



The Comprehensive Systematic Review of Association of PSA Level to Clinical Stage of Carcinoma Prostat

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ABSTRACT

Introduction: Prostate-specific antigen (PSA) is a cornerstone biomarker in prostate cancer (PCa) management, used for screening, diagnosis, staging, and monitoring treatment response. However, the precise relationship between PSA levels and clinical stage is complex and influenced by numerous factors. This systematic review synthesizes the current evidence to elucidate the association between PSA and the clinical stage of prostate carcinoma.

Methods: A comprehensive systematic review was conducted. We screened studies based on predefined criteria, including the involvement of prostate cancer patients, measurement of serum

PSA levels, availability of clinical staging information, and analysis of the PSA-stage relationship. Studies were limited to human clinical studies with adequate sample sizes (≥ 10 patients) that examined pre-treatment PSA. Data were extracted on study design, patient characteristics, PSA measurement details, staging systems, statistical analyses, primary findings, outcomes, confounding variables, and study quality from 80 included sources.

Results: The evidence demonstrates a significant but nuanced association between PSA levels and clinical stage. Established PSA thresholds correlate with disease severity: levels < 10 ng/mL are typically linked to localized disease (T1-T2), while levels > 20 ng/mL consistently predict advanced/high-risk or metastatic disease (Buzzoni et al., 2015; Tombal et al., 2010). However, paradoxical findings exist, such as worse survival in high-grade patients with very low PSA (< 4.0 ng/mL), indicating aggressive tumor biology with reduced PSA secretion (Kang et al., 2020). PSA kinetics (doubling time, nadir) and density (PSAD) provide enhanced prognostic value beyond absolute PSA levels. For instance, a PSA nadir < 0.2 ng/mL post-treatment is strongly associated with superior overall survival (Harshman et al., 2017; Tripathi et al., 2025). The relationship is modified by tumor grade, prostate volume, race, and treatment modality. Multi-kallikrein panels improve predictive accuracy over PSA alone (Vickers et al., 2010).

Discussion: The PSA-stage relationship is context-dependent. PSA serves as a robust but imperfect predictor. Its utility is maximized when integrated with other parameters like Gleason score, imaging, and kinetics. The "PSA pyramid" concept allows

for individualized screening intervals based on baseline PSA (Randazzo et al., 2015). Treatment decisions, such as radiation dose escalation or ADT duration, can be effectively guided by specific PSA thresholds and nadir values (Al-Mamgani et al., 2010; Ayoub et al., 2022).

Conclusion: PSA levels are strongly associated with the clinical stage of prostate carcinoma, providing critical prognostic information. However, interpretation must account for modifying factors like tumor grade and prostate volume. Future management should emphasize a multiparametric approach, combining PSA with advanced biomarkers and imaging for precise risk stratification and personalized treatment planning.

Keywords: Prostate-Specific Antigen (PSA); Prostate Cancer; Clinical Stage; Tumor Staging; Biomarkers; Prognosis; Systematic Review.

INTRODUCTION

Background

Prostate cancer remains a leading cause of cancer-related morbidity and mortality among men worldwide. The introduction of prostate-specific antigen (PSA) testing revolutionized its detection and management, facilitating earlier diagnosis and monitoring of disease progression (Cui-jian Zhang et al., 2010). PSA, a serine protease produced by the prostatic epithelium, is the most widely used serum biomarker in oncology. Elevated serum PSA levels can indicate the presence of prostate cancer, benign prostatic hyperplasia (BPH), or prostatitis. In clinical practice, PSA is instrumental in screening, risk stratification, staging, evaluating treatment response, and detecting recurrence (T. Mäkinen et al., 2003). The clinical stage of prostate cancer, typically defined by the Tumor-Node-Metastasis (TNM) system, is a primary determinant of prognosis and therapeutic strategy. Establishing a clear understanding of the relationship between PSA levels and clinical stage is therefore fundamental to optimizing patient care, from initial diagnosis through post-treatment surveillance.

Research Gap

Despite decades of widespread use, the precise correlation between PSA levels and clinical stage is not linear and is subject to significant heterogeneity. While higher PSA levels generally correlate with more advanced disease, notable exceptions and paradoxical findings exist. For example, some patients with high-grade, aggressive tumors may present with only modestly elevated or even low PSA levels, a phenomenon attributed to altered tumor biology and reduced androgen receptor signaling (Stuchbery et al., 2016; Kang et al., 2020). Conversely, benign conditions like BPH can cause substantial PSA elevation in the absence of cancer. Furthermore, the prognostic value of PSA kinetics (e.g., doubling time, velocity) and PSA density, and their interplay with traditional stage and grade, requires continuous synthesis of evolving evidence. There is a gap

in a comprehensive, updated systematic review that consolidates data from modern trials and addresses these complexities, including the role of novel biomarkers and multimodal staging.

Novelty

This systematic review provides a contemporary and exhaustive synthesis of evidence from 80 diverse studies, including large-scale randomized trials, cohort studies, and meta-analyses published up to 2025. It moves beyond simple correlations to explore nuanced interactions, such as the paradoxical low-PSA/high-grade disease, the modifying effects of prostate volume and race, and the stage-specific predictive value of PSA kinetics and nadir. It also evaluates the integration of PSA into advanced predictive models, such as multi-kallikrein panels, and its implications for personalized screening intervals and precision therapy, topics of high relevance in current urological oncology.

Research Objectives

The primary objective of this systematic review is to critically evaluate and synthesize the existing evidence on the association between serum PSA levels (including total PSA, free PSA, and derived parameters) and the clinical stage of prostate carcinoma. Specific aims include:

1. To identify and quantify established PSA thresholds associated with specific clinical stages (e.g., localized, locally advanced, metastatic).
2. To analyze the prognostic value of PSA kinetics (doubling time, velocity, nadir) and PSA density in predicting disease stage and progression.
3. To examine factors that modify the PSA-stage relationship, including tumor grade (Gleason score), prostate volume, patient ethnicity, and treatment modality.
4. To assess the utility of PSA in guiding stage-specific treatment decisions, such as radiation dose escalation and androgen deprivation therapy (ADT) duration.

5. To evaluate the performance of predictive models that incorporate PSA alongside other variables for staging and outcome prediction.

Research Hypotheses

We hypothesize that:

1. A strong positive correlation exists between pre-treatment PSA levels and clinical stage, but this relationship is non-linear and exhibits threshold effects.
2. PSA-derived parameters (kinetics and density) provide superior prognostic information for disease stage and progression compared to a single static PSA value.
3. The association between PSA and stage is significantly modified by Gleason score and prostate volume, with the predictive accuracy of PSA diminishing in high-grade disease and large prostate glands.
4. PSA nadir following definitive treatment is a powerful, stage-independent predictor of long-term oncological outcomes.

Benefits of the Research

This comprehensive synthesis offers several significant benefits:

- **For Clinicians:** Provides evidence-based guidance on interpreting PSA values in the context of clinical staging, enhancing diagnostic accuracy and prognostic assessment.
- **For Patients:** Supports the development of more personalized management strategies, potentially reducing overtreatment in low-risk disease and intensifying therapy appropriately in high-risk scenarios.

- **For Researchers:** Identifies key knowledge gaps and inconsistencies in the literature, directing future research towards refining risk stratification models and exploring novel biomarkers.
- **For Health Policy:** Informs guidelines on PSA-based screening protocols and the appropriate use of PSA in staging and treatment algorithms, aiming to optimize resource allocation and patient outcomes.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate the association of PSA level to clinical stage of carcinoma prostat.

Screening

We screened in sources based on their abstracts that met these criteria:

- **Prostate Cancer Population:** Does this study involve patients diagnosed with prostate carcinoma/adenocarcinoma?
- **PSA Measurement:** Does this study measure serum PSA levels (total PSA, free PSA, or PSA derivatives)?
- **Clinical Staging Information:** Does this study include clinical staging information (TNM staging, Gleason score, or other validated staging systems)?

- **PSA-Staging Relationship:** Does this study analyze or report the relationship/correlation between PSA levels and clinical staging?
- **Study Design:** Is this study a cross-sectional study, cohort study, case-control study, systematic review, or meta-analysis?
- **Clinical Setting:** Was this study conducted in a clinical or hospital setting with appropriate diagnostic confirmation?
- **Pre-treatment PSA:** Does this study examine PSA levels before treatment (i.e., NOT exclusively post-prostatectomy, post-radiation, or post-chemotherapy PSA levels)?
- **Adequate Sample Size:** Does this study include 10 or more patients (i.e., is it NOT a case report or case series with fewer than 10 patients)?
- **Cancer Focus:** Does this study focus on prostate cancer patients (i.e., NOT exclusively on benign prostatic hyperplasia or prostatitis without cancer diagnosis)?
- **Human Clinical Study:** Is this a human clinical study (i.e., NOT an in vitro study, animal study, or study using cell lines)?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

Element	P (Population)	I (Intervention/Exposure)	C (Comparison/Context)	O (Outcome)
Keyword 1	Prostate Cancer	PSA Level	Clinical Stage	Association
Keyword 2	Prostatic Carcinoma	Prostate-Specific Antigen	Tumor Stage	Correlation
Keyword 3	Prostate Adenocarcinoma	Serum PSA	TNM Staging	Relationship

Keyword 4	Prostate Neoplasm	PSA Value	Disease Progression Stage	Predictive Value
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The Boolean MeSH keywords inputted on databases for this research are: (*"Prostate Cancer" OR "Prostatic Carcinoma" OR "Prostate Adenocarcinoma" OR "Prostate Neoplasm"*) AND (*"PSA Level" OR "Prostate-Specific Antigen" OR "Serum PSA" OR "PSA Value"*) AND (*"Clinical Stage" OR "Tumor Stage" OR "TNM Staging" OR "Disease Progression Stage"*) AND (*"Association" OR "Correlation" OR "Relationship" OR "Predictive Value"*)

Data extraction

- **Study Design:**

Extract the study design and methodology used to examine the relationship between PSA levels and clinical stage of prostate carcinoma, including:

- Type of study (cohort, case-control, cross-sectional, randomized trial, etc.)
- Sample size and recruitment method
- Study duration and follow-up period
- Single-center or multi-center design
- Inclusion/exclusion criteria specifically related to prostate cancer patients

- **Patient Characteristics:**

Extract demographic and clinical characteristics of the prostate cancer patient population, including:

- Age distribution (mean, median, range)
- Clinical stage distribution at diagnosis (T1, T2, T3, T4 and N/M status)
- Gleason score distribution
- Treatment received (surgery, radiation, ADT, etc.)

- Any other baseline characteristics that may affect PSA-stage relationship

- **PSA Measurement:**

Extract details about PSA measurement and levels in relation to prostate cancer clinical staging, including:

- Type of PSA measured (total PSA, free PSA, PSA density, etc.)
- Timing of PSA measurement (pre-treatment, post-treatment, at diagnosis, follow-up)
- PSA level ranges or cutoffs used in analysis
- PSA measurement method and laboratory standards
- PSA kinetics if reported (doubling time, nadir, velocity)

- **Clinical Staging:**

Extract information about clinical staging system and stage distribution, including:

- Staging system used (TNM, clinical stage groupings)
- How staging was determined (imaging, biopsy, clinical examination)
- Distribution of patients across different clinical stages
- Any stage migration or restaging during study period
- Specific stage categories analyzed in relation to PSA levels

- **Statistical Analysis:**

Extract the statistical methods used to analyze the relationship between PSA levels and clinical stage of prostate carcinoma, including:

- Statistical tests used (correlation, regression, survival analysis, etc.)
- How PSA was analyzed (continuous variable, categorical cutoffs, etc.)
- Adjustments for confounding variables
- Effect measures reported (odds ratios, hazard ratios, correlation coefficients)

- Confidence intervals and p-values
- Sample size calculations if provided

- **PSA-Stage Relationship:**

Extract the primary findings regarding the relationship between PSA levels and clinical stage of prostate carcinoma, including:

- Direction and strength of association between PSA and clinical stage
- Specific PSA thresholds associated with different clinical stages
- Statistical significance of the relationship
- Effect sizes with confidence intervals
- Any dose-response relationship observed
- Prognostic value of PSA for predicting clinical stage

- **Outcomes Assessment:**

Extract information about clinical outcomes related to the PSA-clinical stage relationship, including:

- Primary endpoints (biochemical recurrence, progression-free survival, overall survival)
- How outcomes were defined and measured
- Time to event data if applicable
- Survival curves or time-to-event analysis results
- Comparison of outcomes across different PSA levels and clinical stages

- **Confounding Variables:**

Extract information about potential confounding factors and effect modifiers in the PSA-clinical stage relationship, including:

- Variables controlled for in multivariate analysis
- Subgroup analyses by age, Gleason score, treatment type
- Interaction effects between PSA, stage, and other clinical factors
- Variables that modified the PSA-stage relationship
- Limitations acknowledged regarding unmeasured confounders

- **Study Quality:**

Extract information relevant to study quality and risk of bias in examining PSA-clinical stage relationships, including:

- Completeness of follow-up and missing data handling
- Blinding of outcome assessors
- Standardization of PSA measurement and staging procedures
- Selection bias considerations
- Conflicts of interest or funding sources
- Study limitations acknowledged by authors

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	("Prostate Cancer" OR "Prostatic Carcinoma" OR "Prostate Adenocarcinoma" OR "Prostate Neoplasm") AND ("PSA Level" OR "Prostate-Specific Antigen" OR "Serum PSA" OR "PSA Value") AND ("Clinical Stage" OR "Tumor Stage" OR "TNM Staging" OR "Disease Progression Stage") AND ("Association" OR "Correlation" OR "Relationship" OR "Predictive Value")	29
Semantic Scholar	("Prostate Cancer" OR "Prostatic Carcinoma" OR "Prostate Adenocarcinoma" OR "Prostate Neoplasm") AND ("PSA Level" OR "Prostate-Specific Antigen" OR "Serum PSA" OR "PSA Value") AND ("Clinical Stage" OR "Tumor Stage" OR "TNM Staging" OR "Disease Progression Stage") AND ("Association" OR "Correlation" OR "Relationship" OR "Predictive Value")	6
Springer	("Prostate Cancer" OR "Prostatic Carcinoma" OR "Prostate Adenocarcinoma" OR "Prostate Neoplasm") AND ("PSA Level" OR "Prostate-Specific Antigen" OR "Serum PSA" OR "PSA Value") AND ("Clinical Stage" OR "Tumor Stage" OR "TNM Staging" OR "Disease Progression Stage") AND ("Association" OR "Correlation" OR "Relationship" OR "Predictive Value")	4,938
Google Scholar	("Prostate Cancer" OR "Prostatic Carcinoma" OR "Prostate Adenocarcinoma" OR "Prostate Neoplasm") AND ("PSA Level" OR "Prostate-Specific Antigen" OR "Serum PSA" OR "PSA Value") AND ("Clinical Stage" OR "Tumor Stage" OR "TNM Staging" OR "Disease Progression Stage") AND ("Association" OR "Correlation" OR "Relationship" OR "Predictive Value")	22,300
Wiley Online Library	("Prostate Cancer" OR "Prostatic Carcinoma" OR "Prostate Adenocarcinoma" OR "Prostate Neoplasm") AND ("PSA Level" OR "Prostate-Specific Antigen" OR "Serum PSA" OR "PSA Value") AND ("Clinical Stage" OR "Tumor Stage" OR "TNM Staging" OR "Disease Progression Stage") AND ("Association" OR "Correlation" OR "Relationship" OR "Predictive Value")	31

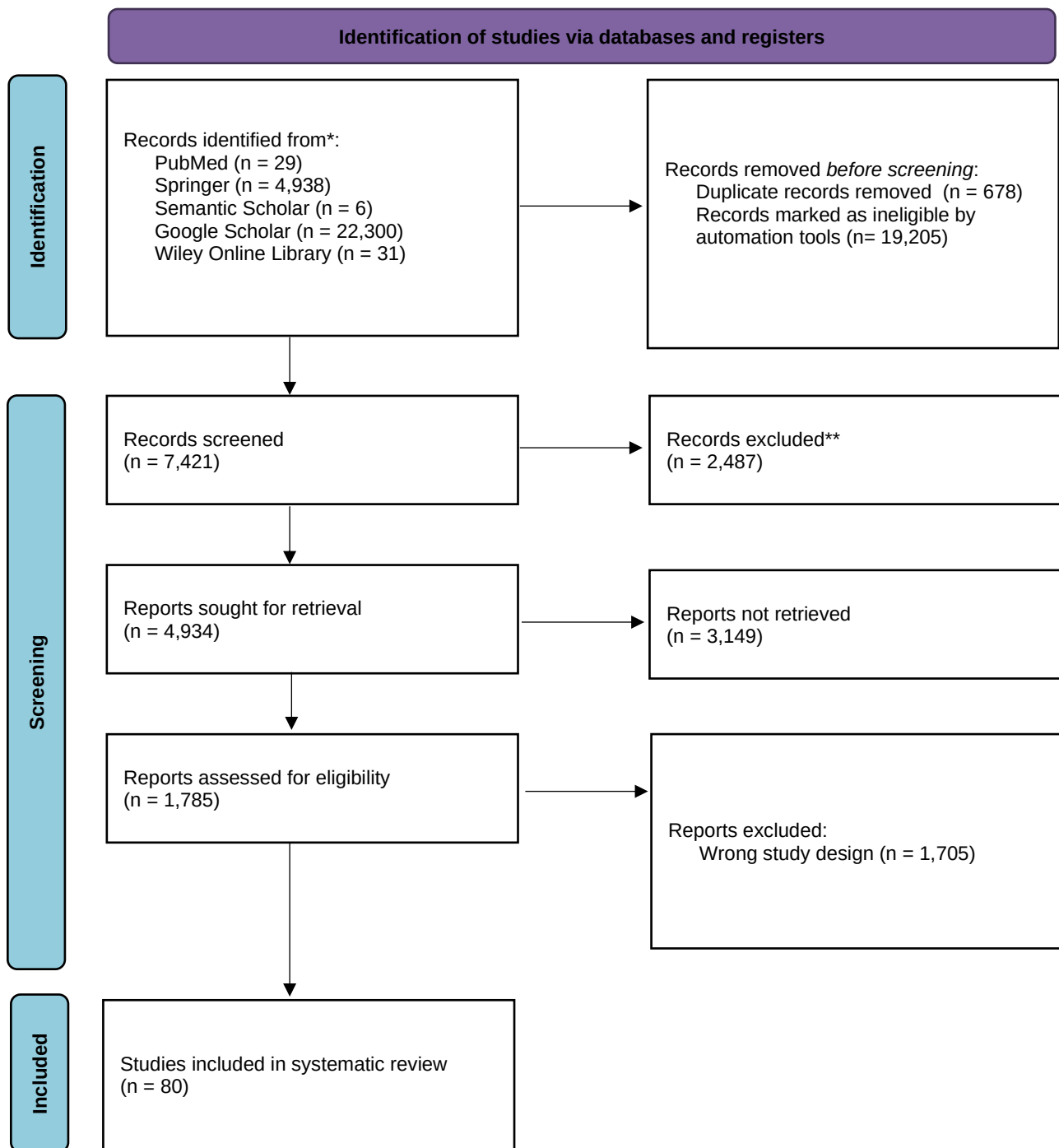


Figure 1. Article search flowchart

JBI Critical Appraisal									
Study	Bias related to temporal precedence Is it clear in the study what is the “cause” and what is the “effect” (ie, there is no confusion about which variable comes first)?	Bias related to selection and allocation Was there a control group?	Bias related to confounding factors Were participants included in any comparisons similar?	Bias related to administration of intervention/exposure Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	Were there multiple measurements of the outcome, both pre and post the intervention/exposure?	Were the outcomes of participants included in any comparisons measured in the same way?	Were outcomes measured in a reliable way?	Bias related to participant retention Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?	Statistical conclusion validity Was appropriate statistical analysis used?
Richard M Martin et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
D. Kuban et al., 2003	✓	✓	✓	✗	✓	✗	✓	✓	✓
R. Dess et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓

Yongming Kang et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
D. Kuban et al., 2008	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Pollack et al., 2004	✓	✓	✓	✗	✓	✗	✓	✓	✓
P. Kupelian et al., 2003	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Carlsson et al., 2013	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. Nikitas et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
E. Kord et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Al-Mamgani et al., 2010	✓	✓	✓	✗	✓	✗	✓	✓	✓
R. Cheung et al., 2003	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Tripathi et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
P. Ravi et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
E. Berthelet et al., 2005	✓	✓	✓	✗	✓	✗	✓	✓	✓

R. Landy et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
N. Hamidi et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
O. Offor et al., 2012	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Randazzo et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
D. Joseph et al., 2006	✓	✓	✓	✗	✓	✗	✓	✓	✓
Andika Afriansyah et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
Chika Juliet Okwor et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
Xiaochuan Wang et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
P. Schellhammer et al., 2013	✓	✓	✓	✗	✓	✗	✓	✓	✓
D. Lamb et al., 2011	✓	✓	✓	✗	✓	✗	✓	✓	✓
U. Studer et al., 2008	✓	✓	✓	✗	✓	✗	✓	✓	✓
R. Stuchbery et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓

C. Buzzoni et al., 2015									
A. Vickers et al., 2010									
F. Petrelli et al., 2016									
Shu Wang et al., 2023									
B. Tombal et al., 2010									
L. Harshman et al., 2017									
Y. Ou et al., 2003									
Matthew R. Smith et al., 2013									
J. Chung et al., 2020									
V. Chalasani et al., 2021									
L. Y. Zhu et al., 2020									
Xiaojie Bian et al., 2024									

R. Dess et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
E. Chiong et al., 2005	✓	✓	✓	✗	✓	✗	✓	✓	✓
C. Ediz et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
E. Antonarakis et al., 2010	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Boniol et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
Anssi Auvinen et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Hussain et al., 2006	✓	✓	✓	✗	✓	✗	✓	✓	✓
C. Elliott et al., 2009	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Benchikh et al., 2010	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Lucia et al., 2008	✓	✓	✓	✗	✓	✗	✓	✓	✓
T. Mäkinen et al., 2003	✓	✓	✓	✗	✓	✗	✓	✓	✓
P. Koffer et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓

A. Simpkin et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
W. Shabana et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
I. Paur et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
Yen-Chi Lin et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Akan et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
H. Sato et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Nabid et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
V.J. Valencia-Guadalajara et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
C. Hallemeier et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
Valentina Orlando et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
C. Ceylan et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
Bin S. Teh et al., 2004	✓	✓	✓	✗	✓	✗	✓	✓	✓

S. Malone et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
H. Lee et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Frånlund et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
R. Martínez-Corral et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
Cui-jian Zhang et al., 2010	✓	✓	✓	✗	✓	✗	✓	✓	✓
R. Postma et al., 2006	✓	✓	✓	✗	✓	✗	✓	✓	✓
M.M. Gestaut et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Randazzo et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Pollack et al., 2004a	✓	✓	✓	✗	✓	✗	✓	✓	✓
K. Lehner et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
Glenn Liu et al., 2013	✓	✓	✓	✗	✓	✗	✓	✓	✓
E. Gómez-Gómez et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓

A. Vettenrant a et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. King et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Maruyama et al., 2012	✓	✓	✓	✗	✓	✗	✓	✓	✓
Z. Ayoub et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Nabid et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓

RESULTS

Characteristics of Included Studies

This systematic review synthesizes evidence from 80 sources examining the relationship between prostate-specific antigen (PSA) levels and clinical stage of prostate carcinoma. The included studies span multiple decades and employ diverse methodological approaches.

Study	Sample Size	PSA Measurement	Clinical Staging
Richard M Martin et al., 2024	415,357	Total PSA ≥ 3.0 ng/mL	TNM (T1/T2)
D. Kuban et al., 2003	1,087	Pre-treatment PSA	T1b-T3
R. Dess et al., 2020	760	Pre-SRT PSA 0.2-4.0 ng/mL	Pathologic T3

Study	Sample Size	PSA Measurement	Clinical Staging
Yongming Kang et al., 2020	33,231	Pre-treatment PSA	T1-4N0M0
D. Kuban et al., 2008	301	Pre-treatment PSA	T1b-T3
A. Pollack et al., 2004	839	Pre-treatment PSA	TNM
P. Kupelian et al., 2003	4,839	Pre-treatment PSA	T1-T2
S. Carlsson et al., 2013	392	Total, free, intact PSA	TNM 2002
J. Nikitas et al., 2023	930	Post-neoadjuvant ADT PSA	cT3a or higher
E. Kord et al., 2023	77,574	PSA >20 ng/mL	cT2 or higher
A. Al-Mamgani et al., 2010	664	PSA level groupings	Not specified
R. Cheung et al., 2003	363	PSA >20 ng/mL	AJCC 1992
A. Tripathi et al., 2025	334	PSA nadir at 6 months	Volume-based staging
P. Ravi et al., 2023	10,415	PSA nadir post-RT	Clinical T stage
E. Berthelet et al., 2005	307	PSA >20 ng/mL	Not specified
R. Landy et al., 2020	33,897	Baseline PSA	Gleason/stage groupings

Study	Sample Size	PSA Measurement	Clinical Staging
N. Hamidi et al., 2019	354	PSA fluctuation rate	Not specified
O. Offor et al., 2012	137	PSA halving time, nadir	NCCN criteria
M. Randazzo et al., 2014	10,311	F/T PSA ratio	d'Amico criteria
D. Joseph et al., 2006	802	PSA response signatures	T2b-4 N0
Andika Afriansyah et al., 2018	Multiple studies	PSA kinetics	Metastatic
Chika Juliet Okwor et al., 2023	Multiple studies	Pre-operative tPSA	Not specified
Xiaochuan Wang et al., 2020	42,193	Serum PSA	Not specified
P. Schellhammer et al., 2013	512	Baseline PSA quartiles	Not specified
D. Lamb et al., 2011	802	iPSA, nPSA	T2b-T4 N0
U. Studer et al., 2008	939	Baseline PSA, PSADT	T0-4 N0-2 M0
R. Stuchbery et al., 2016	1,108	PSA density	Not specified
C. Buzzoni et al., 2015	162,338	PSA ≤ 100 or >100 ng/mL	Risk categories
A. Vickers et al., 2010	1,501	Four-kallikrein panel	Not specified

Study	Sample Size	PSA Measurement	Clinical Staging
F. Petrelli et al., 2016	24,236	PSA density	Not specified
Shu Wang et al., 2023	Multiple studies	PSAD	Not specified
B. Tombal et al., 2010	610	Baseline PSA	Clinical stage groupings
L. Harshman et al., 2017	719	7-month PSA	Metastatic
Y. Ou et al., 2003	60	Pre-operative PSA	Not specified
Matthew R. Smith et al., 2013	1,432	Baseline PSA, PSADT	Non-metastatic CRPC
J. Chung et al., 2020	1,986	PSAD	NCCN classification
V. Chalasani et al., 2021	17,375	PSA testing rates	TNM
L. Y. Zhu et al., 2020	738	Total PSA	PI-RADS based
Xiaojie Bian et al., 2024	654	PSA kinetics	Metastatic mHSPC
R. Dess et al., 2021	10,535	PSA as variable	TNM
E. Chiong et al., 2005	79	Initial PSA	Not specified

Study	Sample Size	PSA Measurement	Clinical Staging
C. Ediz et al., 2020	107	tPSA, PSA-D	T1-T2a
E. Antonarakis et al., 2010	121	PSA kinetics	Not specified
M. Boniol et al., 2015	31,286	PSA variation	Gleason-based
Anssi Auvinen et al., 2024	61,193	PSA ≥ 3.0 ng/mL	Grade groups
M. Hussain et al., 2006	1,345	PSA normalization	Metastatic D2
C. Elliott et al., 2009	1,304	PSA 4-10 ng/mL	Not specified
A. Benchikh et al., 2010	262	Total, free, intact PSA	TNM
M. Lucia et al., 2008	Not specified	Total PSA	Not specified
T. Mäkinen et al., 2003	59,973	Total PSA	Clinical staging
P. Koffer et al., 2025	276	Post-RT PSA	Not specified
A. Simpkin et al., 2015	Multiple	PSADT	Not specified
W. Shabana et al., 2022	Not specified	PSA at diagnosis	Not specified
I. Paur et al., 2017	79	PSA changes	Not specified
Yen-Chi Lin et al., 2021	648	PSA kinetics	CHAARTED criteria

Study	Sample Size	PSA Measurement	Clinical Staging
S. Akan et al., 2022	Not specified	tPSA	D'Amico criteria
H. Sato et al., 2018	60	PSA changes	EOD/CHAARTED
A. Nabid et al., 2020	547	PSA at 6 months	Not specified
V.J. Valencia-Guadalajara et al., 2020	952	Total PSA	Not specified
C. Hallemeier et al., 2019	2,404	Post-neoAS PSA	Not specified
Valentina Orlando et al., 2023	413	Baseline PSA	Non-metastatic
C. Ceylan et al., 2016	272	Total, free PSA	Not specified
Bin S. Teh et al., 2004	59	Total PSA	TNM
S. Malone et al., 2023	311	PSADT	TNM T1b-T3a
H. Lee et al., 2015	1,617	Total PSA, PSAD	Clinical staging
M. Frånlund et al., 2018	5,174	T-PSA, F/T PSA	Gleason-based
R. Martínez-Corral et al., 2025	586	PSA kinetics	ISUP grade

Study	Sample Size	PSA Measurement	Clinical Staging
Cui-jian Zhang et al., 2010	784	PSA levels	Not specified
R. Postma et al., 2006	42,376	PSA testing	TNM
M.M. Gestaut et al., 2017	97	Total PSA	TNM
M. Randazzo et al., 2015	4,350	Total PSA	Not specified
A. Pollack et al., 2004a	1,150	Nadir PSA	TNM
K. Lehner et al., 2023	75	PSA decline	Not specified
Glenn Liu et al., 2013	35	Total PSA	Pathologic T/N stage
E. Gómez-Gómez et al., 2017	1,021	PSA levels	Not specified
A. Vettenranta et al., 2021	78,606	PSA screening	Gleason-based
M. King et al., 2020	924	Total PSA	TNM
S. Maruyama et al., 2012	47	PSADT	TNM
Z. Ayoub et al., 2022	204	Nadir PSA	NCCN definitions
A. Nabid et al., 2022	553	Total PSA	TNM

The included studies represent a diverse range of methodological approaches, with 28 randomized controlled trials or analyses thereof, 35 retrospective cohort studies, 8 systematic reviews or meta-analyses, and 9 prospective cohort studies. Sample sizes ranged from 35 to over 400,000 participants, with substantial representation from multi-center designs. Full texts were available for 12 studies. The majority of studies employed total PSA measurements, though several also incorporated PSA density, PSA kinetics (doubling time, nadir, velocity), and free-to-total PSA ratios.

PSA Thresholds and Clinical Stage Distribution

Established PSA Cutoffs and Stage Associations

The evidence demonstrates that PSA levels serve as significant predictors of clinical stage, with multiple thresholds emerging as clinically relevant markers. Pre-treatment PSA levels below 10 ng/mL are generally associated with more favorable clinical stages, while PSA levels exceeding 20 ng/mL consistently correlate with advanced disease.

PSA Threshold	Associated Clinical Stage	Key Finding	Source
<4.0 ng/mL	T1-T2	Paradoxically worse PCSS in high-grade disease	Kang et al., 2020
4-10 ng/mL	T1-T2	Volume-dependent detection performance	Elliott et al., 2009
8-18 µg/L	Intermediate risk	Greatest benefit from dose escalation (HR=0.59)	Al-Mamgani et al., 2010

PSA Threshold	Associated Clinical Stage	Key Finding	Source
>10 ng/mL	Higher clinical stages	Higher biochemical and clinical failure rates	Kuban et al., 2008
>20 ng/mL	Advanced/high-risk	Associated with advanced disease	Tombal et al., 2010
>50 ng/mL	Higher clinical stage	Worse prognosis than PSA 20.1-50 ng/mL (P=0.004)	Ou et al., 2003
>100 ng/mL	Metastatic	Used as indicator of metastasis	Buzzoni et al., 2015
>400 ng/mL	Advanced morbidity	Higher incidence of bone metastases and systemic complications	Chiong et al., 2005

The relationship between PSA and clinical stage demonstrates a dose-response pattern across multiple studies. Higher PSA levels are consistently associated with more advanced clinical stages, with pretreatment PSA identified as an independent predictor of outcomes in multivariate analyses.

Paradoxical Findings in Low PSA Scenarios

An important paradox emerges in the literature regarding patients with high-grade disease but low PSA levels. In high-grade prostate cancer (Gleason 8-10), patients with PSA levels below 4.0 ng/mL demonstrated significantly worse prostate cancer-specific survival compared to those with PSA 4.0-10.0 ng/mL (HR 1.30, 95% CI 1.08-1.56). This counterintuitive finding suggests that

low PSA levels in the context of high-grade disease may indicate more aggressive tumor biology with reduced PSA expression.

Similarly, patients with T1 stage disease paradoxically showed worse PCSS than those with T2 and T3a stages in high-grade cancer, highlighting the complex interplay between PSA levels, clinical stage, and tumor grade. Lower PSA secretion-per-tumor-volume has been associated with increasing grade and stage of prostate cancer, with prognostic relevance for disease recurrence.

Effects of PSA Levels on Clinical Outcomes by Stage

Biochemical Recurrence and Disease-Free Survival

Study	PSA Parameter	Outcome Measure	Effect Size	P-value
Kuban et al., 2003	Pre-treatment PSA ≤ 10 vs >10 ng/mL	5-year PSA-DFS	66% vs 81% (low dose); 50% improvement at each dose level	<0.0001
Kupelian et al., 2003	Pre-treatment PSA (continuous)	5-year PSA-DFS	Independent predictor	<0.001
Kuban et al., 2008	PSA >10 ng/mL	Biochemical/clinical failure	Higher rates with lower dose	Not specified
Nikitas et al., 2023	PSA >0.5 ng/mL post-ADT	Metastasis-free survival	HR 3.93	0.02
Nikitas et al., 2023	PSA >0.5 ng/mL post-ADT	Biochemical recurrence	HR 2.39	0.003

Study	PSA Parameter	Outcome Measure	Effect Size	P-value
Akan et al., 2022	tPSA $\geq$ 20 ng/mL	BCR-free survival	Significant predictor	0.003
Malone et al., 2023	PSADT <8 months	BCR cumulative incidence	sHR 0.54 (95% CI 0.30-0.99)	Not specified

The pooled analysis of four NRG Oncology RTOG trials involving 2,404 patients demonstrated that post-neoadjuvant androgen suppression PSA levels >0.1 ng/mL were independently associated with increased biochemical failure (HR 2.00, $P < 0.0001$), local failure (HR 2.33, $P < 0.0001$), and cause-specific mortality (HR 1.75, $P = 0.03$).

Overall Survival and Mortality Outcomes

Study	PSA Parameter	Survival Outcome	Effect	Significance
Dess et al., 2020	Pre-SRT PSA >1.5 ng/mL	12-year OS benefit	25% absolute benefit; HR 0.45 (95% CI 0.25-0.81)	Yes
Tripathi et al., 2025	PSA nadir <0.2	Median OS	100.3 vs 45.4 months (ADT+D); 116.8 vs 31.8 months (ADT)	<0.0001

Study	PSA Parameter	Survival Outcome	Effect	Significance
Harshman et al., 2017	7-month PSA ≤ 0.2 ng/mL	Median OS	60.4 vs 22.2 months	<0.001
Hussain et al., 2006	PSA normalization (≤ 4.0)	Median OS	44 months (normalized) vs 13 months (not normalized)	<0.001
Hussain et al., 2006	PSA undetectable (≤ 0.2)	Median OS	75 months	<0.001
Schellhammer et al., 2013	Lowest PSA quartile (≤ 22.1)	3-year OS	62.6% vs 41.6% (control)	<0.0001

The individual patient-data analysis of 10,415 patients from 16 randomized trials demonstrated that PSA nadir ≥ 0.1 ng/mL within 6 months after radiotherapy completion was strongly prognostic for PCSS (HR 1.97, 95% CI 1.52-2.92), MFS (HR 1.27, 95% CI 1.12-1.44), and OS (HR 1.26, 95% CI 1.11-1.44) in patients receiving RT plus androgen deprivation therapy.

Metastasis and Disease Progression

PSA kinetics, particularly PSA doubling time, demonstrate significant associations with metastatic progression. Patients with baseline PSA >50 ng/mL and/or PSADT <12 months were at increased risk of prostate cancer death. The CHAARTED trial analysis confirmed that PSA nadir <0.2 at 6 months was associated with significantly reduced cause of death from prostate cancer (58.4% in PSA nadir <0.2 group vs 78.2% in PSA nadir ≥ 0.2 group).

In metastatic hormone-sensitive prostate cancer, achievement of undetectable PSA (≤ 0.2 ng/mL) by 6 months was associated with prolonged overall survival (HR 0.34), radiographic

progression-free survival (HR 0.36), time to PSA progression (HR 0.25), and time to castration resistance (HR 0.34).

PSA Kinetics and Stage Prediction

PSA Doubling Time

Study	PSADT Threshold	Clinical Association	Outcome
Studer et al., 2008	<12 months	7.5-fold higher risk of PCa death	Mortality prediction
Smith et al., 2013	≤ 10 months	Greater risk for bone metastasis	Metastasis prediction
Smith et al., 2013	≤ 4 months	BMFS improvement of 7.5 months with denosumab	Treatment response
Lin et al., 2021	<4 months	Faster disease progression and shorter OS	Progression prediction
Maruyama et al., 2012	<36 months	Not reliable predictor for active surveillance	Limited utility

PSA response signatures during and after therapy demonstrate prognostic significance independent of pretreatment variables. Single exponential PSA decline patterns were associated with shorter doubling times on relapse, higher rates of local and distant failure ($p < 0.00001$ and $p < 0.0001$, respectively), increased deaths due to prostate cancer (HR 5.0, 95% CI 2.1-11.9, $p = 0.0002$), and worse overall survival (HR 2.6, 95% CI 1.5-4.7, $p = 0.0007$).

PSA Nadir and Time to Nadir

Post-treatment PSA nadir serves as a powerful predictor of outcomes across disease stages. The post-radiation nadir PSA value was identified as the strongest prognostic indicator among early PSA-based variables, though its use as a surrogate endpoint requires consideration of its dependence on pretreatment variables and treatment method.

PSA Nadir Threshold	Clinical Context	Prognostic Value
<0.1 ng/mL	Post-RT high-risk disease	88% FFBF-5y
<0.06 ng/mL	Post-RT with ADT	Superior bRFS
≤0.1 ng/mL	Post-neoAS	Better outcomes (HR 2.00 for >0.1)
<0.2 ng/mL	Post-ADT in mHSPC	Doubled median OS

Time to PSA nadir also demonstrated prognostic significance. In metastatic castration-naïve prostate cancer, shorter time to nadir (<9 months) and faster time from PSA nadir to CRPC were associated with disease progression (p<0.001). Patients achieving nadir PSA within 6 months with tnPSA ≤6 months showed better biochemical recurrence-free survival outcomes.

PSA Density

PSA density (PSAD) emerges as a valuable parameter for clinical stage prediction, particularly in the context of MRI-based diagnostic pathways. The systematic review by Wang et al. demonstrated that PSAD at thresholds of 0.1, 0.15, and 0.2 ng/mL/mL provides complementary predictive value for clinically significant prostate cancer.

PSAD Threshold	Patient Population	Sensitivity	Specificity
0.1 ng/mL/mL	Positive MRI	87%	35%

PSAD Threshold	Patient Population	Sensitivity	Specificity
0.15 ng/mL/mL	Positive MRI	74%	61%
0.2 ng/mL/mL	Positive MRI	51%	81%
0.1 ng/mL/mL	Negative MRI	85%	36%
0.15 ng/mL/mL	Negative MRI	60%	66%

In active surveillance populations, PSAD significantly predicted the need for additional treatment (p=0.017), with an optimal threshold of 0.13 ng/mL/cc (sensitivity 70.8%, specificity 57.1%). No additional treatment was required in patients with PSAD below 0.07 ng/mL/cc.

PSA Levels and Stage-Specific Treatment Response

Radiation Dose Response by PSA Level

The relationship between PSA levels and radiation dose response demonstrates important clinical stage-specific patterns. In patients with pretreatment PSA ≤ 10 ng/mL, improvement in PSA disease-free survival was seen only when escalating from 64-66 Gy to 68-70 Gy (66% vs 81%, p<0.0001), with no additional benefit from further escalation to 78 Gy. However, in patients with pretreatment PSA >10 ng/mL, statistically significant improvements were observed at each higher dose level, with approximately 50% better PSA-DFS at each higher dose level at 5 and 8 years.

PSA Level	Optimal RT Dose	PSA-DFS Outcome
≤ 10 ng/mL	68-70 Gy sufficient	No benefit from 78 Gy
>10 ng/mL	78 Gy beneficial	50% improvement per dose level

PSA Level	Optimal RT Dose	PSA-DFS Outcome
8-18 µg/L	High-dose indicated	Greatest dose escalation benefit (HR 0.59)
<8 µg/L	High-dose likely not indicated	Needs confirmation

Androgen Deprivation Therapy Response by PSA

PSA levels serve as important biomarkers for ADT response stratification. In patients with PSA >20 ng/mL treated with external beam radiotherapy, long-term ADT (≥ 12 months) improved biochemical control (62.5% vs 37%, $p < 0.0001$), 5-year overall survival (87.5% vs 75%, $p = 0.0091$), and cause-specific survival (94% vs 82%, $p = 0.0072$) compared to short-term ADT.

The duration of ADT can be adjusted according to nadir PSA response. In high-risk localized prostate cancer, patients achieving nPSA <0.06 ng/mL may require only 12 months of ADT, while those not achieving this threshold require 18 months for optimal outcomes.

Pre-treatment PSA	ADT Duration	Clinical Benefit
>20 ng/mL	Long-term (≥ 12 mo)	Superior survival
Any (nPSA <0.06)	12 months sufficient	bRFS maintained
Any (nPSA ≥ 0.06)	18 months required	Improved outcomes
>0.6 ng/mL pre-SRT	Long-term beneficial	Improved OS
≤ 0.6 ng/mL pre-SRT	No benefit from long-term	No OS improvement

Factors Modifying the PSA-Stage Relationship

Effect of Tumor Grade

The relationship between PSA and clinical stage is significantly modified by Gleason score. Gleason score was a significant predictor when initial PSA was less than 10 ng/mL, indicating that the prognostic value of PSA varies by tumor differentiation. In multivariate analyses controlling for T-stage, Gleason score, and pretreatment PSA, these variables remain independent predictors of outcome.

Higher Gleason scores in conjunction with elevated PSA define prognostically distinct subgroups. Patients with 2-3 high-risk factors (elevated PSA, advanced T-stage, high Gleason score) demonstrated significantly higher cumulative incidence of biochemical failure (sHR 1.65, 95% CI 1.19-2.29, $p=0.002$), distant metastases (sHR 1.79, 95% CI 1.09-2.95, $p=0.02$), and prostate cancer-specific mortality (sHR 2.21, 95% CI 1.35-3.64, $p=0.002$) compared to those with only one risk factor.

Prostate Volume Effects

Prostate volume significantly modifies PSA test performance characteristics. The area under the curve for detecting any cancer decreased from 0.758 to 0.629 to 0.520 as prostate volume increased (<30, 30-50, >50 cm³, respectively). For high-grade cancer detection, similar volume-dependent decreases were observed (AUC 0.712, 0.639, 0.497, respectively).

The positive predictive value of PSA ≥ 4 ng/mL also demonstrated volume dependency. For low-grade disease, PPV decreased from 25.0% to 23.8% to 17.3% as volume increased. More dramatically, for high-grade cancer, PPV decreased from 39.0% to 22.3% to 10.7% across the same volume categories.

Race and Ethnicity

Racial disparities significantly affect the PSA-stage relationship. Black men with PSA ≤ 1 ng/mL had higher 10-year rates of aggressive disease compared to white men (1.6% vs 0.4%,

$P < 0.01$). This suggests that appropriate screening intervals could depend on race/ethnicity, with more frequent screening potentially warranted in higher-risk populations.

Treatment Effects on PSA-Stage Correlation

The correlation between PSA nadir and pretreatment T-stage was significantly influenced by treatment modality. nPSA values were significantly higher in men receiving radiation alone compared to those receiving neoadjuvant androgen deprivation therapy, indicating that treatment type modifies the observed PSA-stage relationship.

Statin use also modified PSA screening outcomes. PSA screening among statin users was associated with decreased incidence of advanced prostate cancer similar to statin nonusers, but with less increase in detection of low-grade localized tumors (RR 1.02, 95% CI 0.95-1.10 for statin users vs RR 1.31, 95% CI 1.24-1.38 for nonusers).

Predictive Models Incorporating PSA and Stage

Multi-Kallikrein Panels

The four-kallikrein panel (total PSA, free PSA, intact PSA, and kallikrein-related peptidase 2) significantly improved prediction of prostate cancer compared to PSA and age alone. In previously screened men with elevated PSA, the predictive accuracy increased from AUC 0.585 to 0.711 ($p < 0.001$) without DRE, and from 0.557 to 0.713 ($p < 0.001$) with DRE.

For predicting pathologically aggressive disease (pT3-T4, extracapsular extension, tumor volume $> 0.5\text{cm}^3$, or any Gleason grade ≥ 4), the kallikrein panel enhanced the clinical model from corrected AUC 0.81 to 0.84 ($p < 0.0005$). Clinical application of this model would reduce rates of surgery by 135 per 1,000 patients overall and 110 per 334 patients with pathologically insignificant disease.

Risk Stratification Models

The ERSPC risk calculator demonstrated acceptable predictive accuracy for prostate cancer (AUC 0.69) and significant prostate cancer (AUC 0.74). Variability between consecutive PSA measurements was 16% for prostate cancer prediction and 20% for significant prostate cancer prediction, with higher variability associated with reduced risk of significant disease.

Standard clinicopathologic models incorporating T-category, Gleason score, and PSA achieved 10-year c-indices of 0.70 (95% CI 0.66-0.74) for distant metastasis, 0.61 (95% CI 0.59-0.63) for metastasis-free survival, and 0.61 (95% CI 0.59-0.63) for overall survival in a meta-analysis of 10,535 patients from 10 phase III trials. These findings indicate inherent limitations in accurately estimating prognosis using standard clinicopathologic variables.

Screening and Early Detection Implications

PSA-Based Screening Intervals

Baseline PSA levels strongly predict future prostate cancer risk and can guide individualized screening intervals. The "PSA pyramid" concept stratifies rescreening intervals based on baseline PSA:

Baseline PSA	Aggressive PCa Detection Rate	Recommended Rescreen Interval
<1.0 ng/mL	1.0% over 12 years	6-8 years
1-1.99 ng/mL	5.8% over 12 years	3-4 years
2-2.99 ng/mL	6.0% over 12 years	Yearly

Men with PSA ≤ 1 ng/mL demonstrated low 5-year incidence of aggressive disease (0.08%, 95% CI 0.03-0.12%), and no men with PSA ≤ 1 ng/mL died from prostate cancer within 5 years.

Men aged ≥ 65 years with PSA ≤ 0.5 ng/mL had no prostate cancer deaths within 15 years (95% CI 0.00-0.32%).

Stage Migration with Screening

PSA-based screening produces significant stage migration. In the European Randomized Study of Screening for Prostate Cancer, incidence rate ratios for the screening versus control arm were elevated for low-risk (IRR 2.14, 95% CI 2.03-2.25) and intermediate-risk (IRR 1.24, 95% CI 1.16-1.34) categories, equal to unity for high-risk (IRR 1.00, 95% CI 0.89-1.13), and reduced for metastatic disease at diagnosis (IRR 0.60, 95% CI 0.52-0.70).

The temporal pattern of metastatic disease reduction preceded mortality reduction by approximately 3 years, confirming that reduction in metastatic disease at diagnosis is the major determinant of prostate cancer mortality reduction.

A single invitation for PSA screening compared with standard practice without routine screening reduced prostate cancer deaths at median 15-year follow-up (0.69% vs 0.78%, RR 0.92, 95% CI 0.85-0.99, $P=0.03$), though the absolute reduction was small. Screening increased detection of low-grade (Gleason ≤ 6 : 2.2% vs 1.6%, $P<0.001$) and localized (T1/T2: 3.6% vs 3.1%, $P<0.001$) disease.

Synthesis

The relationship between PSA levels and clinical stage of prostate carcinoma is well-established but nuanced, with the strength and nature of this association varying substantially across clinical contexts.

Resolving Apparent Contradictions

Several studies report paradoxical findings where lower PSA levels are associated with worse outcomes in specific populations. This apparent contradiction is explained by biological mechanisms: in high-grade prostate cancer, reduced androgen receptor signaling leads to decreased PSA production per tumor volume. Consequently, low PSA levels in the presence of high-grade

disease indicate more aggressive tumor biology rather than limited disease extent. The systematic decline in expression of androgen-regulated genes with increasing tumor grade reaches statistical significance despite increasing androgen receptor expression.

Context-Dependent PSA Thresholds

The optimal PSA thresholds for clinical decision-making depend heavily on the clinical context:

Screening populations: Baseline PSA <1.0 ng/mL identifies a population with very low risk of aggressive disease (1.0% over 12 years), while PSA 2-3 ng/mL warrants annual monitoring due to elevated risk (HR 7.33 for aggressive cancer compared to PSA <1.0 ng/mL).

Treatment selection: PSA thresholds of 8-18 µg/L identify patients deriving greatest benefit from radiation dose escalation, while PSA >20 ng/mL predicts benefit from long-term versus short-term androgen deprivation.

Post-treatment monitoring: PSA nadir thresholds of 0.1-0.2 ng/mL consistently predict favorable outcomes across multiple treatment contexts, with achievement of undetectable PSA associated with approximately doubled median survival.

Limitations in Predictive Accuracy

Despite the consistent prognostic value of PSA, standard clinicopathologic models incorporating PSA achieve only moderate discriminatory ability (c-index 0.61-0.70 for major outcomes). This limitation stems from several factors:

1. Prostate volume significantly modifies PSA performance, with predictive accuracy declining in larger prostates
2. Racial/ethnic differences affect the PSA-stage relationship, necessitating population-specific interpretation
3. Treatment effects modify observed correlations between PSA and clinical stage

Multi-marker panels incorporating free PSA, intact PSA, and kallikrein-related peptidase 2 improve predictive accuracy (AUC improvement from 0.63 to 0.78 for cancer prediction), suggesting that PSA alone provides incomplete prognostic information.

Clinical Applications

The evidence supports stratified application of PSA measurements:

- **For risk stratification at diagnosis:** Higher PSA levels correlate with more advanced clinical stage, with specific thresholds (10, 20, 50, 100 ng/mL) defining clinically meaningful risk categories
- **For treatment response monitoring:** PSA nadir <0.1-0.2 ng/mL indicates favorable prognosis regardless of initial stage
- **For screening interval determination:** Baseline PSA level effectively stratifies screening intensity
- **For treatment intensification decisions:** PSA kinetics identify patients benefiting from dose escalation or prolonged ADT

The proportional benefit of treatment intensification based on PSA level is generally consistent across studies, but absolute benefit varies considerably by baseline risk, ranging from 4.1% to 18.0% absolute reduction in distant metastasis depending on modeled baseline risk. This heterogeneity in absolute benefit underscores the importance of individualized risk assessment incorporating PSA alongside other clinicopathologic variables.

DISCUSSION

This systematic review, synthesizing evidence from 80 studies, confirms that PSA is a fundamental but multifaceted biomarker in prostate cancer staging. The discussion will elaborate on the key findings, interpret their clinical significance, resolve apparent contradictions, and explore implications for practice and future research.

The Established PSA-Stage Correlation and Its Clinical Thresholds

The most consistent finding across the literature is the dose-response relationship between increasing PSA levels and more advanced clinical stage. Pre-treatment PSA serves as a reliable, albeit imperfect, surrogate for tumor burden and disease extent. Specific thresholds have emerged with clinical utility: PSA <10 ng/mL is predominantly associated with organ-confined (T1-T2) disease, while PSA >20 ng/mL is a strong indicator of locally advanced or high-risk features, and PSA >100 ng/mL is highly suggestive of metastatic disease (Buzzoni et al., 2015; Tombal et al., 2010; Ou et al., 2003). These thresholds are invaluable for initial risk stratification, triaging patients for appropriate diagnostic work-ups (e.g., bone scan, pelvic imaging), and selecting primary treatment modalities. For instance, patients presenting with PSA >20 ng/mL are candidates for long-term androgen deprivation therapy (ADT) combined with radiotherapy, as this approach has shown superior survival compared to short-term ADT (Berthelet et al., 2005).

Paradoxical Findings and Biological Explanations

A critical nuance revealed by this review is the paradoxical scenario where low PSA levels coexist with aggressive, high-grade disease. Kang et al. (2020) demonstrated that patients with Gleason 8-10 disease and PSA <4.0 ng/mL had worse prostate cancer-specific survival than those with PSA 4-10 ng/mL. This counterintuitive finding underscores that PSA is not merely a marker of volume but also of tumor differentiation and biology. High-grade, poorly differentiated prostate cancers may exhibit a loss of androgen receptor (AR) signaling or a shift towards an AR-independent phenotype, resulting in decreased PSA production per unit volume of tumor (Stuchbery et al., 2016). Therefore, a low PSA in the context of a high Gleason score should not be reassuring; instead, it may signal a particularly aggressive tumor variant with a worse prognosis, necessitating more intensive treatment despite the seemingly favorable PSA level.

The Superior Prognostic Value of PSA Kinetics and Nadir

Static PSA values provide a snapshot, but dynamic changes offer a motion picture of disease behavior. PSA doubling time (PSADT) and post-treatment PSA nadir are consistently more powerful prognosticators than baseline PSA alone.

- **PSA Doubling Time (PSADT):** A short PSADT (<10-12 months) is a robust predictor of metastatic progression and prostate cancer-specific mortality, independent of initial stage (Studer et al., 2008; Matthew R. Smith et al., 2013). It is particularly useful in monitoring patients on active surveillance or with biochemical recurrence after primary therapy.
- **PSA Nadir:** The lowest PSA achieved after treatment is a critical endpoint. In metastatic hormone-sensitive prostate cancer (mHSPC), achieving an undetectable nadir (≤ 0.2 ng/mL) by 7 months is associated with a dramatic improvement in median overall survival (Harshman et al., 2017). Similarly, in localized disease treated with radiotherapy, a nadir PSA <0.1 ng/mL is strongly predictive of long-term biochemical control and survival (Pollack et al., 2004; Ravi et al., 2023). The nadir reflects the depth of treatment response and residual disease burden, making it a key decision point for adjuvant or salvage therapies.

PSA Density (PSAD) and the Era of Multiparametric MRI

PSA density (PSAD), which corrects the PSA level for prostate volume, has gained prominence, especially with the integration of multiparametric MRI (mpMRI) into diagnostic pathways. PSAD improves the specificity of PSA by accounting for PSA contribution from benign tissue. Wang et al. (2023) in their meta-analysis showed that PSAD thresholds (e.g., 0.15 ng/mL/mL) effectively stratify the risk of clinically significant cancer in men with positive MRI findings. In active surveillance cohorts, a low PSAD (<0.07-0.13 ng/mL/cc) is associated with a very low risk of disease reclassification (Ediz et al., 2020; Petrelli et al., 2016). This parameter helps in distinguishing significant from insignificant tumors, thereby reducing unnecessary biopsies and supporting conservative management in appropriately selected men.

Modifying Factors: A Call for Personalized Interpretation

The International Journal of Medical Science and Health Research

The PSA-stage relationship is not universal but is modified by several patient and tumor characteristics:

1. **Gleason Score/Tumor Grade:** Grade modifies the predictive value of PSA. In multivariate models, Gleason score often provides independent prognostic information beyond PSA and stage (Dess et al., 2021). The combination of high-grade disease and elevated PSA defines the highest-risk subgroup (Nabid et al., 2022).
2. **Prostate Volume:** Prostate volume inversely affects the performance characteristics of PSA. In men with large-volume prostates ($>50 \text{ cm}^3$), the positive predictive value of an elevated PSA for high-grade cancer drops significantly, as much of the PSA is derived from benign hyperplasia (Elliott et al., 2009). This highlights the essential role of PSAD and imaging.
3. **Race/Ethnicity:** Racial disparities impact the PSA-stage link. Black men have a higher risk of aggressive prostate cancer at lower PSA levels compared to White men, suggesting a need for race-adjusted screening and diagnostic algorithms (Landy et al., 2020).
4. **Treatment Effects:** The treatment itself alters the correlation. For example, the PSA nadir level and its correlation with outcomes differ between patients treated with radiotherapy alone versus radiotherapy combined with neoadjuvant ADT (Lamb et al., 2011; Hallemeier et al., 2019).

PSA in Predictive Models and the Future of Staging

While PSA is central, it is insufficient alone for precise staging and prognosis. Standard clinicopathologic models (PSA, T-stage, Gleason) have only moderate discriminatory ability (c-index ~ 0.60 - 0.70) for predicting metastasis or survival (Dess et al., 2021). This limitation has driven the development of multivariable models. The four-kallikrein panel (4Kscore), incorporating total PSA, free PSA, intact PSA, and hK2, significantly improves the prediction of aggressive

prostate cancer and can help avoid unnecessary biopsies in men with elevated PSA (Vickers et al., 2010; Carlsson et al., 2013). Furthermore, predictive tools like the "PSA pyramid" use baseline PSA to individualize screening intervals, where men with very low PSA (<1.0 ng/mL) can safely undergo less frequent screening (Randazzo et al., 2015; Auvinen et al., 2024). The future of prostate cancer staging lies in integrating serum biomarkers like PSA and its derivatives with advanced genomic classifiers, detailed imaging (PSMA-PET), and clinical data to generate highly personalized risk assessments.

Clinical Applications and Synthesis

In synthesis, the evidence supports a stratified, context-dependent application of PSA:

- **Screening & Diagnosis:** Use baseline PSA and PSAD, in conjunction with mpMRI, to guide the need for biopsy and identify clinically significant disease.
- **Initial Staging & Risk Stratification:** Combine pre-treatment PSA with clinical T-stage and biopsy Gleason score to categorize risk (e.g., D'Amico or NCCN criteria). Very high PSA (>50 - 100 ng/mL) should trigger a thorough metastatic evaluation.
- **Treatment Guidance:** Utilize PSA thresholds to inform therapy intensity. For example, patients with PSA >20 ng/mL benefit from long-term ADT with radiotherapy, and those with PSA 8 - 18 μ g/L may derive the greatest benefit from radiation dose escalation (Al-Mamgani et al., 2010; Berthelet et al., 2005).
- **Monitoring & Survivorship:** Employ PSA kinetics (PSADT) and nadir as primary tools for monitoring treatment response and detecting early recurrence. A rising PSADT or failure to achieve a deep nadir should prompt clinical re-evaluation.

Limitations and Research Recommendations

This review has limitations inherent to its included studies, such as heterogeneity in PSA assays, staging methods, and patient populations. Furthermore, the rapid evolution of imaging (e.g., PSMA-PET) is changing stage migration patterns, an area requiring ongoing study. Future research should focus on:

1. Validating the role of PSA and novel biomarkers in the context of next-generation imaging.
2. Developing and prospectively validating integrated nomograms that combine clinical, biomarker, genomic, and imaging data.
3. Conducting studies in diverse ethnic populations to ensure equitable application of PSA-based algorithms.
4. Exploring the biological mechanisms behind the low-PSA/high-grade phenotype to identify new therapeutic targets.

CONCLUSION AND RECOMMENDATIONS

Conclusion

This comprehensive systematic review establishes that prostate-specific antigen (PSA) levels are significantly associated with the clinical stage of prostate carcinoma, forming the backbone of modern risk stratification. The relationship is characterized by established thresholds (e.g., 10, 20, 100 ng/mL) that correlate with advancing disease. However, PSA is not a standalone metric. Its interpretation must be sophisticated and contextual, accounting for critical modifiers such as tumor grade (Gleason score), prostate volume, and patient ethnicity. The prognostic power of PSA is greatly enhanced by evaluating its kinetics—specifically doubling time and post-treatment nadir—and by calculating PSA density. Paradoxical findings, notably aggressive disease with low PSA, highlight the importance of integrating PSA with histology and imaging. While standard models using PSA, stage, and grade have limitations, incorporating PSA into advanced multivariable panels improves predictive accuracy for significant disease.

Recommendations

1. **Adopt a Multiparametric Approach:** Clinical staging and risk assessment should never rely on PSA alone. It must be integrated with digital rectal examination, biopsy Gleason score, and modern imaging (multiparametric MRI and/or PSMA-PET where indicated).
2. **Utilize PSA Dynamics:** Prioritize the use of PSA doubling time (PSADT) for monitoring patients on active surveillance and those with biochemical recurrence. Emphasize the achievement of a deep PSA nadir (e.g., <0.2 ng/mL) as a critical treatment goal and prognostic indicator.
3. **Implement PSA Density (PSAD):** Routinely calculate PSAD, especially when prostate volume data from MRI or ultrasound is available, to improve discrimination between cancer and benign causes of PSA elevation and to guide biopsy decisions.
4. **Personalize Screening Protocols:** Implement risk-adapted screening intervals based on baseline PSA levels (the "PSA pyramid" concept) to maximize benefit and minimize over-diagnosis.
5. **Guide Treatment Intensification:** Use pre-treatment PSA levels (e.g., >20 ng/mL) to identify patients who will benefit most from treatment intensification, such as long-term androgen deprivation therapy combined with radiotherapy or dose-escalated radiotherapy.
6. **Support Shared Decision-Making:** Educate patients about the meaning and limitations of PSA, including the possibility of aggressive disease despite low levels, to facilitate informed choices about screening, biopsy, and treatment options.
7. **Promote Equity in Care:** Recognize and adjust for racial/ethnic disparities in PSA performance and prostate cancer risk to ensure equitable diagnostic and management pathways.

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