Research Article

Investigation of the Relationship Between Prostate-Specific Antigen Levels and Prostate Cancer in Patients Attending a Urology Clinic from 2014 to 2023

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Abstract

Background: Prostate cancer is the second most common neoplasm and the fifth most aggressive cancer among men worldwide, with approximately 1.4 million new cases diagnosed annually. The incidence and mortality of prostate cancer increase with age, with a mean age at diagnosis of 66 years. Prostate cancer may be asymptomatic in its early stages and often has a latent period. The use of the Prostate-Specific Antigen (PSA) Index in the definitive diagnosis of prostate cancer remains a challenge for many urologists, and further research in this area can help to better understand the precise relationship between PSA levels and prostate cancer.

Objectives: The present study aimed to investigate the relationship between PSA levels and prostate cancer in patients attending a urology clinic from 2014 to 2023, with the goal of improving diagnosis, developing effective treatments, and enhancing clinical outcomes.

Methods: In this cross-sectional study, 242 patients with prostate cancer who attended a urology surgical clinic over a nine-year period from 2014 to 2023 were included. The patients were divided into two groups—youngest and oldest—based on the duration of their disease diagnosis. Demographic and clinical laboratory data were collected and entered into a checklist. Subsequently, the patients underwent a biopsy, and the results were recorded. Upon completion of the study, the collected data were entered into SPSS software for statistical analysis. Multiple regression analysis was used for correlation tests, while nonparametric tests, such as the Kruskal-Wallis test and the Mann-Whitney U test, were applied for nonparametric data analysis.

Results: This study included 242 out of 276 samples for analysis. The ages of the participants ranged from 41 to 90 years, with a mean age of 67 ± 9.42 years. The data indicated that at PSA concentrations of 4 - 10 ng/mL, 5% of the samples were healthy, 15.2% had cancer, 46% had benign prostatic hyperplasia (BPH), and 33% had prostate intraepithelial neoplasia (PIN). At PSA concentrations of 10 - 50 ng/mL, 6% of the samples were healthy, 37% had cancer, 26% had BPH, and 29% had PIN. At PSA concentrations greater than 50 ng/mL, 3% of the samples were healthy, 76% had cancer, 14% had BPH, and 7% had PIN. A chi-square test revealed a significant association between PSA levels and pathological response ($P < 0.001$). Additionally, an analysis of variance (ANOVA) test showed a significant difference between different age and severity groups ($P < 0.001$). The free PSA-to-total PSA ratio in this study was 0.18, and the PSA-to-prostate volume ratio was 0.15, both of which were significantly associated with biopsy results ($P < 0.01$).

Conclusions: Overall, the data obtained from this study indicated that plasma PSA levels were directly associated with the likelihood of prostate cancer. Additionally, the results showed that plasma PSA levels were not only directly associated with age but also correlated with the severity of trophic disorders, such as cancer, as indicated by biopsy results.

Keywords: Prostate Cancer, Prostate-Specific Antigen, Biopsy, Benign Prostatic Hyperplasia, Prostate Intraepithelial Neoplasia

1. Background

Prostate-specific antigen (PSA) is a protease enzyme belonging to the family of serine proteases, functioning similarly to chymotrypsin. It is also considered a

member of the Kallikrein family based on its function, structure, and genetic locus. Prostate-specific antigen's primary physiological role is in liquefying the semen clot (coagulated semen) following ejaculation. Although the role of PSA in other tissues is not well understood, some researchers suggest that this protein may function as a cell growth factor ([1]). Prostate-specific antigen exists in plasma in various forms, with the majority bound to alpha-1-antichymotrypsin (ACT) and a smaller portion bound to alpha-2-macroglobulin (AMG). These proteins are normal plasma proteins that bind to proteases, inhibiting their function. Prostate-specific antigen is the most widely used tumor marker available for the diagnosis and follow-up of prostate cancer; however, the sensitivity and specificity of this method are not high enough to be considered an ideal tumor marker ([2]).

While PSA is currently regarded as a significant tumor marker for prostate cancer and a prostate tissue-specific antigen, recent reports have identified the presence of PSA in various tissues, serum, and other biological fluids, including milk, umbilical cord fluid, cerebrospinal fluid (CSF), glands around the urogenital ducts, and anal glands in both men and women, even in non-prostatic origins ([3]). Recent studies have shown that the progression of prostate cancer is faster, and mortality is higher in patients with low tissue PSA levels compared to those with high tissue PSA levels ([4]). Given the widespread use of PSA testing for prostate cancer and the development of screening programs, more than 60% of prostate cancer cases are now diagnosed in asymptomatic patients with normal digital rectal examinations and elevated PSA levels ([5]). Prostate cancer is the second most common cancer among men worldwide, the third most common among Iranian men, and the sixth most common cancer overall in Iran. It is often asymptomatic and frequently diagnosed at a late stage ([6]). However, the mortality rate from prostate cancer is lower than that of other cancers, accounting for 3.8% of all cancer-related deaths. A systematic review of biopsy studies indicates that the prevalence of prostate cancer is 5% in individuals under 30 years of age and increases to 59% in those over 79 years of age. The mortality rate of prostate cancer, however, varies by race and country of residence. The incidence of prostate cancer has been rising since the 1990s, particularly in developed countries, following the approval of PSA testing ([7]).

Prostate-specific antigen is a serum protease inhibitor produced exclusively by prostate tissue in response to androgen stimulation. It typically forms a complex with ACT, contributing to semen liquefaction. Serum PSA levels are usually correlated with prostate volume. Various conditions can elevate PSA levels, including benign prostatic hyperplasia (BPH), prostate cancer, prostate infection, prostate manipulation, and ejaculation. Conversely, androgen deprivation or castration, certain medications such as 5α-reductase inhibitors, and prostate removal or ablation can decrease PSA levels ([8]).

Prostate-specific antigen testing began in the late 1980s in the United States, leading to a significant increase in the diagnosis of prostate cancer. By 2013, more than 80% of prostate cancers detected through PSA testing were organ-confined. Although multiple isoforms of PSA, such as free and complex PSA, have been identified and utilized, the effectiveness of PSA as a screening test remains limited. Mildly elevated PSA values should prompt a repeat serum PSA test before proceeding to prostate biopsy, as a significant number of men will show normal PSA levels in subsequent tests ([9]).

2. Objectives

This research was conducted to investigate the relationship between PSA levels and prostate cancer in patients attending a urology clinic from 2014 to June 2023. The goal was to establish a causal relationship that could lead to improved diagnosis, the development of effective treatments, and better clinical outcomes, ultimately enhancing the management of this disease.

3. Methods

The present research was a cross-sectional analytical study.

3.1. Statistical Population, Sampling Method, and Sample Size

The statistical population consisted of all men in Ardabil province who visited a urology clinic from 2014 to June 2023, with the sampling method being full-census. The minimum and maximum ages of participants were 41 and 90 years, respectively, with a mean age of 67 ± 9.42 years.

3.2. Data Collection Method

Data collection for this study involved filling out a checklist using information extracted from patient files. The required data, such as age, prostate volume (measured by ultrasound), free and total PSA levels, urea, creatinine, and urine culture and analysis results, were gathered and recorded in the checklist. Pathological data were also obtained from the

pathology center. Based on previous studies, a cut-off point of 0.18 was used to determine the free PSA-to-total PSA ratio for diagnosing prostate cancer (10). This ratio has been found to have suitable sensitivity and specificity; a ratio below 0.18 suggests a higher probability of cancer, while a ratio above 0.18 indicates a lower probability (11). Additionally, a cut-off point of 0.15 was used to determine PSA density (12), which serves as an indicator for diagnosing prostate cancer. Higher PSA density may suggest that the cancer is more aggressive or advanced (12). The Gleason score, a critical measure of prostate cancer aggressiveness, was also calculated using the pathological data (13, 14).

3.3. Inclusion and Exclusion Criteria

The inclusion criteria for this study included a history of transrectal ultrasound (TRUS)-guided prostate biopsy and an abnormal blood PSA level (above 4 ng/mL) (15). The exclusion criteria were the absence of prostate volume data in the patient file, the absence of blood PSA level results, and the absence of urine culture and analysis results.

3.4. Data Analysis Method and Statistical Analysis

SPSS version 21 software was used for data analysis. In this study, the mean and standard deviation were utilized to describe quantitative data, while frequency and percentage (presented in diagrams and tables) were used to describe qualitative data. The chi-square test was employed to assess the relationship between qualitative variables, such as the association of biopsy results with the Gleason score and PSA level variables. Additionally, the analysis of variance (ANOVA) test was used to compare age among the four groups: BPH, PIN, cancer, and normal.

3.5. Ethical Considerations

The current research was approved by the Research Ethics Committee of Ardabil University of Medical Sciences (code of ethics: IR.ARUMS.MEDICINE.REC.1402.045). Additionally, patients' privacy and confidentiality were fully maintained throughout the study.

4. Results

4.1. The Relationship Between Prostate-Specific Antigen Levels and Prostate Biopsy Results

According to Table 1, for PSA concentrations less than 10 ng/mL, the highest proportion was observed in the PIN group (46.5%), while the lowest was in the normal group (5.1%). For PSA concentrations between 10 - 50 ng/mL, the highest proportion was in the cancer group (37.7%), and the lowest was in the normal group (6.1%). For PSA concentrations over 50 ng/mL, the highest proportion was again in the cancer group (75.9%), and the lowest was in the normal group (3.4%).

Additionally, based on the chi-square test results, there is a significant relationship between PSA levels and biopsy results (P < 0.0001). Specifically, as PSA concentration decreases, the frequency of individuals with cancer also decreases, and conversely, as PSA concentration increases, the frequency of cancer cases increases.

4.2. The Relationship Between Age and Biopsy Results

Based on the ANOVA test results in Table 2, which displays the age distribution of the investigated subjects based on biopsy results (including healthy, cancer, BPH, and PIN), a significant difference in age was observed between the different biopsy result groups (P < 0.001, F = 8.252) (Figure 1).

According to the ANOVA (Tukey) post-hoc test results in Table 3, there is a significant difference in age between the cancer group and the other three groups (P < 0.05); however, no significant difference was observed between the other groups.

4.3. The Relationship Between Prostate-Specific Antigen Levels and the Gleason Score in Individuals with Prostate Cancer

According to the data in Table 4, the chi-square test indicates that there is no significant relationship between PSA levels and the severity of adenocarcinoma as determined by the Gleason score (P > 0.05).

4.4. The Statistical Analysis of the Relationship Between Prostate Cancer and the Free Prostate-Specific Antigen-to-Total Prostate-Specific Antigen Ratio and the Prostate-Specific Antigen-to-Prostate Density

According to Table 5, the free PSA-to-total PSA ratio in this study was 0.18. The chi-square test indicated a significant relationship between prostate cancer and the free PSA-to-total PSA ratio (P < 0.05). Furthermore, according to Table 6, the cut-off value for the PSA-to-prostate volume (prostate density) ratio is 0.15. The chi-square test demonstrated a significant relationship between prostate cancer and the PSA-to-prostate volume (prostate density) ratio (P < 0.001).

Table 1. The Relationship Between Prostate-Specific Antigen Levels and Biopsy Results [a]

	Biopsy Result				
PSA Values	Normal	Cancer	PIN	BPH	Total
Less than 10	5 (5.1)	15 (15.2)	46 (46.5)	33 (33.3)	99 (100)
10 - 50	7 (6.1)	43 (37.7)	30 (26.3)	34 (29.8)	114 (100)
Over 50	1 (3.4)	22 (75.9)	4 (13.8)	2 (6.9)	29 (100)

Abbreviations: PSA, prostate-specific antigen; PIN, prostate intraepithelial neoplasia; BPH, benign prostatic hyperplasia.

[a] Values are expressed as No (%).

Table 2. The Age Distribution of the Investigated Subjects Based on Biopsy Results

Variables	Age		
Biopsy results	Number	Mean	Standard Deviation
Normal	13	64	8.9
Cancer	85	71	8.7
BPH	82	64.4	9.1
PIN	70	66.6	9.2
Total	250	67.3	9.4

Abbreviations: BPH, benign prostatic hyperplasia; PIN, prostate intraepithelial neoplasia.
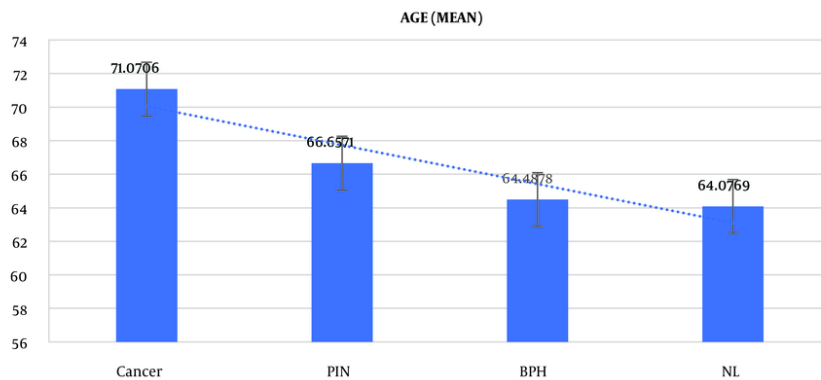

Figure 1. The relationship trend of age and different biopsy results

4.5. The Statistical Analysis of the Relationship Between Active Urinary Infection, Prostate-Specific Antigen Levels, and Biopsy Results

In Table 7, 26% of the samples had a urinary infection at PSA levels less than 10 ng/mL, 54% at PSA levels between 10 - 50 ng/mL, and 20% at PSA levels over 50 ng/mL. The chi-square test indicated a significant relationship between PSA levels and urinary infection ($P < 0.05$). The incidence rate of urinary infection was 3.8% in the normal group, 36.5% in the cancer and BPH groups, and 23.1% in the PIN group (Table 8). However, the chi-square test showed no significant relationship between urinary tract infection and the different biopsy results ($P > 0.05$). Notably, the biopsies were performed after the completion of the urinary infection treatment course and following a negative urine culture.

5. Discussion

Table 3. The Age Difference Between Different Groups (Based on Biopsy Results) [a]

Dependent Variable: Age, Tukey Post-hoc Test	
Biopsy Results	**Significance**
Healthy	
Cancer	0.048
BPH	0.999
PIN	0.78
Cancer	
Healthy	0.048
BPH	0.0001
PIN	0.014
BPH	
Healthy	0.000
Cancer	0.0001
PIN	0.454
PIN	
Healthy	0.78
Cancer	0.014
BPH	0.454

abbreviations: PIN, prostate intraepithelial neoplasia; BPH, benign prostatic hyperplasia.
[a] The mean difference is significant at the 0.05 level.

Table 4. The Relationship Between Prostate-Specific Antigen, Adenocarcinoma, and the Gleason Score [a]

Three PSA Levels	Gleason Score			Total
	Low	**Moderate**	**High**	
Less than 10	10 (71.4)	2 (14.3)	2 (14.3)	14
10 - 50	22 (53.7)	12 (29.3)	7 (17.1)	41
Over 50	7 (31.8)	9 (40.9)	6 (27.3)	22

Abbreviation: PSA, prostate-specific antigen.
[a] Values are expressed as No (%) unless otherwise indicated.

Table 5. The Relationship Between the Free Prostate-Specific Antigen-to-Total Prostate-Specific Antigen Ratio and Prostate Cancer [a]

Categorization Based on the Cut-off Point of FPSA/TPSA	Biopsy				Total	P-Value
	Normal	**Cancer**	**BPH**	**PIN**		
0.18 <	4 (3.3)	39 (32.5)	38 (31.7)	39 (32.5)	120	0.001
0.18 >	6 (8.2)	18 (24.7)	36 (49.3)	13 (17.8)	73	

Abbreviations: FPSA, free prostate-specific antigen; TPSA, total prostate-specific antigen; PIN, prostate intraepithelial neoplasia; BPH, benign prostatic hyperplasia.
[a] Values are expressed as No (%) unless otherwise indicated.

Table 6. The Relationship Between Prostate-Specific Antigen-to-Prostate Volume Ratio with Prostate Cancer [a]

Density in Two Categorizations in the Cut-off Point of 0.15		Biopsy			Total	P-Value
Normal	**Cancer**	**BPH**	**PIN**			
0.15 <	3 (3.7)	9 (11.1)	38 (46.9)	31 (38.3)	81	P < 0.001
0.15 >	10 (6.2)	71 (44.1)	42 (26.1)	38 (23.6)	161	

Abbreviations: FPSA, free prostate-specific antigen; TPSA, total prostate-specific antigen; PIN, prostate intraepithelial neoplasia; BPH, benign prostatic hyperplasia.
[a] Values are expressed as No (%) unless otherwise indicated.

The present research aimed to investigate the relationship between abnormal PSA levels and biopsy

Table 7. The Frequency of Urinary Tract Infection Rate at Different Prostate-Specific Antigen Levels [a]

Urinary Tract Infection	Categorization of PSA Levels			Total	P-Value
Less Than 10	10 - 50	Over 50			
Yes	13 (26)	27 (54)	10 (20)	50	< 0.05
No	86 (44.8)	87 (45.3)	19 (9.9)	192	

Abbreviation: PSA, prostate-specific antigen.

[a] Values are expressed as No (%) unless otherwise indicated.

Table 8. The Frequency of Urinary Tract Infection Rates in Different Biopsy Results [a]

Urinary Tract Infection	Biopsy				Total	P-Value
Normal	Cancer	BPH	PIN			
Yes	2 (3.80)	19 (36.50)	19 (36.50)	12 (23.10)	52	> 0.05
No	11 (5.6)	66 (33.3)	63 (31.80)	58 (29.3)	198	

Abbreviations: BPH, benign prostatic hyperplasia; PIN, prostate intraepithelial neoplasia.

[a] Values are expressed as No (%) unless otherwise indicated.

results in patients who visited a urology clinic in Ardabil from 2014 to June 2023. Overall, the data from this study indicated a direct relationship between plasma PSA concentrations and the likelihood of prostate cancer. The results also demonstrated that plasma PSA concentrations, while directly related to age, are also associated with the severity of trophic disorders such as cancer, as reflected in biopsy results.

The data indicated that as PSA concentrations increased, the prevalence of prostate cancer among the samples also increased. For instance, at PSA concentrations less than 10 ng/mL, 5% of the samples were healthy, 15.2% had cancer, 46% had BPH, and 33% had PIN. Silva et al. reported these values as 33% for cancer, 33% for BPH, and 15% for PIN, suggesting that differences in genetic and racial characteristics between the samples of the two studies could account for the discrepancies (16). On the other hand, Freitas reported the prevalence rate of BPH at this PSA level to be around 40%, which is consistent with the results of this study (17). Lazzeri et al. reported a value of 27% for BPH at this level (18). These findings suggest that PSA concentrations below 10 ng/mL remain a diagnostic challenge (19). In this regard, Merriel et al. indicated that while PSA is highly sensitive for diagnosing prostate cancer in symptomatic patients, it has low specificity, which aligns with the findings of this research (20). Prostate cancer detected via biopsy, including high-grade cancers, was not rare among men with PSA levels of 4 ng/mL or less, supporting the findings of this study

that cancer incidence is possible at this concentration, although with a low probability.

Similarly, at PSA concentrations of 10 - 50 ng/mL, 6% of the samples were healthy, 37% had cancer, 26% had BPH, and 29% had PIN. PutRA et al. suggested that the incidence rate of cancer in this range is around 33.5%, which is close to the findings of this research (21). Venkatachalapathy et al. reported the prevalence rate of cancer at this level to be 50%; the discrepancy may stem from the different objectives of the two studies (22), as the mentioned research focused primarily on identifying individuals with cancer, while this research examined the entire patient population.

At PSA concentrations above 50 ng/mL, 3% of the samples were healthy, 76% had cancer, 14% had BPH, and 7% had PIN. Lojanapiwat et al. reported the prevalence of prostate cancer at PSA levels of 4.1 - 10, 10.1 - 20, 21.1 - 50, 50.1 - 100, and >100 ng/mL to be 9.3%, 55.5%, 87.5%, 98.2%, and 99.7%, respectively (23). Overall, these findings suggest that higher PSA concentrations are associated with worse biopsy outcomes. The rate of PSA expression in individuals was directly associated with the incidence of cancer, and measuring PSA levels could potentially reduce mortality rates due to prostate cancer; however, this marker may also lead to overdiagnosis in some patients. Nam et al. also found that PSA tissue expression was related to the incidence of prostate cancer; however, they emphasized that this method should be used in conjunction with radiological findings, such as magnetic resonance imaging (MRI), to increase its diagnostic value (24).

Additionally, the data show that plasma PSA levels, while directly related to age, are also directly related to the severity of trophic disorders such as cancer in biopsy results. This relationship can be interpreted in two ways. First, increasing age is associated with worse biopsy outcomes. Second, as age increases, PSA levels tend to rise, further indicating a correlation between age, PSA levels, and the severity of prostate cancer.

Liu et al. found in China that the impact of age on the occurrence and mortality of prostate cancer tends to increase with age, particularly in the elderly (25). Similarly, the findings of Vickers et al. are noteworthy because, as in our study, the prognosis of prostate trophic disorders worsened with age. Additionally, their research indicated that elevated PSA levels were more pronounced in older individuals and were associated with the occurrence of malignancies (26). In a 20-year cohort study, Pierre-Victor also demonstrated that PSA levels increase with age, which in turn elevates the likelihood of developing prostate cancer, aligning with the results of our study (27). As discussed, the incidence rate of prostate cancer becomes more prevalent among elderly men as they age, and according to the present findings, this increase is associated with worse biopsy outcomes. It is therefore plausible that as this prognosis worsens, PSA levels in the plasma of elderly individuals may show higher concentrations.

The current data also demonstrated that with a free PSA-to-total PSA ratio of 0.18, the severity of biopsy results worsened. Additionally, the data showed that a PSA-to-prostate volume ratio of 15% was associated with greater severity. The free PSA-to-total PSA ratio of 0.18 for diagnosing prostate cancer, as found in our study, is similar to the findings reported by Jansen et al., who identified this ratio between 20% and 30%, which is somewhat consistent with our research (28). Given the varying results, further research is needed to determine the exact ratio, taking into account different factors such as ethnicity. It is expected that PSA levels would be higher in men with larger prostates due to increased PSA production, while higher PSA density may indicate the presence of cancer (29). In this regard, Lopes Vendrami et al. suggested that PSA density could play a crucial role in determining the severity of prostate neoplasms (30). The association between a PSA density greater than 0.15 and a higher likelihood of prostate cancer (up to 80%) is consistent with the findings of this study. Abonyo et al. also indicated that density values above 0.15 could be related to a worse prognosis, with increasing density leading to more severe biopsy outcomes (31). Furthermore, Wang et al. showed that while higher PSA density values could indicate cancer,

blood PSA levels might be falsely low (below 4 ng/mL), leading to misdiagnoses (32). Based on this evidence, these two criteria—PSA density and free PSA-to-total PSA ratio—could help improve the diagnosis of prostate cancer when used alongside PSA level measurements, though further research is necessary to fully understand these relationships.

In the present research, 13% of samples had infections at PSA levels less than 10 ng/mL, 54% had infections at levels of 10 - 50 ng/mL, and 20% had infections at levels over 50 ng/mL, and this trend was significant. At PSA levels less than 10 ng/mL, the rate of urinary infection was 11% - 15%, which aligns with our findings. This rate increased to 19% at levels over 10 ng/mL, though this difference could stem from variations in measurement methods. The incidence of urinary tract infections, particularly near the prostate gland, can cause blood PSA levels to rise significantly, though not to the same extent as in cases of prostate malignancy, which is consistent with the results obtained in this study. Additionally, it has been shown that after administering antibiotics and resolving the urinary infection, PSA levels typically return to normal, i.e., less than 4 ng/mL. At PSA levels over 10 ng/mL, the sensitivity of this criterion for detecting urinary tract infection could be over 69%, which aligns with the findings of this research. Prostate-Specific Antigen levels above 10 ng/mL have also been linked to the occurrence of inflammation and urinary tract infections after kidney transplantation, generally supporting the results obtained, although that research had different objectives than the present study (33). Based on these findings, PSA levels of 10 - 50 ng/mL appear to be associated with the likelihood of urinary tract infection. This relationship can be seen as both an opportunity and a challenge. On one hand, it could improve the diagnosis of infections in the urinary ducts. On the other hand, this overlap might lead to false diagnoses, as mentioned in some studies (34, 35).

On the one hand, the evidence indicated that the incidence rate of urinary infection was 3.8% in the normal group, 36.5% in the cancer and BPH groups, and 23.10% in the PIN group. Onyebueke et al. reported the prevalence rate of urinary tract infection among BPH patients to be 93% (36). In contrast, the prevalence rate among BPH patients was 62%, while Safwat et al. calculated this value to be 9% (37). Additionally, Tolani et al. calculated the occurrence rate of urinary tract infection among individuals with prostate cancer to be 35%, which is close to our findings (38). Heyns also reported this value to be 36% (39). Based on the aforementioned data, it appears that although the incidence of urinary tract infection in the current

research showed no significant relationship with biopsy prognosis, it follows a certain trend that requires further investigation to be fully understood.

5.1. Limitations

The relationship between age and PSA density was not investigated. The relationship between confounding factors and the occurrence of prostate cancer was not explored. The effect of race on the occurrence of prostate cancer was not examined. The incompleteness of the files led to the exclusion of a large number of them from the study. The absence of computerized records for the files resulted in significant time being spent reviewing them manually.

5.2. Conclusions

Prostate cancer is now recognized as one of the leading causes of mortality in men. Various diagnostic approaches have been developed to assess its severity, each with specific advantages and disadvantages. Among these, plasma PSA level is considered an accessible and relatively cost-effective marker. Although numerous studies have been conducted to understand the trends in PSA level changes, a complete understanding of this process is still lacking, and further research is needed. The present evidence demonstrated that plasma PSA concentration is directly linked to the likelihood of prostate cancer. Additionally, the current results indicated that plasma PSA concentration, while directly related to age, is also associated with the severity of trophic disorders such as cancer, as seen in biopsy results. However, it is noteworthy that 84.8% of biopsies at PSA concentrations less than 10 ng/mL, 63% of biopsies at PSA concentrations of 10 - 50 ng/mL, and 24% of biopsies at PSA concentrations over 50 ng/mL were not cancerous, suggesting that biopsies may not be necessary for all patients. Furthermore, the data demonstrated that a PSA density greater than 0.15 ng/mL and a free PSA-to-total PSA ratio less than 0.18 are associated with an increased risk of cancer.

Footnotes

Authors' Contribution: Study concept and design, Ali Hosseinkhani; acquisition of data, Mahdie Aali; analysis and interpretation of data, Mahdie Aali; drafting of the manuscript, Hamed Mohseni Rad; critical revision of the manuscript for important intellectual content, Hamed Mohseni Rad; statistical analysis, Mahdie Aali, Emad Hosseinkhani; administrative, technical, and material

support, Hamed Mohseni Rad; study supervision, Ali Hosseinkhani, Hamed Mohseni Rad.

Conflict of Interests Statement: The second and third authors are father and son.

Data Availability: The dataset presented in the study is available on request from the corresponding author during submission or after publication.

Ethical Approval: The current research was approved by the Research Ethics Committee of Ardabil University of Medical Sciences (code of ethics: IR.ARUMS.MEDICINE.REC.1402.045). Additionally, patients' privacy and confidentiality were strictly maintained throughout the study.

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Informed Consent: Informed consent was obtained from all participants.

References

1. Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, Penson DF, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med.* 2010;**363**(5):411-22. [PubMed ID: 20818862]. https://doi.org/10.1056/NEJMoa1001294.

2. Loeb S, Sanda MG, Broyles DL, Shin SS, Bangma CH, Wei JT, et al. The prostate health index selectively identifies clinically significant prostate cancer. *J Urol.* 2015;**193**(4):1163-9. [PubMed ID: 25463993]. [PubMed Central ID: PMC4404198]. https://doi.org/10.1016/j.juro.2014.10.121.

3. Llop E, Ferrer-Batalle M, Barrabes S, Guerrero PE, Ramirez M, Saldova R, et al. Improvement of Prostate Cancer Diagnosis by Detecting PSA Glycosylation-Specific Changes. *Theranostics.* 2016;**6**(8):1190-204. [PubMed ID: 27279911]. [PubMed Central ID: PMC4893645]. https://doi.org/10.7150/thno.15226.

4. Jemal A, Fedewa SA, Ma J, Siegel R, Lin CC, Brawley O, et al. Prostate Cancer Incidence and PSA Testing Patterns in Relation to USPSTF Screening Recommendations. *JAMA.* 2015;**314**(19):2054-61. [PubMed ID: 26575061]. https://doi.org/10.1001/jama.2015.14905.

5. Descotes JL. Diagnosis of prostate cancer. *Asian J Urol.* 2019;**6**(2):129-36. [PubMed ID: 31061798]. [PubMed Central ID: PMC6488713]. https://doi.org/10.1016/j.ajur.2018.11.007.

6. Pakzad R, Rafiemanesh H, Ghoncheh M, Sarmad A, Salehiniya H, Hosseini S, et al. Prostate Cancer in Iran: Trends in Incidence and Morphological and Epidemiological Characteristics. *Asian Pac J Cancer Prev.* 2016;**17**(2):839-43. [PubMed ID: 26925689]. https://doi.org/10.7314/apjcp.2016.17.2.839.

7. Ito K, Kimura T. Complex epidemiology of prostate cancer in Asian countries. *J Urol Oncol.* 2023;**21**(1):5-13.

8. Scarpato KR, Albertsen PC. Prostate-Specific Antigen Screening Guidelines. In: Mydlo JH, Godec CJ, editors. *Prostate Cancer.* San Diego: Academic Press; 2016. p. 111-6.

9. Dasgupta A, Wahed A. *Clinical Chemistry, Immunology and Laboratory Quality Control: A Comprehensive Review for Board Preparation, Certification and Clinical Practice.* Amsterdam, Netherlands: Elsevier Science; 2021.

10. Lee J, Yang SW, Jin L, Lee CL, Lee JY, Shin JH, et al. Is PSA density of the peripheral zone as a useful predictor for prostate cancer in patients

with gray zone PSA levels? *BMC Cancer*. 2021;**21**(1):472. [PubMed ID: 33910525]. [PubMed Central ID: PMC8082970]. https://doi.org/10.1186/s12885-021-08216-6.

11. Erol B, Gulpinar MT, Bozdogan G, Ozkanli S, Onem K, Mungan G, et al. The cutoff level of free/total prostate specific antigen (f/t PSA) ratios in the diagnosis of prostate cancer: a validation study on a Turkish patient population in different age categories. *Kaohsiung J Med Sci*. 2014;**30**(11):545-50. [PubMed ID: 25458043]. https://doi.org/10.1016/j.kjms.2014.03.008.

12. Pellegrino F, Tin AL, Martini A, Vertosick EA, Porwal SP, Stabile A, et al. Prostate-specific Antigen Density Cutoff of 0.15 ng/ml/cc to Propose Prostate Biopsies to Patients with Negative Magnetic Resonance Imaging: Efficient Threshold or Legacy of the Past? *Eur Urol Focus*. 2023;**9**(2):291-7. [PubMed ID: 36270887]. [PubMed Central ID: PMC10578357]. https://doi.org/10.1016/j.euf.2022.10.002.

13. Yan JQ, Huang D, Huang JY, Ruan XH, Lin XL, Fang ZJ, et al. Prostate Health Index (phi) and its derivatives predict Gleason score upgrading after radical prostatectomy among patients with low-risk prostate cancer. *Asian J Androl*. 2022;**24**(4):406-10. [PubMed ID: 34782549]. [PubMed Central ID: PMC9295477]. https://doi.org/10.4103/aja202174.

14. Humphrey PA. Histopathology of Prostate Cancer. *Cold Spring Harb Perspect Med*. 2017;**7**(10). [PubMed ID: 28389514]. [PubMed Central ID: PMC5629988]. https://doi.org/10.1101/cshperspect.a030411.

15. Mottet NPJB, Bellmunt J, Briers E, Van den Bergh RCN, Bolla M, Van Casteren NJ, et al. Guidelines on prostate cancer. *Europ Assoc Urol*. 2015;**56**. e137.

16. da Silva RL, de Lima IT, Luís Almeida Paes F, Souza da Silva SM, Almeida Diniz Gurgel AP, Santos F, et al. Matrix Metalloproteinase 26 (Mmp-26) Overexpression In Prostatic Adenocarcinoma. *medRxiv*. 2021;**Preprint**:2021.05. 28.21257789.

17. Freitas DMDO. *Relevância clínica da hiperplasia de células basais em espécimes de biópsia de próstata*. Universidade Federal do Rio Grande do Sul; 2020. Available from: https://lume.ufrgs.br/bitstream/handle/10183/217598/001121974.pdf?sequence=1.

18. Lazzeri M, Abrate A, Lughezzani G, Gadda GM, Freschi M, Mistretta F, et al. Relationship of chronic histologic prostatic inflammation in biopsy specimens with serum isoform [-2]proPSA (p2PSA), %p2PSA, and prostate health index in men with a total prostate-specific antigen of 4-10 ng/ml and normal digital rectal examination. *Urol*. 2014;**83**(3):606-12. [PubMed ID: 24315305]. https://doi.org/10.1016/j.urology.2013.10.016.

19. Rafikova G, Gilyazova I, Enikeeva K, Pavlov V, Kzhyshkowska J. Prostate cancer: genetics, epigenetics and the need for immunological biomarkers. *Int J Mol Sci*. 2023;**24**(16):12797.

20. Merriel SWD, Pocock L, Gilbert E, Creavin S, Walter FM, Spencer A, et al. Systematic review and meta-analysis of the diagnostic accuracy of prostate-specific antigen (PSA) for the detection of prostate cancer in symptomatic patients. *BMC Med*. 2022;**20**(1):54. [PubMed ID: 35125113]. [PubMed Central ID: PMC8819971]. https://doi.org/10.1186/s12916-021-02230-y.

21. Putra PCA, Umbas R, Hamid ARAH, Mochtar CA. Age, prostate volume, prostate-specific antigen and prostate-specific antigen density as predictor factors in results of transrectal ultrasonography-guided prostate biopsy. *F1000Res*. 2019;**8**:875.

22. Venkatachalapathy VSS, Rajeshkannan R, Sarma M, Pooleri GK. Comparison of whole-body bone scintigraphy with axial skeleton magnetic resonance imaging in the skeletal evaluation of carcinoma prostate. *Indian J Urol*. 2021;**37**(1):72-8. [PubMed ID: 33850359]. [PubMed Central ID: PMC8033235]. https://doi.org/10.4103/iju.IJU_238_20.

23. Lojanapiwat B, Anutrakulchai W, Chongruksut W, Udomphot C. Correlation and diagnostic performance of the prostate-specific

antigen level with the diagnosis, aggressiveness, and bone metastasis of prostate cancer in clinical practice. *Prostate Int*. 2014;**2**(3):133-9. [PubMed ID: 25325025]. [PubMed Central ID: PMC4186957]. https://doi.org/10.12954/PI.14054.

24. Nam R, Patel C, Milot L, Hird A, Wallis C, Macinnis P, et al. Prostate MRI versus PSA screening for prostate cancer detection (the MVP Study): a randomised clinical trial. *BMJ Open*. 2022;**12**(11). e059482. [PubMed ID: 36351725]. [PubMed Central ID: PMC9644313]. https://doi.org/10.1136/bmjopen-2021-059482.

25. Liu X, Yu C, Bi Y, Zhang ZJ. Trends and age-period-cohort effect on incidence and mortality of prostate cancer from 1990 to 2017 in China. *Public Health*. 2019;**172**:70-80. [PubMed ID: 31220754]. https://doi.org/10.1016/j.puhe.2019.04.016.

26. Vickers AJ, Sjoberg DD, Ulmert D, Vertosick E, Roobol MJ, Thompson I, et al. Empirical estimates of prostate cancer overdiagnosis by age and prostate-specific antigen. *BMC Med*. 2014;**12**:26. [PubMed ID: 24512643]. [PubMed Central ID: PMC3922189]. https://doi.org/10.1186/1741-7015-12-26.

27. Pierre-Victor D, Parnes HL, Andriole GL, Pinsky PF. Prostate Cancer Incidence and Mortality Following a Negative Biopsy in a Population Undergoing PSA Screening. *Urol*. 2021;**155**:62-9. [PubMed ID: 34186135]. https://doi.org/10.1016/j.urology.2021.05.060.

28. Jansen FH, van Schaik RH, Kurstjens J, Horninger W, Klocker H, Bektic J, et al. Prostate-specific antigen (PSA) isoform p2PSA in combination with total PSA and free PSA improves diagnostic accuracy in prostate cancer detection. *Eur Urol*. 2010;**57**(6):921-7. [PubMed ID: 20189711]. https://doi.org/10.1016/j.eururo.2010.02.003.

29. Zheng S, Jiang S, Chen Z, Huang Z, Shi W, Liu B, et al. The roles of MRI-based prostate volume and associated zone-adjusted prostate-specific antigen concentrations in predicting prostate cancer and high-risk prostate cancer. *PLoS One*. 2019;**14**(11). e0218645. [PubMed ID: 31743339]. [PubMed Central ID: PMC6863612]. https://doi.org/10.1371/journal.pone.0218645.

30. Lopes Vendrami C, McCarthy RJ, Chatterjee A, Casalino D, Schaeffer EM, Catalona WJ, et al. The Utility of Prostate Specific Antigen Density, Prostate Health Index, and Prostate Health Index Density in Predicting Positive Prostate Biopsy Outcome is Dependent on the Prostate Biopsy Methods. *Urol*. 2019;**129**:153-9. [PubMed ID: 30926382]. [PubMed Central ID: PMC6592745]. https://doi.org/10.1016/j.urology.2019.03.018.

31. Abonyo C, Ndaguatha P, Owillah FA. To assess the correlation between prostate specific antigen density and prostate biopsy results of patients with raised prostatic specific antigen levels at the Kenyatta National Hospital. *East African Medical Journal*. 2020;**97**(8):2975-82.

32. Wang C, Wang YY, Wang SY, Ding JX, Ding M, Ruan Y, et al. Peripheral zone PSA density: a predominant variable to improve prostate cancer detection efficiency in men with PSA higher than 4 ng ml(-1). *Asian J Androl*. 2021;**23**(4):415-20. [PubMed ID: 33473011]. [PubMed Central ID: PMC8269833]. https://doi.org/10.4103/aja.aja_72_20.

33. Camargo LF, Esteves AB, Ulisses LR, Rivelli GG, Mazzali M. Urinary tract infection in renal transplant recipients: incidence, risk factors, and impact on graft function. *Transplant Proc*. 2014;**46**(6):1757-9. [PubMed ID: 25131029]. https://doi.org/10.1016/j.transproceed.2014.05.006.

34. Wang R, Ye Y. PSA derivative indicators in the diagnosis of prostate cancer: Advances in studies. *Zhonghua nan ke xue= National J Androl*. 2019;**25**(7):655-9.

35. Findakly D, Wang J. Misdiagnosis of Small Cell Prostate Cancer: Lessons Learned. *Cureus*. 2020;**12**(5). e8356. [PubMed ID: 32494549]. [PubMed Central ID: PMC7263708]. https://doi.org/10.7759/cureus.8356.

36. Onyebueke EA, Udoh IP, Ezeli OF. Prevalence of urinary tract infection and antibiotic resistance pattern of isolates in benign prostatic

hyperplasia patients with urinary catheter seen at a tertiary hospital in Enugu state, Nigeria. *Arch*. 2020;**1**:92-104.

37. Safwat AS, Hasanain A, Shahat A, AbdelRazek M, Orabi H, Abdul Hamid SK, et al. Cholecalciferol for the prophylaxis against recurrent urinary tract infection among patients with benign prostatic hyperplasia: a randomized, comparative study. *World J Urol*. 2019;**37**(7):1347-52. [PubMed ID: 30361957]. https://doi.org/10.1007/s00345-018-2536-8.

38. Tolani MA, Suleiman A, Awaisu M, Abdulaziz MM, Lawal AT, Bello A. Acute urinary tract infection in patients with underlying benign prostatic hyperplasia and prostate cancer. *Pan Afr Med J*. 2020;**36**:169. [PubMed ID: 32952813]. [PubMed Central ID: PMC7467887]. https://doi.org/10.11604/pamj.2020.36.169.21038.

39. Heyns CF. Urinary tract infection associated with conditions causing urinary tract obstruction and stasis, excluding urolithiasis and neuropathic bladder. *World J Urol*. 2012;**30**(1):77-83. [PubMed ID: 21720861]. https://doi.org/10.1007/s00345-011-0725-9.