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ORIGINAL RESEARCH

Association of Serum PSA, fPSA, and CEA Levels with Prognosis and Clinicopathological Characteristics in Prostate Cancer

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Objective: To investigate the expression and influencing factors of serum prostate specific antigen (PSA), free prostate specific antigen (fPSA) and carcinoembryonic antigen (CEA) in patients with prostate cancer.

Methods: Retrospective methods were used to select 120 patients with prostate cancer admitted to our hospital from January 2021 to December 2023 as prostate cancer group and 100 patients with benign hyperplasia of prostate as benign hyperplasia group. During the same period, 100 healthy subjects in physical examination center were selected as the healthy control group. Serum PSA, fPSA and CEA levels of the three groups of subjects were detected, and their differences in patients with different clinicopathological characteristics were compared. Multivariate logistic regression was used to analyze their independent risk factors.

Results: The serum levels of PSA, fPSA and CEA in prostate cancer group were significantly higher than those in benign hyperplasia group, and the levels of PSA, fPSA and CEA in benign hyperplasia group were significantly higher than those in healthy control group, the difference was statistically significant ($P<0.05$). Serum PSA, fPSA and CEA levels were significantly higher in patients aged ≥60 years old, Gleason score ≥7, TNM stage III+IV, high differentiated, with lymph node metastasis and bone metastasis than in patients aged < 60 years old, Gleason score < 7, TNM stage I+II, low differentiated, without lymph node metastasis or bone metastasis, the difference was statistically significant ($P<0.05$). PSA≥10.05 μg/mL, fPSA≥1.50 μg/mL, CEA≥20 ng/mL were independent risk factors for poor prognosis of prostate cancer ($P<0.05$).

Conclusion: Serum PSA, fPSA and CEA are significantly elevated in patients with prostate cancer, which are independent risk factors for poor prognosis and can be used as important indicators for clinicopathological evaluation and prognosis prediction.

Keywords: prostate cancer, prostate-specific antigen, free prostate specific antigen, carcinoembryonic antigen, pathological features

Introduction

Prostate cancer has become the most common malignant tumor in the male reproductive system. Prostate cancer ranks second in mortality rates among men, following lung cancer, according to the 2018 cancer mortality data released by the American Cancer Society.[1] In Asian countries, the incidence of prostate cancer has been steadily increasing, with rising age-standardized incidence and prevalence rates observed across almost all countries in the region.[2] The early symptoms of prostate cancer are often not apparent, and many cases are detected through abnormal prostate-specific antigen (PSA) levels during routine physical examinations. Early-stage prostate cancer can be effectively treated with radical surgery or radiotherapy. However, as the disease progresses, patients frequently develop symptoms of compression and metastasis, indicating advanced stages of the disease. At this point, endocrine therapy becomes the preferred treatment, though its efficacy is limited.

Prostate-specific antigen (PSA) is indeed a crucial serological screening marker for prostate cancer due to its high organ specificity.[3–6] PSA, a protein produced in the prostate gland, is primarily detected through blood tests, with elevated levels indicating potential prostate cancer presence. Various forms of PSA, such as total PSA, free PSA, and [−2] proPSA, play essential roles in screening, diagnosis, and monitoring of prostate cancer. Studies have shown that combining total PSA with free PSA measurements can enhance the prediction of clinically significant and fatal prostate

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cancer, aiding in risk stratification for screening purposes. PSA's accuracy in distinguishing between benign and malignant prostatic conditions underscores its significance as an early detection marker, guiding further diagnostic procedures like biopsies when levels exceed certain thresholds.

Carcinoembryonic antigen (CEA) is a crucial tumor marker found on tumor cell surfaces and as a structural protein in the tumor cell membrane, with elevated serum levels indicating abnormal proliferation of tumor cells.[7–11] CEA is overexpressed in various cancers, including colorectal, lung, prostate, ovarian, and thyroid cancers, making it a valuable target for early detection and monitoring of cancer recurrence.[10] Studies have shown that CEA is abundantly expressed in a wide range of epithelial neoplasms, emphasizing the importance of CEA serum monitoring and anti-CEA therapies for CEA-positive cancers. Additionally, the development of novel constructs like GrB-Fc-huMFE, which specifically target CEA-expressing solid tumors, shows promising results in inducing cytotoxicity in CEA-positive tumor cell lines and inhibiting tumor growth in preclinical studies.[12–16] Furthermore, the combination of CTC enumeration with CEA levels has been identified as a more effective prognostic model for colorectal cancer patients, with higher CTC counts correlating with worse overall survival outcomes, highlighting the significance of CEA in predicting prognosis and therapeutic responses in cancer patients.[7,17]

This study aims to analyze the expression levels of PSA, fPSA, and CEA in prostate cancer patients and to explore their relationship with various clinicopathological characteristics. Understanding these relationships can provide valuable insights into the prognosis and management of prostate cancer. However, it is essential to note that this study is based on cases from a single hospital, which may introduce selection bias. Therefore, future large-scale, multicenter studies are necessary to confirm the accuracy and generalizability of these findings.

Materials and Methods

General Information

This study enrolled a total of 320 patients from January 2022 to July 2024. Among them, 120 patients with prostate cancer who were admitted to our hospital were selected as the prostate cancer group. They were aged 35–75 years, with an average age of (66.12 ± 13.38) years, and had a disease duration of 3–8 years, with an average duration of (4.61 ± 1.05) years. Additionally, 100 patients with benign prostatic hyperplasia (BPH) were collected as the benign hyperplasia group. They were aged 35–75 years, with an average age of (65.83 ± 12.38) years, and had a disease duration of 3–8 years, with an average duration of (4.34 ± 1.28) years. All were diagnosed through imaging and histopathology and had no history of malignant tumors. Simultaneously, 100 healthy individuals undergoing physical examinations at the health check-up center were selected as the healthy control group. They were aged 35–75 years, with an average age of (65.11 ± 13.56) years. There were no statistically significant differences in the baseline characteristics among the three groups ($P>0.05$), making them comparable.

Inclusion and Exclusion Criteria for PCa Patients

Inclusion Criteria

①Met the diagnostic criteria for prostate cancer according to the "Prostate Cancer Clinical Guidelines" by the European Association of Urology (EAU) or the American Urological Association (AUA). ②Negative digital rectal examination (DRE) results during routine physical examination. Availability of complete and comprehensive medical records. ④ Total PSA (tPSA) level > 4 ng/mL. ⑤Participants aged between 35 and 75 years. ⑥ All participants provided informed consent, agreed, and voluntarily participated in the study.

Exclusion Criteria

① Presence of hypertension, diabetes, or other significant comorbidities. ②History of taking anti-cancer drugs, anti-androgens, 5α-reductase inhibitors, or undergoing chemical castration within three months prior to inclusion. ③ Patients with known coagulation disorders. History of prostate surgery. ④ Presence of concurrent urinary system infections. ⑤ Patients who withdrew from the study midway. Patients who had undergone cystoscopy, catheterization, or similar examinations within one week prior to inclusion. Patients with a history of other types of malignant tumors. ⑥Patients with Parkinson's disease or dementia.

Inclusion and Exclusion Criteria for BPH Patients

Inclusion Criteria

①Histopathological Diagnosis: Confirmation of BPH through histopathology. ②Age Range: Patients aged between 35 and 75 years.③Absence of Malignancy: No history of prostate cancer or other malignancies. ④ Medical Records: Availability of complete and comprehensive medical records.

Exclusion Criteria

①Prior Prostate Cancer: History of prostate cancer or any other malignant tumor. ②Use of Medications: Use of 5α-reductase inhibitors within three months prior to inclusion.③Systemic Illnesses: Presence of systemic illnesses (eg, hypertension, diabetes) that could influence biomarker levels or interfere with the study. Urinary System Infections: History of urinary system infections within the recent period. Prior Prostate Surgery: Any history of prostate-related surgical procedures. Coagulation Disorders: Known coagulation disorders that could complicate participation.⑦Exclusion by Other Conditions: Patients who have undergone recent procedures such as cystoscopy, catheterization, or other examinations within one week prior to inclusion, or those with neurological disorders such as Parkinson's disease or dementia.

Detection Methods

Collect 3.0 mL of venous blood into a yellow-topped blood collection tube without anticoagulant but with separation gel. Immediately invert the tube 10 times to mix thoroughly. Allow the blood to stand at room temperature for 30 minutes until completely coagulated. Centrifuge at 3000 rpm for 10 minutes to separate the serum. Store the separated serum at 2–8°C within 24 hours. If storage exceeds 24 hours, aliquot and store at −20°C for up to 30 days, avoiding repeated freeze-thaw cycles. If precipitation appears in the specimen, centrifuge before analysis. To ensure accurate test results, inspect all samples for bubbles, hemolysis, and lipemia. Positive reference values are PSA ≥10.05 μg/mL, fPSA ≥1.50 μg/mL, and CEA ≥20 ng/mL.

For this experiment, Abbott's fully automated chemiluminescent immunoassay analyzer i2000SR and its corresponding reagents are used for testing, completed within 3 hours. Ensure internal controls are within specifications before all tests. Calibration of testing items must be qualified, and strictly follow the reagent instructions.

Prognosis Evaluation Methods

All patients were followed up for one year after surgery. During the follow-up period, if rectal ultrasound, CT, or other imaging showed new lesions or extra prostatic invasion, lymph node metastasis, etc, it was determined as metastasis or recurrence.

Statistical Analysis

All test data were statistically analyzed using SPSS 20.0 software. Measurement data conforming to normal distribution were expressed as mean ± standard deviation ($\overline{X} \pm S$). The *t*-test was used for comparisons between two groups, and the F-test was used for multiple group comparisons. Count data were expressed as case numbers and composition ratios, and the $\chi 2$ test was used. Multivariate logistic regression analysis was used to identify influencing factors, with $P<0.05$ considered statistically significant. A forest plot was constructed to display the odds ratios and 95% confidence intervals for the independent risk factors identified through logistic regression analysis.

Results

Comparison of Serum PSA, fPSA, and CEA Levels Among the Three Groups

The levels of PSA, fPSA, and CEA in the prostate cancer group were significantly higher than those in the benign hyperplasia group. Similarly, the levels in the benign hyperplasia group were significantly higher than those in the healthy control group. The differences were statistically significant ($P<0.05$). See Table 1.

Table 1 Comparison of Serum PSA, fPSA, and CEA Levels Among Three Study Groups

Group	n	PSA(μg/mL)	fPSA(μg/mL)	CEA (ng/mL)
Prostate cancer group	120	12.87±1.35	1.89±0.27	30.34±10.27
Benign hyperplasia group	100	9.75±1.01	1.04±0.31	6.01±1.47
Healthy control group	100	2.03±0.76	0.42±0.06	3.06±1.02
F value		18.453	17.544	16.406
P value		<0.001	<0.001	<0.001

Relationship Between Serum PSA, fPSA, CEA Levels and Clinicopathological Characteristics of Prostate Cancer Patients

The positive expression rates of serum PSA, fPSA, and CEA levels were higher in patients aged ≥60 years, with a Gleason score ≥7, TNM stage III+IV, high differentiation, lymph node metastasis, and bone metastasis, compared to patients aged <60 years, with a Gleason score <7, TNM stage I+II, low differentiation, no lymph node metastasis, and no bone metastasis (P<0.05). See Table 2.

Analysis of Factors Influencing Poor Prognosis in Prostate Cancer Patients

Using PSA ≥10.05 μg/mL, fPSA ≥1.50 μg/mL, and CEA ≥20 ng/mL as independent variables, and the occurrence of poor prognosis in prostate cancer patients as the dependent variable (0 for no occurrence, 1 for occurrence), a multivariate logistic regression model was established. The results showed that PSA ≥10.05 μg/mL, fPSA ≥1.50 μg/mL, and CEA ≥20 ng/mL are independent risk factors for poor prognosis in prostate cancer (P<0.05). See Table 3. The multivariate logistic regression analysis identified PSA ≥10.05 μg/mL, fPSA ≥1.50 μg/mL, and CEA ≥20 ng/mL as independent risk factors for poor prognosis in prostate cancer patients. These associations are presented visually in Figure 1 using a forest plot, illustrating the odds ratios and 95% confidence intervals for each factor.

Table 2 Comparison of Serum PSA, fPSA, and CEA Levels in Prostate Cancer Patients with Different Clinicopathological Characteristics

Clinical Characteristic	n	PSA(μg/mL)		*Z/P Value*	fPSA(μg/mL)		*Z/P Value*	CEA (ng/mL)		*Z/P Value*
		Negative	Positive		Negative	Positive		Negative	Positive	
Age										
≥60years	89	14	75	3.009	16	73	2.01	12	77	3.687
<60years	31	13	18	0.006	11	20	0.044	14	17	0.002
Gleason score										
≥7points	52	12	40	2.395	15	37	2.025	10	42	3.017
<7points	68	30	38	0.017	32	36	0.0428	31	37	0.002
TNM stage										
I+IIstage	70	30	40	2.866	29	41	1.985	31	39	2.523
III+IVstage	50	9	41	0.0042	12	38	0.047	11	39	0.016
Tumor grading										
High grade	61	30	31	3.967	28	33	2.546	25	36	2.448
Low grade	59	9	50	<0.01	14	45	0.109	12	47	0.014
Lymph node metastasis										
Yes	41	10	31	2.515	12	29	2.112	11	30	2.502
No	79	38	41	0.119	39	40	0.0347	40	39	0.012
Bone metastasis										
Yes	48	6	42	3.005	6	42	1.99	8	40	2.884
No	72	27	45	0.003	20	52	0.047	30	42	0.004

Table 3 Analysis of Factors Influencing Poor Prognosis in Prostate Cancer Patients

Influencing Factor	β value	Standard Error(s)	χ2value	P value	OR value	95% CI (Lower–Upper)
PSA≥10.05 μg/mL	0.578	0.783	3.003	0	1.604	1.290–3.766
fPSA≥1.50 μg/mL	0.633	0.691	2.904	0	1.209	1.003–2.803
CEA≥20 ng/mL	0.712	0.553	2.876	0	1.337	1.115–4.011

Discussion

Prostate cancer is a prevalent malignancy affecting men globally, with increasing incidence rates, especially in older age groups. Early detection is crucial for improving treatment outcomes, yet many cases are diagnosed late due to the lack of early symptoms. Studies have focused on biomarkers like prostate-specific antigen (PSA), free prostate-specific antigen (fPSA), and carcinoembryonic antigen (CEA) to aid in the diagnosis and management of prostate cancer. PSA, a widely used biomarker, has been controversial in screening due to false positives, while fPSA and CEA have shown promise in improving diagnostic accuracy.[18,19] Monitoring these biomarkers alongside clinicopathological characteristics can provide valuable insights into disease progression and guide personalized treatment strategies, emphasizing the importance of ongoing research in this field.[10]

Prostate-specific antigen (PSA) is a crucial biomarker for prostate cancer screening, primarily secreted by prostate epithelial cells. PSA has good organ specificity and is currently the most widely used serological screening marker for prostate cancer in clinical practice.[20] Studies have consistently shown significantly higher serum PSA levels in prostate cancer patients compared to those with BPH and healthy individuals, supporting its role as a screening tool for detecting prostate cancer. This study confirmed that serum PSA levels were significantly higher in prostate cancer patients compared to those with benign prostatic hyperplasia and healthy controls, consistent with previous findings.[21–23] However, PSA levels can also increase in cases of prostate hyperplasia, inflammation, or acute urinary retention, which presents certain limitations in its diagnostic accuracy for prostate cancer.

Free prostate-specific antigen (fPSA) and total prostate-specific antigen (tPSA) are two forms of PSA found in the blood, with fPSA typically constituting 10% to 20% of the total PSA levels. Research indicates that in healthy adult males, fPSA levels are usually low and originate from benign prostate cells; however, in cases of malignancy, fPSA levels significantly rise. Studies have demonstrated that fPSA can enhance the diagnostic specificity of prostate cancer, particularly within the diagnostic gray zone of PSA levels, which is crucial for accurate cancer detection and

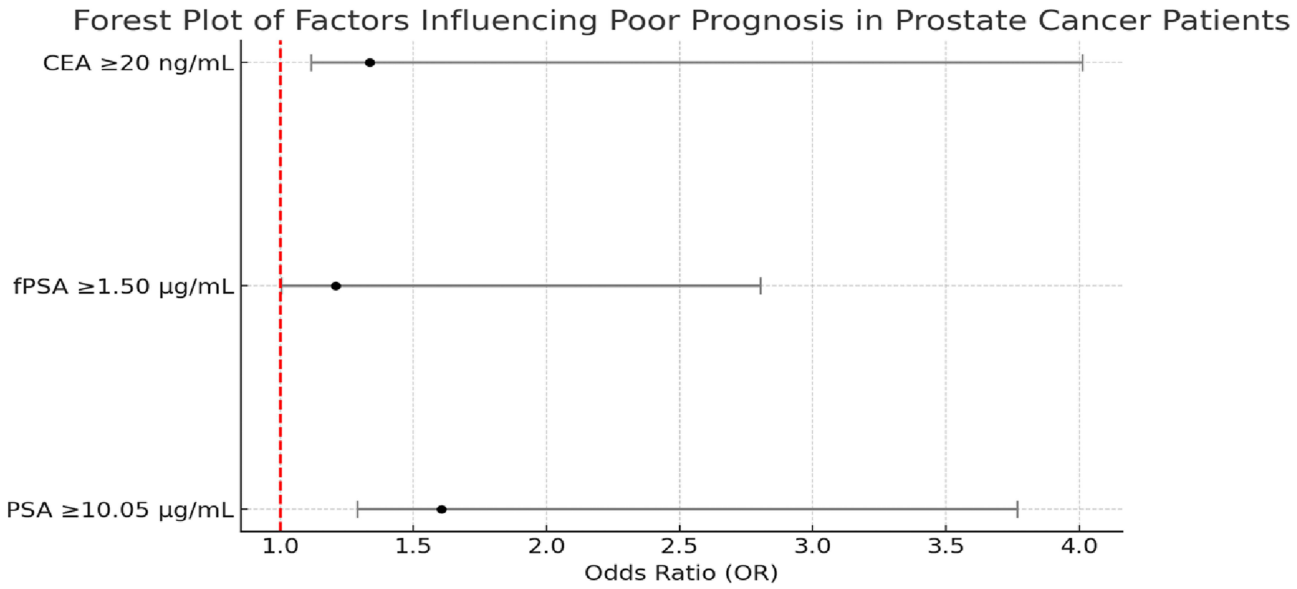

Figure 1 Odds Ratios and 95% Confidence Intervals for Independent Risk Factors Associated with Poor Prognosis in Prostate Cancer Patients.

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management.[5,24] Additionally, the relationship between tPSA and prostate volume may vary depending on the PSA level, with fPSA showing better predictive performance in the gray zone of PSA levels, further emphasizing its importance in prostate cancer diagnosis.[24]

This study observed significantly elevated levels of free prostate-specific antigen (fPSA) in prostate cancer patients when compared to those with benign prostatic hyperplasia (BPH) and healthy controls. This finding seems to challenge the well-established inverse relationship between the fPSA/tPSA ratio and prostate cancer risk, where typically a lower fPSA/tPSA ratio is associated with a higher probability of malignancy factors may explain this discrepancy. One possibility is that the prostate cancer cohort in our study may represent a more advanced stage of disease. Previous research suggests that in more aggressive or metastatic prostate cancer, the levels of fPSA may increase, even as the ratio of fPSA to tPSA decreases. As prostate cancers, the composition of PSA isoforms may shift, leading to elevated absolute fPSA levels despite a lower fPSA/tPSA ratio. This highlights an importation for clinicians: in advanced prostate cancer, absolute fPSA levels might carry more prognostic weight than the fPSA/tPSA ratio alone.[5,20,22,24]

To better understand the role of fPSA in disease progression, it is essential to conduct further research exploring the molecular mechanisms behind this phenomenon. This research should aim to clarify the role of fPSA as a potential biomarker for monitoring prostate cancer progression, particularly in high-risk or advanced-stage disease. Given the increasing recognition of fPSA's potential value, future studies should also investigate how it can be integrated with other biomarkers to improve diagnostic and prognostic capabilities.

Carcinoembryonic antigen (CEA) is a cell surface glycoprotein overexpressed in various cancers, detectable in 54.2% of tumor categories, with high expression linked to high-grade tumors and invasive growth in urinary bladder cancer and specific characteristics in breast cancer.[25] In prostate cancer, elevated serum CEA levels are used to identify aggressive variant prostate cancer (AVPC).[9] In this study, serum levels of PSA, fPSA, and CEA were significantly elevated in the prostate cancer group, and the levels in the benign prostatic hyperplasia group were also significantly higher than those in the healthy control group, with statistically significant differences ($P<0.05$). Studies have found that the incidence of prostate cancer significantly increases among elderly people over 60 years old.[26,27] In this study, patients aged ≥60 years showed significantly elevated levels of serum tumor markers. This may be due to the decline in immunity with increasing age.

Carcinoembryonic antigen (CEA) was selected as a biomarker in this study due to its established role in other cancers, such as colorectal and lung cancer, and its potential utility in aggressive variant prostate cancer (AVPC).[9,10] While prostate-specific membrane antigen (PSMA) and prostate cancer antigen 3 (PCA3) are well-established prostate-specific markers, CEA offers a broader perspective on tumor biology and may complement existing biomarkers in predicting prognosis.[25,28] PSMA, in particular, has gained prominence in prostate cancer diagnostics and therapy due to its high specificity for prostate tissue and its role in PSMA-targeted imaging and radioligand therapy.[24] Similarly, PCA3 has been shown to improve diagnostic accuracy in conjunction with PSA, especially in the "gray zone" of PSA levels (4–10 ng/mL).[12] However, CEA's overexpression in aggressive prostate cancer variants and its association with tumor proliferation and metastasis make it a valuable addition to the biomarker panel. Future studies should directly compare CEA with PSMA and PCA3 to validate its prognostic value and explore its potential in combination with other markers for enhanced risk stratification.

PSA levels are significantly correlated with Gleason score in prostate cancer patients, particularly in the whole-body stage of Ga68-PSMA PET/CT scans, indicating a relationship between serum PSA levels and tumor malignancy.[28] Similarly, studies from Australia and Indonesia support the notion that a PSA level below 20 ng/mL is highly predictive of the absence of skeletal metastasis, advocating for the selective use of bone scans based on PSA values to optimize diagnostic strategies and cost-effectiveness.[29] Furthermore, findings from India suggest that even patients with PSA levels below 10 ng/mL may exhibit bone metastases, highlighting the complexity of disease presentation and the need for individualized risk assessment strategies.[30–32] Moreover, advanced imaging parameters like prostate PSMA tumor volume have been found to differentiate metastatic from non-metastatic patients, with higher PSMA-TV values indicating a higher likelihood of metastatic disease.[25] Studies have shown a significant association between prostate-specific antigen (PSA) levels and the presence of bone metastases in prostate cancer patients. Research conducted in India revealed that patients with PSA levels below 10 ng/mL can still exhibit bone metastases, highlighting the positive correlation between PSA levels and skeletal involvement.

Additionally, a study focusing on patients with metastatic castration-sensitive prostate cancer found that a deeper decline in PSA levels was linked to longer radiographic progression-free survival (rPFS), with very low PSA levels (<0.02 ng/mL) associated with a median rPFS of 49.8 months. Moreover, another investigation emphasized the role of 18 F-DCFPyL PET/CT in detecting disease in prostate cancer patients with low PSA levels (≤0.2 ng/mL), particularly in those with a Gleason score of 8 or higher at diagnosis.[33] These findings collectively underscore the importance of PSA levels in predicting disease aggressiveness and outcomes in prostate cancer patients. These findings collectively support the notion that PSA levels are positively associated with Gleason score and TNM stage, reflecting the tumor's aggressiveness and likelihood of metastasis.

This study found that patients aged ≥60 years, with a Gleason score ≥7, TNM stage III+IV, high differentiation, lymph node metastasis, and bone metastasis had high positive expression rates of PSA, fPSA, and CEA (P<0.05), indicating that these markers may be closely related to the occurrence and progression of prostate cancer. Furthermore, multivariate logistic regression analysis revealed that PSA ≥10.05 μg/mL, fPSA ≥1.50 μg/mL, and CEA ≥20 ng/mL are also risk factors for poor prognosis in prostate cancer patients. In this study, the forest plot was utilized to visually present the odds ratios and confidence intervals of the identified risk factors, providing an intuitive interpretation of the relative strength and significance of each factor's association with poor prognosis in prostate cancer. This graphical representation allows for a more accessible comparison of the risk factors, clearly illustrating how PSA ≥10.05 μg/mL, fPSA ≥1.50 μg/mL, and CEA ≥20 ng/mL independently contribute to poorer outcomes. By visually emphasizing the magnitude and precision of each association, the forest plot aids clinicians and researchers in quickly identifying the most impactful prognostic indicators, supporting informed decision-making in clinical practice.Despite these promising results, the study has limitations. All cases were sourced from a single institution, which may introduce selection bias. Additionally, the sample size was relatively small. Future research should focus on large-scale, multicenter studies to validate these findings and explore the potential of combining these biomarkers with other diagnostic tools to enhance the accuracy and reliability of prostate cancer screening and prognosis. The exclusion of patients with hypertension and diabetes to avoid confounding effects on biomarkers limits the generalizability of the findings to individuals with these common comorbidities. CEA was selected as a tumor marker due to its association with aggressive prostate cancer phenotypes. However, other markers like PSMA and PCA3 were not included due to study limitations. Future research should explore these additional biomarkers to further enhance diagnostic accuracy.

Conclusion

In summary, serum levels of PSA, fPSA, and CEA are significantly elevated in prostate cancer patients and are risk factors for poor prognosis. These markers can serve as important indicators for assessing clinicopathological characteristics and predicting prognosis. However, all cases in this study were sourced from our hospital, which may introduce selection bias. Future large-scale, multicenter studies are needed to verify the accuracy of these findings.

Data Sharing Statement

The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Statement

This study was conducted in accordance with the Declaration of Helsinki. The studies involving human participants were reviewed and approved by Medical Laboratory Departments of Yangzhou University Affiliated Hospital.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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