P (Friedman)*
CRP (mg/L)	52.85 (28.50–79.28)	33.15 (24.65–58.45)	23.35 (19.28–43.73)	19.85 (16.65–22.83)	<0.001
Total PSA (ng/ml)	8.92 (6.25–12.41)	6.27 (4.40–9.87)	4.40 (3.25–8.03)	4.35 (3.18–7.93)	0.003
Free/Total PSA Ratio %	18.85 (14.63–26.03)	25.50 (14.80–33.30)	33.15 (19.88–44.83)	36.00 (21.75–48.48)	0.133

Source: Authors' own data

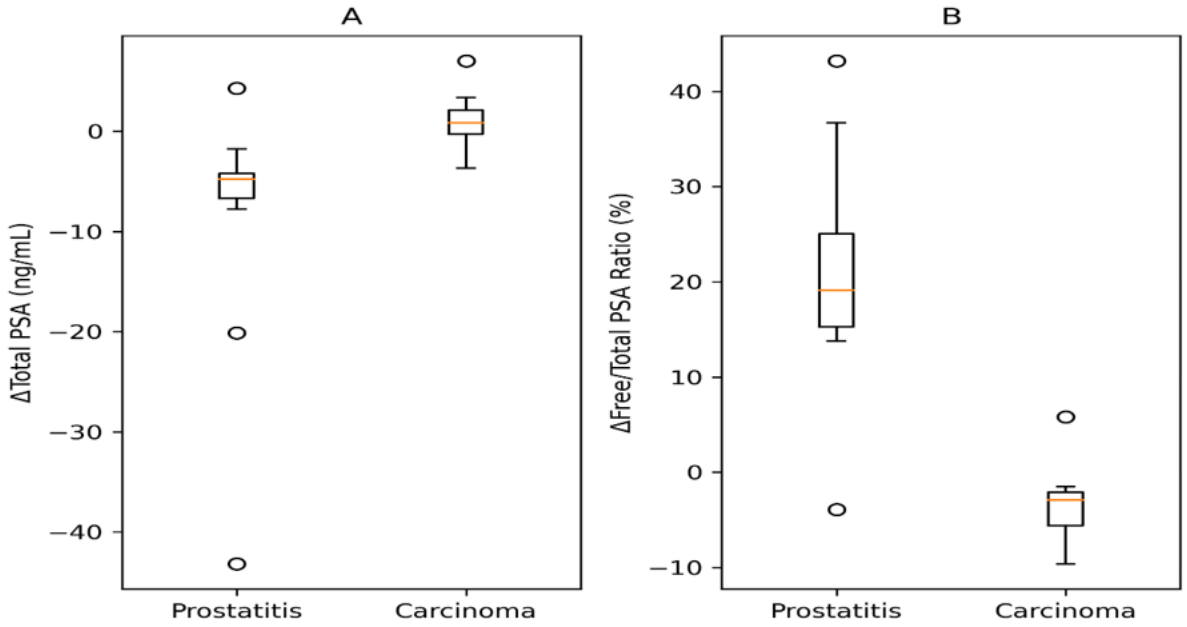
When analysis was restricted to biopsied patients, distinct differences emerged between histopathologic groups. The median change in total PSA (T4–T1) was −4.78 ng/mL (IQR −6.70 to −4.22) in patients with chronic prostatitis, compared with +0.83 ng/mL (IQR −0.25 to 2.09) in patients with prostate carcinoma (p = 0.003). Similarly, the median change in free-to-total PSA ratio was +19.10% (IQR 15.25 to 25.05) in prostatitis and −2.90% (IQR −5.60 to −2.10) in carcinoma (p < 0.001) (Table 3). The distribution of biomarker changes is illustrated in Figure 1. The subgroup that declined biopsy was reported descriptively and was not included in inferential comparisons.

Table 3. T4–T1 Changes in Biopsied Patients

Parameter	*Prostatitis (n=11) Median (IQR)*	*Carcinoma (n=9) Median (IQR)*	*p (Mann-Whitney)*
ΔTotal PSA (ng/mL)	-4.78 (-6.70 to -4.22)	+0.83 (-0.25 to 2.09)	0.003
ΔFree/Total Ratio (%)	+19.10 (15.25 to 25.05)	-2.90 (-5.60 to -2.10)	<0.001

Source: Authors' own data

Figure 1. Boxplot Representation of ΔTotal PSA (A) and ΔFree-to-Total PSA Ratio (B) (T4–T1) According to Histopathologic Diagnosis. Panel A shows ΔTotal PSA (ng/mL). Panel B shows ΔFree-to-Total PSA Ratio (%).



Source: Authors' own data

5. DISCUSSION

The present longitudinal study demonstrates that inflammatory activity and PSA kinetics are closely interrelated in men with benign prostatic hyperplasia undergoing culture-guided antibiotic therapy. While CRP showed a progressive decline across timepoints, total PSA levels also decreased significantly in the overall cohort. However, the most clinically relevant finding emerged when biomarker dynamics were stratified according to histopathology.

Patients with biopsy-confirmed chronic prostatitis exhibited a marked reduction in total PSA accompanied by a substantial increase in the free-to-total PSA ratio. In contrast, patients with prostate carcinoma demonstrated stable or slightly increased total PSA levels and a reduction in the free-to-total PSA ratio. These opposing kinetic patterns suggest that longitudinal biomarker trajectories may provide more meaningful clinical insight than isolated PSA measurements, consistent with prior observations regarding PSA variability and inflammatory contribution (Loeb et al., 2020; Shariat et al., 2022).

Contemporary literature increasingly supports the interpretation of PSA as a dynamic marker influenced by inflammatory processes rather than a cancer-specific biomarker (Nickel et al., 2019; Ferro et al., 2024). Several recent studies have shown that PSA variability may reflect prostatic inflammation, and that short-term PSA reductions after antimicrobial therapy are frequently associated with benign inflammatory conditions (Mari et al., 2023). However, systematic reviews emphasize that PSA decline alone cannot safely exclude malignancy (Buddingh et al., 2017). Our findings align with this perspective, as the pattern of combined PSA and ratio kinetics, rather than PSA reduction in isolation, distinguished inflammatory disease from carcinoma.

The free-to-total PSA ratio remains an established tool for risk stratification in the diagnostic gray zone (Heo et al., 2024), yet inflammatory conditions may alter its behavior (Jung et al., 1998; Stancik et al., 2004). In the present study, ratio increase in prostatitis and ratio decline in carcinoma created a clear separation between groups. This observation reinforces the importance of interpreting PSA derivatives within longitudinal and clinical context rather than as static thresholds.

From a practical standpoint, integration of systemic inflammatory markers such as CRP with PSA kinetics may enhance decision-making in patients with suspected inflammatory contribution. CRP has been investigated as a biomarker reflecting systemic inflammatory burden in prostate disease (Zhou et al., 2023). Serial biomarker assessment under microbiologically guided therapy may provide a structured approach that reduces diagnostic uncertainty prior to biopsy.

Several limitations should be acknowledged. The study was conducted in a single center with a modest sample size. Antibiotic regimens were individualized based on culture results, introducing

treatment heterogeneity. Additionally, the subgroup that declined biopsy was not included in inferential analysis. Larger prospective studies with standardized follow-up protocols are warranted to validate these findings.

6. CONCLUSION

Serial assessment of CRP and PSA parameters across repeated timepoints during culture-guided antibiotic therapy reveals distinct biomarker trajectories in chronic prostatitis compared with prostate carcinoma. Interpretation of PSA kinetics in conjunction with inflammatory markers may support risk stratification and assist clinical decision-making regarding prostate biopsy in selected patients with BPH and suspected inflammatory contribution.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

FUNDING

This research received no external funding.

ETHICAL APPROVAL

This retrospective observational study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was reviewed and approved by the Institutional Ethics Committee of the General Hospital “Ferid Murad”, Gostivar. Due to the retrospective nature of the study and the use of anonymized clinical data, the requirement for written informed consent was waived by the ethics committee.

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