THE NEW ARMENIAN MEDICAL JOURNAL
Volume18 (2024), Issue 4, p.67-72

DOI: https://doi.org/10.56936/18290825-3.v18.2024-68

PROGNOSTIC FACTORS FOR ENLARGED PROSTATE IN HEALTHY MEN'S ADULTS: A CROSS-SECTIONAL STUDY

Shojaei S., Hanafi M.G.*, Sarkarian M., Fazelinejad Z.

Department of Radiology, Golestan Hospital, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

Received 19.02.2024 Accepted for printing 10.11.2024

Abstract

***Introduction**: Given the significance of the association between anthropometric variables and disease outlook, alongside prostate-specific antigen levels and prostate volume preceding prostate cancer diagnosis, coupled with limited research in this domain, our current investigation endeavors to explore the correlation between prognosis and prostate-specific antigen levels, as well as prostate volume metrics, among adult men.*

***Material and methods:** This cross-sectional study was conducted in 2020 on adult male patients over 40 years old who had been referred to Imam Khomeini Hospital in Ahvaz, Iran for annual screening. Demographic factors along with prostate-specific antigen level and prostate volume were collected by the physician and the study evaluator to examine the relationship with disease prognosis from all patients.*

***Results**: By examining 180 adult men with a mean age of 58.61 ± 10.01 years; the results show that the mean prostate volume in the total study population was 40 ± 6.93 milliliters.*

Analytical analysis shows that body mass index has a direct but relatively weak significant relationship with prostate volume (r=0.155, p=0.038). This is while the patients' age showed a stronger and more direct significant relationship with volume (r=0.862, p<0.001) and prostate-specific antigen (r=0.403, p<0.001). On the other hand, the relationship between prostate volume and prostate-specific antigen of patients was reported as a strong direct significant relationship (r=0.314, p<0.001). This is while the relationship between body mass index and prostate-specific antigen in the community was weak and insignificant (r=0.135, p<0.072).

***Conclusion**: The study results indicate that the patient's age is an important factor for screening in men for prostate examination and in men over 40 years old it is considered a valuable prognostic factor. Also, body mass index level can be used as a factor to control prostate volume in adult men.*

***Keywords:** prostate cancer, prognosis, prostate-specific antigen, serum, prostate volume.*

Introduction

Prostate carcinoma ranks as the second most prevalent cancer among males worldwide and stands as a primary contributor to cancer-related fatalities in developed regions [*WHO 2012, Ferlay J et al., 2015; Torre L et al., 2015*]. Annually, the World Health Organization identifies prostate cancer in 1.1 million men globally, constituting 15% of all male cancer diagnoses [*Gann P, 2002*]. This malignancy claims the lives of 307,000 individuals annually across the globe. Although prostate tu-

Cite This Article as:

***Shojaei S., Hanafi M.G., Sarkarian M., Fazelinejad Z.** (2024).* Prognostic factors for enlarged prostate in healthy men's adults: A cross-sectional study. The New Armenian Medical Journal, vol.18(4), 67-72; https://doi.org/10.56936/18290825-4.v18.2024-67

Address for Correspondence:

Mohammad G. Hanafi, Associate Professor
Department of Radiology, Golestan HospitalAhvaz Jundishapur University of Medical Sciences, Golestan Street, Ahvaz 6135715794, Iran
Tel.: (+98) 061-33738580
E-mail: hanafi-m@ajums.ac.ir

mors often progress slowly and remain asymptomatic in initial stages, they can disseminate to bones, lungs, and the brain, resulting in delayed treatment initiation for many patients [*Ferlay J et al., 2015*]. Prostate cancer screening engenders controversy due to contradictions, overtreatment risks, psychological distress, and excessive healthcare expenses [*Coric J et al., 2015; Dunn M, 2017*]. Prostate-specific antigen serves as the principal tumor marker for prostate cancer detection and initial assessment [*Seo D et al., 2017; Lin D et al., 2021*]. However, ambiguity surrounds the optimal prostate-specific antigen threshold for conducting prostate biopsies, and elevated prostate-specific antigen levels lack specificity for prostate cancer, also occurring in benign prostate ailments, posing limitations for prostate-specific antigen as a tumor marker [*Krumholtz J et al., 2002; Thompson I et al., 2004*]. Approximately 70% of males with increased serum prostate-specific antigen levels, indicated by *ng/mL* > 0.4, undergo unnecessary biopsy assessments without having prostate cancer [*Punglia R et al., 2006*]. Adjusting this threshold reveals fewer yet clinically relevant cancer cases [*Auprich M et al., 2012*]. However, prostate-specific antigen remains pivotal in prostate cancer screening and detection [*Seo D et al., 2017*]. Body mass index, reflecting height and weight correlation, correlates with several cancer types [*Kyrgiou M et al., 2017*], including prostate cancer's various aspects. Although the biochemical process linking obesity to cancer remains unclear, experts propose that weight gain and obesity trigger endocrine alterations [*Ylli D et al., 2022*], influenced by physiological factors altering adipose tissue metabolism, structure, and phenotype, thereby contributing to prostate cancer's etiology [*Cannarella R et al., 2021*]. Considering the importance of the relationship between anthropometric factors and disease prognosis along with prostate-specific antigen level and prostate volume before the diagnosis of prostate cancer and the limited studies in this area, the present study was conducted to determine the relationship between prognosis and parameters of prostate-specific antigen concentration and prostate volume in adult men.

Material and methods

Study design: In the year 2020, a survey of male individuals aged 40 years and older undergoing yearly screening at Ahvaz's Imam Khomeini Hospital in Iran was conducted. The research complied with the ethical standards laid out by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences and abided by the Helsinki Declaration regarding the confidentiality of human research. Before they participated in the study, written consent was obtained from all enrolled patients.

Community: Entrance criteria for the study: Individuals who were older than 40 years and had come for a physical examination were asked to participate in the study after obtaining informed consent. They underwent prostate-specific antigen test and prostate sonography.

Exclusion criteria for the study: The Exclusion criteria for the study included prostate-specific antigen level ≥ *ng/mL* 10, history of prostate cancer, prostate surgery, obvious abnormality in prostate sonography, benign prostatic hyperplasia, and history of bladder cancer or neurogenic bladder.

Measurement of variables: At the outset, all participants underwent clinical evaluations, and their fundamental characteristics were documented in the data collection form. Prostate ultrasonography findings and associated examinations were noted. The variables under scrutiny included age, height, weight, prostate-specific antigen level, and prostate volume. Blood samples were collected for serum prostate-specific antigen analysis, while standard methods were employed for anthropometric measurements. Body surface area was determined using the Mosteller formula, and prostate volume was assessed through transrectal ultrasonography. Furthermore, the body mass index (BMI) was determined by dividing the individual's weight in kilograms by the square of their height in meters. Participants were categorized into four cohorts based on the World Health Organization's BMI classification: underweight BMI < 18.5 *kg/m²* n=46 (25.5%), normal weight BMI 18.5 to 24.9 *kg/m²* n=46 (25.5%), overweight BMI 25 to 29.9 *kg/m²* n=52 (29.0%) and obese BMI ≥ *30 kg/m²* n=36 (20.0%).

Statistical analysis: The results of the data from this research were analyzed by SPSS 22 software. Quantitative data were presented as Mean ±SD assuming normal distribution. The normality of the data was checked by Kolmogorov-Smirnov test

and Q-Q plot and the homogeneity of variances was checked by Leven test. Pearson correlation coefficient with heat map plot was used to compare the variables. In this study, p value less than 0.05 was considered statistically significant.

Results

The study comprised a cohort of 180 males aged 40 and older, with an average age of 58.61 ± 10.01 years. The mean of prostate-specific antigen was 2.35 ± 0.79 *ng/mL*, and the prostate volume was 40.00 ± 6.93 *ml* respectively.

Results indicated that the mean prostate volume for the entire sample was 40 ± 6.93 *milliliters*, with 46.1% experiencing enlargement exceeding 40 *milliliters*. Moreover, 7.8% demonstrated elevated levels of prostate antigen surpassing 4 *ng/mL*. Statistical analyses revealed a direct albeit modest correlation between BMI and prostate volume (r=0.155, p=0.038). Conversely, age exhibited a strong and direct correlation with both volume (r=0.862, p<0.001) and prostate-specific antigen (r=0.403, p<0.001). Additionally, a significant direct correlation emerged between prostate volume and prostate-specific antigen (r=0.314, p<0.001). However, the relationship between body mass index and prostate-specific antigen among participants proved weak and statistically insignificant (r=0.135, p<0.072) (Figure).

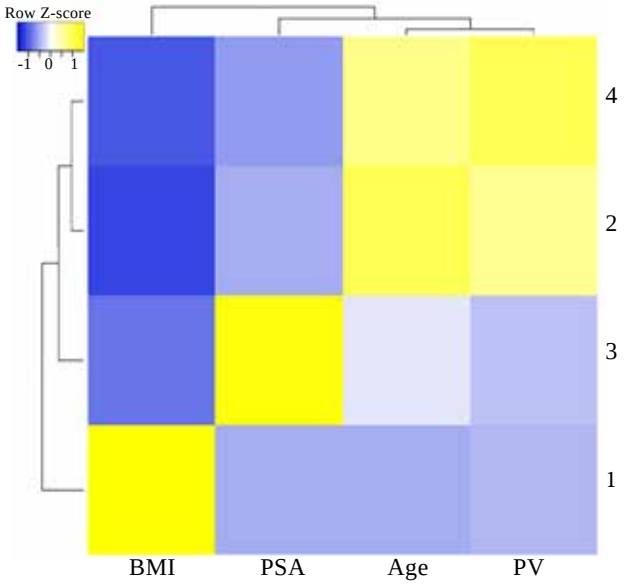

Figure. *Heatmap correlation matrix of all prognosis factors, where BMI -Body mass index, PSA-Prostate-specific antigen, PV-Prostate volume.*

Discussion

The investigation underscores a robust correlation between patients' age and prostate-specific antigen levels, alongside prostate volume in individuals aged over 40, indicating predictive potential. Conversely, BMI exhibits a noteworthy association with prostate volume, offering promise for prostate disease management through reduction, potentially mitigating associated risks.

Findings from a study reveal that, upon age adjustment, prostate volume positively correlates with prostate-specific antigen level (r=0.227, p<0.001), while BMI shows a negative correlation with these levels (r=-0.057, p<0.001) [*Lin D et al., 2021*]. The recent investigation indicates that BMI solely correlates directly with prostate volume, while no significant association was found with prostate-specific antigen AS level. A meta-analysis revealed that a 5 kg/m^2 BMI increase led to a 5.88% prostate-specific antigen change. Additionally, based on BMI categories, men with normal BMIs exhibited prostate-specific antigen levels 3.43% lower than overweight and 12.9% lower than obese individuals. Thus, scant evidence exists regarding BMI's impact on prostate cancer or advanced prostate cancer risk. However, substantial evidence highlights an inverse and nonlinear relationship between BMI and prostate-specific antigen. It's plausible that BMI's effect on cancer underdiagnosis could introduce bias [*Harrison S et al., 2020*]. Another study confirmed a significant negative correlation between BMI and this antigen (p<0.001). There was a non-linear relationship between BMI and prostate-specific antigen on both sides of the inflection point. Therefore, there is an inverse and non-linear relationship between the antigen [*Zhao Y et al., 2020*]. Other studies have also reported an inverse relationship between BMI and prostate-specific antigen levels [*Price M et al., 2008; Fowke J, Matthews C, 2010; Bonn S et al., 2016; Lin D et al., 2021; Popovici D et al., 2023*], however, this relationship may vary depending on geographical regions and genetic factors, as evidenced by this study. Higher BMI may increase prostate volume and consequently prostate-specific antigen levels [*Lin D et al., 2021; Alcantara-Zapata D et al., 2023*]. Obesity disrupts the metabolism of sex hormones and insulin levels and excess accumulation of adipose tissue in the

body. Weight gain can be associated with increased levels of estrogen, estradiol, and decreased levels of testosterone, serum globulin-binding protein, and consequently benign prostatic hyperplasia [*Pasquali R et al., 1991*]. Serum total testosterone has an inverse relationship with BMI and obesity is usually directly related to low testosterone levels. Since prostate-specific antigen production is under androgenic control, this suggests that obesity may be associated with reduced levels of this antigen [*Freedland S et al., 2006*]. On the other hand, an increased estrogen-to-testosterone ratio may increase the ratio of stromal to epithelial cells in benign prostatic hyperplasia nodules [*Giovannucci E et al., 1994; Porcaro A et al., 2019*]. Obese men with prostate cancer may be at risk of underdiagnosis due to having larger prostates [*Wallner L et al., 2011*]. Obesity can be associated with changes in prostate-specific antigen and prostate enlargement and has a significant impact on cancer detection as a factor related to cancer biology. Benson and colleagues showed prostate volume as a useful tool to increase specificity that can indicate the advantage of comparing prostate volume with serum prostate-specific antigen levels [*Benson M et al., 1993*]. Many studies that have found a direct or indirect relationship between prostate-specific antigen and prostate volume [*Coric J et al., 2015; Putra I et al., 2016; Omri N et al., 2020*], and the present study also confirmed this significant direct relationship. The evidence from this study indicated that age is a significant prognostic factor for prostate dysfunction. In elderly men, there is a noticeable reconstruction of the prostate tissue. This prostate growth is the result of a disturbed balance between apoptotic and proliferative activities, which is accompanied by a decrease in apoptotic activity. Histological analyses also showed a reduction in apoptotic activity in the glandular and basal epithelial cells of the prostate [*Untergasser G et al., 2005; Konwar R et al., 2008; Briganti A et al., 2009*]. Therefore, it can be said that with increasing age, there is also a tendency to increase prostate volume. Prostate-specific antigen is a prostate-specific organ biomarker that is circulated by the prostate epithelial cells. Disruption of the natural anatomical tissue of the prostate or changes in its size leads to an increase in serum prostate-specific antigen. This increase may be due to malignant or benign prostate diseases or prostate manipulation, such as catheterization [*Lieber M et al., 2001; Payne H, Cornford P, 2011*].

This study faced a limitation. Since the southwest of Iran is populous and has ethnic and social diversity and has a hot and humid climate in terms of geography, therefore, geographical confounding factors can also affect the results of this study, which should be considered in future studies.

Conclusion

The results of this study show that the age of patients is an important factor for screening in men for prostate examination and is a valuable prognostic factor in men over 40 years old. Also, body mass index level can be a factor in controlling prostate volume in adult men.

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THE NEW ARMENIAN MEDICAL JOURNAL

Volume18 (2024). Issue 4

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Address for correspondence:

Yerevan State Medical University
2 Koryun Street, Yerevan 0025,
Republic of Armenia

Phones:

(+37410) 582532 YSMU
(+37493 588697 Editor-in-Chief
Fax: (+37410) 582532
E-mail:namj.ysmu@gmail.com, ysmiu@mail.ru
URL:http//www.ysmu.am

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Copy editor: Tatevik R. Movsisyan

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Director: Suren A. Simonyan
Armenia, 0023,Yerevan,
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THE NEW ARMENIAN MEDICAL JOURNAL
Volume18 (2024). Issue 4

CONTENTS