MEDICAL SCIENCE

Prostate cancer severity prediction in advanced age groups in low incidence region

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ABSTRACT

Objectives: To explore the relationship between prostate cancer (PCa) aggressiveness and the advanced age at diagnosis. *Materials and methods:* Men who had high Prostate-specific antigen (PSA) (>4ng/ml) were referred to the urology clinic for further evaluation by MRI, and those with positive findings were scheduled for a biopsy. Depending on its size, a systematic 12-core procedure was employed in each patient, following the extraction of 2-6 cores from the identified lesion. Non-significant prostate cancer had a Gleason score (GS) lower than 3 + 4, whereas significant PCa was categorized as having a GS of 3 + 4 or higher. *Results:* Out of all screened 6482 cases, 75 were diagnosed as clinically significant cancer (CSC) cases, and 21 were non-clinically significant. Age was significantly correlated with CSC in univariate analysis, where the percentage of CSC cases increased with increased age categories, and it was a significant independent predictor in all multivariate models. Its discriminative ability is high (AUC=0.75). The percentage of CSC cases (63.6%) is significantly higher in the smallest volume category (≤33 cc) in comparison to the 34-60 cc category (29.5%) and >60 cc category (31.8%). The interaction parameter, age-prostate volume, was a significant independent predictor of CSC, particularly for the smaller prostate volume (<33 cc). *Conclusions:* Age is considered a significant independent predictor of CSC, in general, and for older men in specific. The ability of prostate size to detect CSC becomes higher when interacting with age, particularly for small prostate size.

Keywords: Prostate cancer, Aggressiveness, Advanced age, Low incidence countries, Saudi Arabia.

1. INTRODUCTION

The prevalence and fatality rates of prostate cancer (PCa) are rising and are projected to increase further in the coming years. Prostate cancer (PCa) ranks as the second most prevalent cancer and the fifth leading cause of cancer-related mortality among males globally. Additionally, PCa is the primary contributor to cancer-related deaths in 48 countries, underscoring its

significant impact on public health (Sung et al., 2021; Culp et al., 2020). The expected rise in the prevalence of prostate cancer can be attributed to the observed population aging and economic expansion. However, the incidence in the Middle East and Arab countries is still much lower; the recent study by Arafa et al., (2017) showed an incidence rate of 0.24% amongst the studied cohort in Saudi Arabia.

Prostate-specific antigen (PSA) was adopted as a means of screening in some developed countries, where mortality rates have dropped ever since (Negoita et al., 2018; Le-Blanc et al., 2019). Patients who presented with a cancer Gleason score of 3+3=6, involvement of fewer than two cores, less than 50% of a core, and demonstrating a PSA density of less than 0.15 ng/ml per cm^3 were deemed to have a slight jeopardy of significant cancer at radical prostatectomy. These criteria were adopted as key elements of the very-low-risk category (Matoso and Epstein, 2019).

Age had already been identified as a PCa risk factor, in addition to the Gleason score (GS), which was found as the most significant prognostic variable (Assel et al., 2018; Milonas et al., 2019). The population in our region is characterized by a low age-standardized incidence rate (Saudi Health Council, 2018) and a lower PSA reference range (Rabah et al., 2019) compared to other countries. Therefore, the aim of this study is to explore the hypothesis of an association between age and advanced prostate cancer in older age groups within our specific population. Investigating this relationship aims to enhance our understanding of PCa dynamics in our region and provide valuable insights into tailored management strategies for this disease.

2. MATERIALS AND METHODS

The data for the current study was derived from prior research carried out at King Saud University Medical City between 2014 and 2016, aimed at establishing age-specific reference ranges of PSA levels in the Saudi population. Detailed information regarding this study can be found elsewhere (Rabah et al., 2019). The final analysis of the current study excluded a cohort of 1332 individuals aged 30-40. After confirmation of high PSA (>4ng/ml), suspected men were referred to the clinic of urology for Magnetic Resonance Imaging (MRI) evaluation. Individuals with positive MRI findings were scheduled for a biopsy using an 18G needle under local anesthesia.

The identified Regions of Interest (ROIs) from the MRI scans were electronically uploaded into the Artemis/profuse system and software (Eigen, CA, USA). Depending on its size, a systematic 12-core procedure was done in each patient after 2-6 cores were extracted from the targeted lesion. The Gleason grading methodology used in this study followed the general amendments introduced in 2005 (Epstein et al., 2005). Non-significant prostate cancer (PCa) was defined as a Gleason score (GS) of less than 3 + 4, while significant PCa was characterized by a GS equal to or greater than 3 + 4. Age was categorized into four groups: Individuals aged 50 years or less, those aged between 51 and 60 years, individuals in the age range of 61 to 70 years, and individuals older than 70 years. Prostate volume was categorized into ≤33 cc, 35-60 cc, and > 61 cc.

Statistical analysis

The association between age, prostate volume, and other variables with the biopsy outcome was examined using the chi-square test. Furthermore, the discriminatory capability of various variables in detecting clinically significant cases was evaluated using the receiver operating characteristic (ROC curve). By analyzing the ROC curve, we assessed the sensitivity and specificity of the variables in predicting clinically significant prostate cancer. Additionally, a multinomial logistic regression model was conducted to examine the influence of age and other factors on the risk of clinically significant prostate cancer (CSC) diagnosis. A significance level of 0.05 was considered statistically significant. IBM SPSS software version 24.0 was utilized for all statistical analyses in this study.

3. RESULTS

Out of all screened 6482 cases, 250 patients were suspected of having prostate cancer and were subjected to MRI, 8 cases were lost to follow-up, and 20 cases had negative findings in MRI and refused to do a biopsy. The final number of patients for whom the analysis was performed was 222. 75 cases were clinically significant, and 21 cases were clinically non-significant (Figure 1).

The association and distribution of clinically significant cases (CSC) are illustrated in Table 1, where the percentage of CSC cases increases with increased age categories; the highest percentage (54.7%) was detected in the oldest age category (>70 years). Both X2 and correlation coefficient (r) were significant.

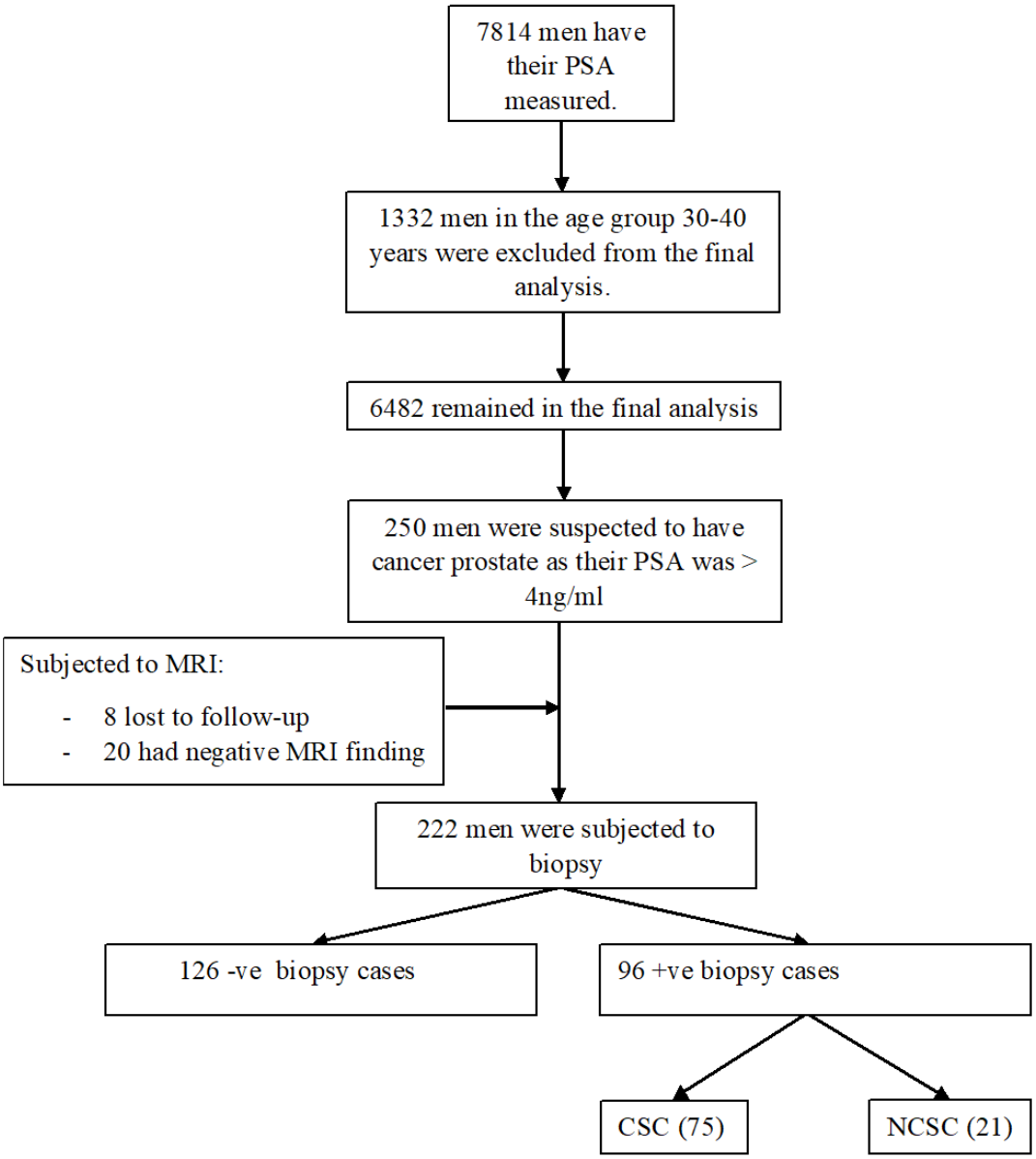

Figure 1 Consort Chart

Table 1 Distribution of CSC of cancer prostate across the age categories

Age categories	Benign lesion	NCSC	CSC	Total
≤ 50 years	7 (5.6%)	0 (0.0%)	2(2.7%)	9
51-60 years	41 (32.5%)	4(19%)	5 (6.7%)	50
61-70 years	60 (47.6%)	9 (42.9%)	27 (36%)	96
> 70 years	18 (14.3%)	8 (38.1%)	41 (54.7%)	67

NCSC=Non-clinically significant cancer; X^2=43.3 & P=0.000; R=0.41 & P=0.000

Figure 2 shows the ROC curve for the three determinants of CSC cases. Both age and PSA had a significant and high discriminative detection ability, AUC for age and PSA was 0.75 (96% CI was 0.69-0.82) & 0.75 (96% CI was 0.69-0.82), respectively. While that for Body mass index was 0.52.

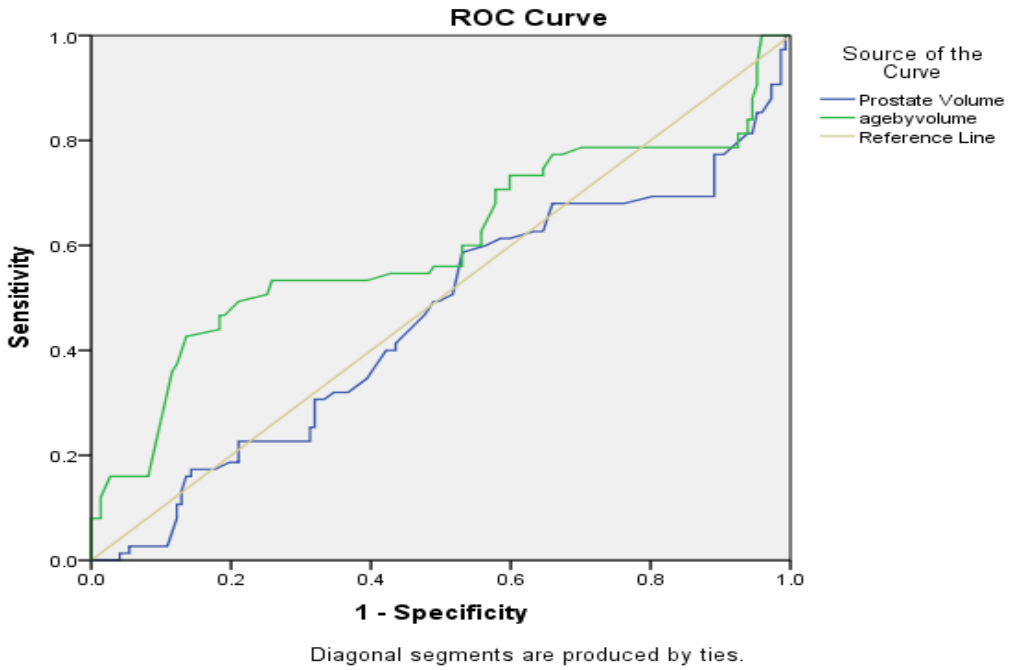

Figure 2 ROC curve for predictors of clinically significant prostate cancer

Significant discriminatory characteristics were observed in both the Prostate Imaging Reporting & Data System (PI-RADS) and digital rectal exam (DRE) findings, enabling the identification of clinically significant prostate cancer (CSC). Notably, PI-RADS demonstrated a higher discriminative ability with an area under the curve (AUC) of 0.81 (95% CI=0.75-0.87), while the AUC for DRE was 0.58 (95% CI=0.50-0.66), as in (Figure 3). These findings highlight the superior discriminative performance of PI-RADS compared to DRE in accurately identifying CSC.

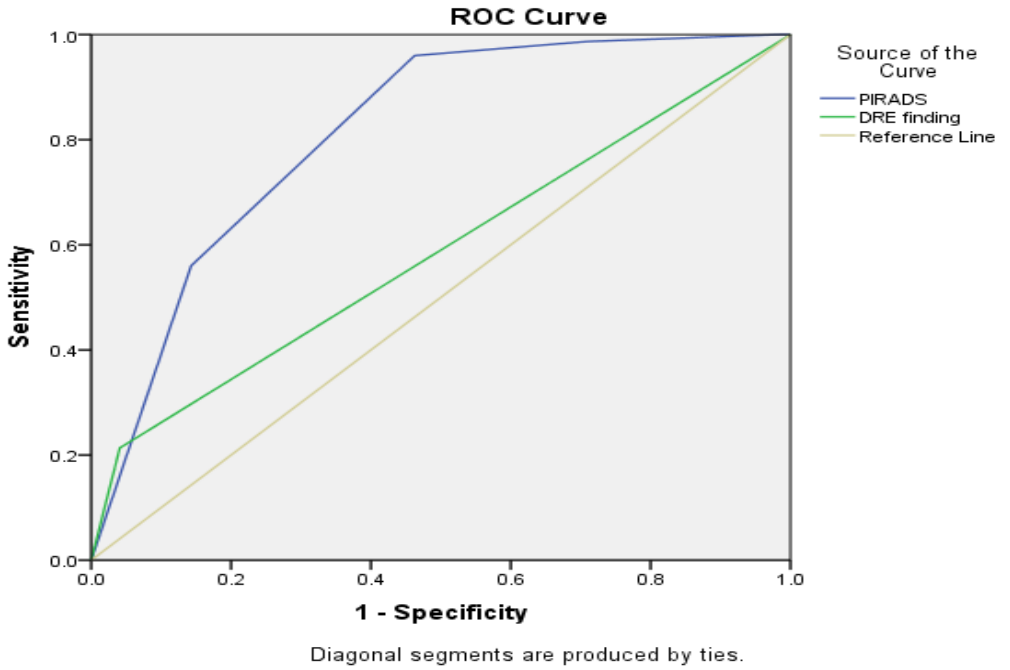

Figure 3 ROC curve for PI-RADs and DRE as predictors of clinically significant prostate cancer

Figure 4 shows that the discriminative ability of prostate volume for the detection of CSC cases increased when age was taken into consideration as an interaction variable with the prostate volume, where the AUC improved from 0.49 (96% CI=0.37-0.54) to 0.62 (95% CI=0.51-0.69).

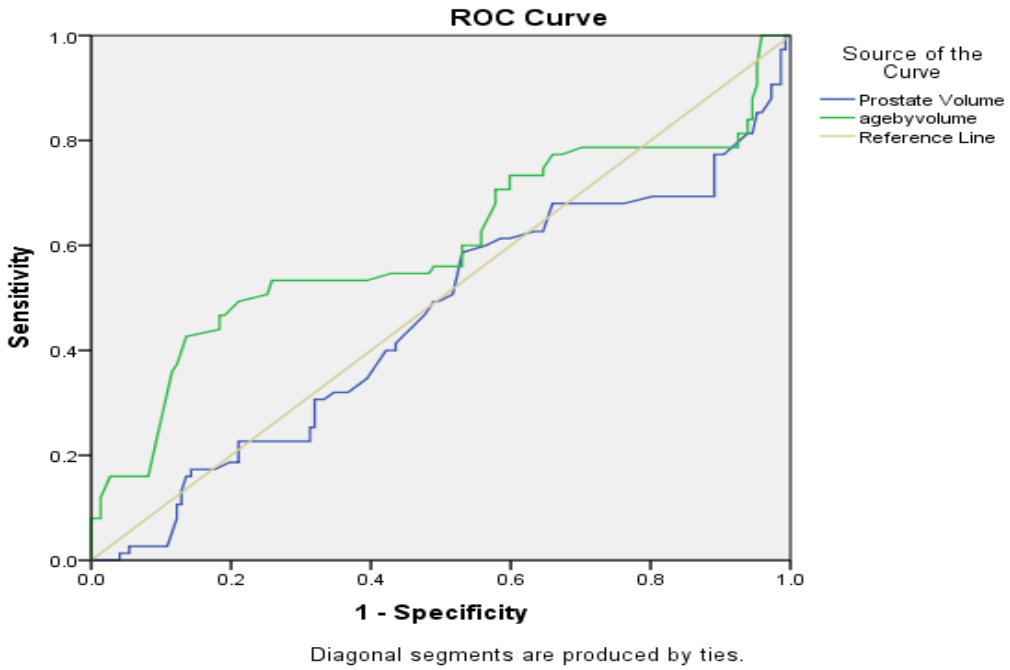

Figure 4 ROC cure for prostate volume and age * prostate volume

Subjects with a prostate volume of lower than 33cc had a positive biopsy rate of 86.6%, while those with a prostate volume of more than 61cc had a positive biopsy rate of 39.8%, P=0.0001. The percentage of CSC (63.6%) is significantly higher in the smallest volume category (≤ 33cc) in comparison to the 34-60 cc category (29.5%) and >60 cc category (31.8%). The correlation coefficient between prostate volume and CSC was negative but not significant (r=-0.12 & P=0.06) (Table 2).

Table 2 Distribution of cancer prostate cases by prostate volume categories

		Biopsy results			Total
		No cancer	CNS cancer	CSC cases	
Prostate volume	≤33 cc	3	5	14	22
		13.6%	22.7%	63.6%	100.0%
	34-60 cc	70	9	33	112
		62.5%	8.0%	29.5%	100.0%
	>60 cc	53	7	28	88
		60.2%	8.0%	31.8%	100.0%
Total		126	21	75	222
		56.8%	9.5%	33.8%	100.0%

X^2=19.1 & p=0.001; R=0.16 & p=0.06

The results of multinomial logistic regression are described in Table 3, considering the three outcomes of biopsy as the dependent variable; 3 models were built. The first one included age categories as a single predictor, and the second included all other variables that could influence the dependent variable. An interaction variable was created between age & prostate volume categories and prostate volume & PSA, and they have been added to the third model. Age was an independent significant predictor of CSC in the three models.

In the first model, the odds of having CSC for men aged 71 years and more were eight times the fold compared to the younger age group. In the second model, prostate volume was reported as a significant negative forecaster of CSC cases. Age was included as a constant factor in the third model, where it was observed that, for each incremental increase in age by one year, the odds of CSC increased by 14%.

Table 3 Multinomial logistic regression; three models result

	Categories	B coefficient	Odds ratio (95 % CI)	R^2	% of cases Correctly classified
Model I	Age ≤ 50 Years		---	22%	66.5%
	Age 51-60 Years	0.45	0.4 (0.06 - 2.6)		
	Age 61-70 Years	0.8	1.5 (0.3 - 81)		
	Age ≥ 71 Years	2.1	7.9 (1.5 - 42) *		
Model II	Age ≤ 50 years		----	33%	66%
	51-60 years	1.7	0.2 (0.03 - 1.7)		
	60-70 years	0.07	1.2 (0.2 - 6.2)		
	≥71 years	1.8	6.3 (1.3 - 41.5) *		
	Prostate volume	-1.2	0.95 (0.93 - 0.98) *		
	BMI	1.03	1.05 (0.97 - 1.13)		
	PSA	0.05	1.06 (1.01 - 1.1) *		
Model III	Age	0.14	1.14 (1.09 - 1.19) *	42%	70.4%
	PSA	0.03	1.03 (1.005 - 1.06) *		
	Age*Prostate volume ≤ 33 cc	0.03	1.04 (1.02 -1.06) *		
	Age*prostate volume 33 – 60 cc	0.1	1.002 (0.99 - 1.01)		
	Age*prostate volume ≥ 61 cc		---		
	PSA*Prostate Volume		Not signifiant		

*Signifiant (P<0.05)

Adjusted R^2 for the third model increased to 42% (42% of the variance in the dependent variable can be clarified by the predictor variables in that model). In addition, the percentage of correctly classified cases increased (70.4%). The interaction parameter (age by prostate volume) significantly predicts the CSC cases, particularly for the smallest prostate volume group (<35cc). The interaction term, PSA by prostate volume, was not significant.

4. DISCUSSION

Our findings suggest a positive and significant correlation between age and CSC detection rates. As men age, their risk of developing clinically significant prostate cancer increases. Each additional year of age corresponds to a 14% increase in the odds of detecting CSC. Moreover, men who are over the age of 70 faces an approximately eightfold higher susceptibility to the diagnosis of CSC compared to younger age groups. Older men have a worse overall survival rate, and the likelihood of being identified with high-risk prostate cancer is higher. As a result, age frequently influences treatment methods in a significant way.

According to Godtman et al., (2022), the chance of diagnosing prostate cancer with a GS ≥ 3 + 4 cancers (vs. <7) is elevated by 11%, while the risk of detecting cancer with a GS ≥4 + 3 (vs. <7) elevated by 8.5% for every year of age increase. The results of two earlier studies mentioned that increasing age significantly impacts CSC detection, and men under the age of 55 had a higher likelihood of having less aggressive clinical and pathological prostate cancer, which in turn has potential implications on therapeutic decision-making (Milonas et al., 2019).

Consequently, understanding the age-related variations in disease presentation can aid in tailoring appropriate treatment strategies and optimizing patient outcomes. Findings of the Mac-Kintosh et al., (2016) showed a significant proportion (77%) of prostate cancer-related deaths occurred in men who were diagnosed between the ages of 70 and 89. This observation suggests that individuals in this age group might present with later-stage tumors, demonstrate more aggressive cancer behavior, or receive less intensive treatment compared to younger men (Mac-Kintosh et al., 2016).

Tang et al., (2010) and Aizer et al., (2014) reported findings indicating that older men with low-risk prostate cancer, whether under active monitoring or receiving therapy, had a higher cancer-specific mortality rate compared to younger men. Similarly, in a study conducted by Scosyrev et al., (2012) it was observed that elderly patients with prostate cancer had an increased likelihood of being diagnosed with metastatic disease at the time of diagnosis.

Our study findings support the findings of Bechis et al., (2011), highlighting the significance of age at diagnosis as a predictor of overall and prostate cancer-specific mortality. Notably, their study revealed that 26% of men aged 75 years and older were diagnosed with high-risk diseases. Furthermore, our analysis of unadjusted Kaplan-Meier survival curves demonstrated a gradual

decline in survival rates with increasing age. However, when considering treatment modality alone or in combination with risk factors, age did not demonstrate consistent predictive value for prostate cancer mortality (Bechis et al., 2011). Thus, our findings underscore the complex interplay between age, treatment modalities, risk stratification, and prostate cancer mortality, indicating that age alone may not be a reliable predictor in isolation.

In accordance with the Milonas et al., (2019) findings, our study identified a higher prevalence of high-risk prostate cancer (HRPC) in the older age group (<65 years) compared to the younger group. Men in the older age group exhibited a 1.5-fold higher risk of HRPC. Conversely, the risk of aggressive disease in the middle age group was comparable to that of the younger group. Calvocoressi et al., (2018) elucidated the relationship between advanced age and aggressive prostate cancer. Their study revealed that molecular markers derived from immunohistochemical staining of prostate tissue, such as B cell lymphoma-2, micro vessel density, and p53, exhibited a significant association with aggressive prostate cancer in men aged 80 years and older (Calvocoressi et al., 2018).

Multivariate analysis showed that the likelihood of detecting CSC decreases when the prostate's size increases; however, its discriminative power is poor (AUC=0.49). The odds of predicting CSC are increased by 4% when age interacts with prostate size ≤ 35 grams, and the discriminative power of such interaction factor has increased (AUC=0.62). The incidence of prostate cancer declines as prostate volume rises, and patients with larger prostates also have better prognoses. When compared to lesser prostate volume (35cc), Al-Khalil et al., (2016) found that larger prostates with a volume >65cc had a 40% significantly lower incidence of PCa. It also indicated a drop of 59.3% in clinically significant cancer when compared to the prostate with a volume between 35 and 65 cc (Al-Khalil et al., 2016).

A reverse relationship between prostate volume and incidence and a higher Gleason score (>7) for prostate cancer was also found by another prospective investigation (Filson et al., 2015). These findings suggest that smaller glands may be more resistant to the spread of prostate cancer. A man's prostate's size may be able to foretell how serious his cancer will be, with a smaller prostate more likely to contain serious disease. This could aid doctors in advising patients on whether it is safe to select a less drastic course of treatment instead of surgically removing or radiation-treating the prostate gland. Nothing about the size would automatically indicate a poor result. The primary factor of importance is the PSA density, as it provides valuable insights.

A small-sized prostate generating a high level of PSA indicates a potentially malignant disease. Conversely, a large prostate producing a significant amount of PSA is more likely to be attributed to benign prostatic hyperplasia (BPH), which refers to non-cancerous enlargement of the prostate (Davies et al., 2011). To summarize, age solely is considered a significant independent predictor of CSC, in general, and for older men in specific. Its discriminative power for the detection of clinically significant cancer is high. The ability of prostate size to detect CSC becomes higher when interacting with age, particularly for small prostate size. A previous study showed that, by carefully selecting appropriate patients, the improvements in life expectancy following radical or laparoscopic prostatectomy for men over 70 are comparable to those observed in men under 70 (Greco et al., 2009).

Limitations

First, PSA density is considered one of the significant predictors of clinically significant cancer. However, it was not measured and was not taken into consideration. The second limitation was about those patients who refused to do the biopsy, as they were not followed up. Thirdly, not all patients were followed up after the radical prostatectomy during the six years after doing radical prostatectomy to determine the recurrence and mortality rates to relate such variables to our results. Lastly, all data in the current study were obtained from a single tertiary hospital and not from different centers.

5. CONCLUSIONS

In clinical practice, particularly for those countries with lower incidences of prostate cancer, the ferociousness of cancer plays a pivotal role in selecting an appropriate treatment approach; the prostate volume should be considered with patients' age when counseling patients with higher PSA regarding their prostate cancer risk.

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Author Contributions

MAA, KHF, HMI: Conception, design, analysis, and interpretation and writing the manuscript. DMR: Critical review of the manuscript. AM, WA, MFF, AAA: Data collection

Ethical approval

Following approval from the King Saud University Faculty of Medicine's ethics committee (approval No. 10/2597/IRB).

Informed consent

Written & Oral informed consent was obtained from all participants in the study. Additional informed consent was obtained from all individual participants for whom identifying information is included in this manuscript.

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Conflict of interest

The authors declare that there is no conflict of interests.

Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

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