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ISSN: 2836-5062

Open Access

Journal of Clinical Oncology Reports

Mini Review

Systemic Inflammation and Extra-prostatic Pathological Processes as Determinants of PSA Levels: A Comprehensive Clinical Review

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Received Date: 20 April 2026; **Accepted Date:** 12 May 2026; **Published Date:** 18 May 2026

Abstract

Background: Prostate-specific antigen (PSA) is an organ-specific rather than a tumor-specific marker. Traditional diagnostics frequently overlook the fact that the prostate gland functions as a biological sensor of the systemic inflammatory response. Misinterpretation of PSA in the "gray zone" (4–10 ng/mL) without considering the comorbid background leads to significant overdiagnosis and unnecessary invasive procedures.

Aim: To conduct a systemic analysis of the impact of extra-prostatic pathologies, metabolic disorders, and pro-inflammatory biomarkers on PSA levels to develop an integrated approach to clinical diagnostics. Main Findings: Systemic mediators (IL-6, TNF-α) activate androgen receptors via the JAK/STAT pathway, enhancing KLK3 gene expression even under androgen-deprived conditions.

Systemic inflammation indices, such as the Systemic Immune-Inflammation Index (SII) and Neutrophil-to-Lymphocyte Ratio (NLR), show a stable positive correlation with PSA levels.

Key determinants of false-positive results include obesity (adiponectin < 6 μg/mL, leptin > 4 ng/mL), chronic kidney disease (accumulation of uremic toxins like indoxyl sulfate), and inflammatory bowel disease (via the gut-prostate axis and shared FOLH1 gene locus).

Conclusions: Clinical interpretation of PSA must incorporate the analysis of systemic inflammatory markers.

A Repeat Testing algorithm 4–8 weeks after correcting systemic factors can prevent up to 40% of unnecessary biopsies.

Keywords: Systemic inflammation, Prostate-specific antigen (PSA), Systemic Immune-Inflammation Index (SII), Gut-prostate axis, Cross-sensitization, JAK/STAT signaling, metaflammation.

Introduction

A New Paradigm of PSA Interpretation

Prostate-specific antigen (PSA), or human kallikrein 3 (hK3), is a 33 kDa serine protease. In the serum, it exists in a free form (~28 kDa) and a form bound to α1-antichymotrypsin (~90 kDa). Understanding this molecular differentiation is critical: the free form has a low molecular weight and is easily filtered by the kidneys, whereas the complexed form has limited renal clearance. Modern systemic biology treats PSA levels as a marker of the integrity of the blood-prostate barrier. Any systemic disturbance of homeostasis—from metaflammation to uremic intoxication—leads to the disruption of tissue barriers and the leakage of hK3 into the bloodstream. In 25–40% of cases, PSA elevation in the "gray zone" (4–10 ng/mL) is caused by extra-prostatic factors

. Ignoring these systemic drivers turns PSA into a tool for overdiagnosis, exposing patients to risks of iatrogenic infection and psychological stress

Systemic Inflammation Biomarkers and PSA Correlation

Systemic inflammation modulates PSA expression through

endocrine signals. The primary mediator is IL-6, which activates the JAK/STAT signaling pathway, stimulating androgen receptors (AR) even in low-testosterone environments. This facilitates PSA hyperproduction by the epithelium unrelated to malignancy. Integral indices are used to objectify this influence:

Systemic Immune-Inflammation Index (SII): Calculated as (P×N)/L. High SII is associated with a decreased f/t ratio, mimicking the profile of prostate cancer (PCa). NHANES data (2003–2010) revealed an inverted U-shaped relationship between SII and PSA, with a turning point at 1168.18.

Neutrophil-to-Lymphocyte Ratio (NLR): Reflects the imbalance between innate and adaptive immunity. Elevated NLR correlates with PSA > 4 ng/mL (OR = 1.14).

Fibrinogen: A strong predictor of PSA elevation (OR = 1.88).

Metabolic and Autoimmune Drivers

Obesity and Metaflammation: Dysfunctional adipose tissue generates over 600 adipokines.

A ratio of adiponectin < 6 μg/mL combined with leptin > 4 ng/mL increases the risk of PCa progression (HR = 4.04).

Chronic Kidney Disease (CKD): CKD creates "multisystem inflammatory amplification".

Reduced renal filtration leads to the accumulation of uremic toxins (e.g., indoxyl sulfate), which activate the NF-κB pathway and provoke oxidative stress in the prostate.

Impaired clearance of IL-6 and TNF-α further contributes to secondary PSA elevation.

Autoimmune States

In Rheumatoid Arthritis (RA), high levels of TNF-α increase PSA levels and enhance vascular permeability (VEGF), facilitating marker translocation into the bloodstream.

The Gut-Prostate Axis and Pancreatic Contribution

Patients with Inflammatory Bowel Disease (IBD) have a 4–5 times higher risk of PCa detection (HR = 4.84).

This is due to cross-sensitization via shared innervation in the dorsal root ganglia (DRG) and shared genetic loci, such as FOLH1 (which encodes PSMA). Additionally, PSA is expressed in pancreatic ductal cells.

While only 5% of men with acute pancreatitis show a PSA spike, this rises to 33% in patients with pancreatic cancer.

Acute and Pharmacological Influences

Viral Infections: Cytokine storms (IL-6, IL-1β) during influenza or other URTI disrupt the blood-prostate barrier via vasodilation and stromal edema.

Pharmacological Traps: Decongestants (pseudoephedrine) and antihistamines can cause acute urinary retention, mechanical epithelial irritation, and sharp PSA spikes. Conversely, NSAIDs (aspirin) may lower PSA (e.g., from 7.58 to 5.17 ng/mL), potentially masking aggressive processes. 5-alpha-reductase inhibitors (5-ARIs) typically halve the PSA value.

Clinical Recommendations and Conclusions

PSA is a dynamic marker of systemic homeostasis; its isolated interpretation without considering SII and NLR indices leads to significant diagnostic errors.

Metabolic syndrome, CKD, and IBD create an "inflammatory mask" of prostate cancer.

Clinical Recommendation

A Repeat Testing algorithm 4–8 weeks after the resolution of systemic inflammation or the correction of acute factors is mandatory to reduce unnecessary biopsies by 40%.

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Citation: Muzichenko Petr. Systemic Inflammation and Extra-prostatic Pathological Processes as Determinants of PSA Levels: A Comprehensive Clinical Review. *J. Clin. Oncol. Rep.* Vol. 5 Iss. 1. (2026) DOI: 10.58489/2836-5062/029