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Comparison of Androgen Receptor Expression in Patients with Benign Prostate Hyperplasia and Adenocarcinoma Prostate

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A B S T R A C T

Introduction: Benign prostate hyperplasia is a proliferation of stromal cells and epithelial cells which results an enlargement of the prostate gland and can cause obstruction of the urinary tract. Adenocarcinoma prostate is an invasive carcinoma consisting of a neoplasm of prostate epithelial cells with secretory cell differentiation. Abnormal growth of the prostate gland like benign lesions and malignant lesions are generally affected by androgen receptor (AR). The aim of this research is to analyse the comparison of AR expression in benign prostate hyperplasia and adenocarcinoma prostate. **Methods:** The design of this research is analiytical study with cross sectional approach. The samples are 18 cases of benign prostate hyperplasia and 20 cases of adenocarcinoma prostate. The samples are observed only once and at a time. **Results:** The average age of the adenocarcinoma prostate case was 63.95 ± 12.03 years (age range 33-84 years) while in the benign prostate hyperplasia case, the average age was 66.78 ± 9.49 (age range 54–89 years). There are no different about the expression of AR in benign prostate hyperplasia and adenocarcinoma prostate used Allred scores. There was a weak and negative correlation between Gleason score and AR expression in the adenocarcinoma prostate case group (p=0.237). **Conclusion**: There are no differences related to the expression of AR between the case of adenocarcinoma prostate and benign prostatic hyperplasia.

1. Introduction

The prostate is one of the male reproductive organs. Abnormalities in the prostate can cause an impaired quality of life in men, such as inflammation, benign prostate hyperplasia (BPH), and adenocarcinoma prostate. In BPH, there is the proliferation of stromal cells and epithelial cells, which results in the enlargement of the prostate gland and often causes obstruction of the urinary tract. Adenocarcinoma prostate is an invasive carcinoma consisting of neoplasms of prostatic epithelial cells with secretory cell differentiation.[1-4]

Androgen hormones play an important role in the pathogenesis of adenocarcinoma prostate. Therefore, adenocarcinoma prostate never occurs in males before puberty. Benign prostate hyperplasia and adenocarcinoma prostate are the most common lesions. The growth of the prostate gland is abnormal. Both benign and malignant lesions are generally influenced by androgens. Androgens work specifically with the help of the androgen receptor (AR).[5-6]

Many criteria are used to establish the diagnosis, but new biomarkers are needed. A diagnostic marker that can be detected by immunohistochemistry is the

AR gene. AR is a phosphoprotein that mediates the action of testosterone and 5-α-dihydro-testosterone (DHT) through the mechanism of action of AR as a transcription factor. AR functions in the growth and differentiation of male urogenital structures. Under abnormal conditions, the mechanism of this AR pathway undergoes changes in the development and progression of prostate lesions, both benign and malignant.[7,10]

Several researchers triedcontributes to assess the relationship between AR expression and therapeutic outcomes. Although in the end, several studies gave different results. Research conducted by Li et al. reported that high AR expression was associated with disease proliferation. AR expression was also stated to be related to the Gleason score because an increase in AR occurred in invasive prostate cancer cells. This is also supported by research conducted by Brendler et al., which states that there is a relationship between the degree of cancer and the number of cells that are positive for AR expression. However, several previous studies stated differently that there was no relationship between the degree of cancer and the amount of AR expressed.[11-13] Research at the RSCM in 2019 found that AR expression in stromal cell nuclei in prostate hyperplasia was higher than in prostate adenocarcinoma. An increase in the Gleason score tends to be followed by a decrease in the intensity of AR expression.[1] The aim of this research is to analyse the comparison of AR expression in benign prostate hyperplasia and adenocarcinoma prostate.

2. Methods

The design of this research is an analytical study with a cross-sectional approach. The samples are 18 cases of prostatic hyperplasia and 20 cases of adenocarcinoma prostate in hospitalized patients at Dr. Mohammad Hoesin General Hospital, Palembang, throughout 2021–2022. The samples are observed only once and at a time. The research was conducted at the Department of Anatomic Pathology Dr. Mohammad Hoesin General Hospital, Palembang. The study population was all cases with a diagnosis of prostate hyperplasia and prostate adenocarcinoma in the period 2021-2022 that met the inclusion/ exclusion criteria and continued with the search for paraffin blocks and the manufacture of unstained slaids, followed by ar immunohistochemistry.

Assessment of the results of ar immunohistochemistry by assessing the immunoexpression of AR-positive if brown is returned in the cell nucleus and cytoplasm. The assessment of AR expression is made by summing the distribution of cells positively discharged by AR and their intensity reactions. The distribution of cells positively returned by AR in the following scores: score 0: < 10%, score 1: 10–20%, score 2: > 20–50%, score 3: > 50%. Reaction intensity in the score : 0 : tumor cells are not colored, 1 : intensity of weak color, 2 : intensity of medium color, 3 : intensity of strong color. The AR immunohistochemistry expression score is assessed from the sum of the distribution and intensity scores. Then, the expression score is categorized into 2 categories, namely the negative expression category (degrees 0 – 2) and the positive expression category (degrees 3 – 6).

The data will be analyzed using: (1) Fisher Exact or Pearson Chi-Square test for categorical variables; and (2) independent T or Mann Whitney test for numerical variables. This statistical test uses the SPSS-20 program. The value of $p<0.05$ is expressed as statistically meaningful.

3. Results

An analytical study with a cross-sectional design to determine differences in AR (Androgen Receptor) expression in patients with prostate hyperplasia (BPH) and adenocarcinoma prostate was conducted at the Anatomical Pathology Laboratory, Dr. Mohammad Hoesin General Hospital Palembang from May 2021 to June 2022. There were 38 tissue paraffin block preparations from the prostate with histopathological diagnosis of benign prostate hyperplasia (18 paraffin block preparations) and adenocarcinoma prostate (20 paraffin block preparations) that met the inclusion criteria.

The average age in adenocarcinoma prostate and benign prostate hyperplasia

In the adenocarcinoma prostate case group, the average age of the patient was 63.95 ± 12.03 years (age range 33 – 84 years), while in the benign prostate hyperplasia (BPH) case group, the patient age average was 66.78 ± 9.49 (age 54 – 89 years). Statistical analysis showed that there was no difference in age (p = 0.430) between the two groups.

Table 1. The average age in adenocarcinoma prostate and benign prostate hyperplasia.

Variable	Case group		p-value
	Adenocarcinoma Prostate (n = 20)	BPH (n = 18)	
Age (years)			
Average ± SD	63,95±12,03	66,78±9,49	0,430*
Median (Min-Max)	63 (33-84)	63,5 (54-89)	

*Independent T-test, p < 0.05.

Immunohistochemistry characteristics of androgen receptor

The sample of the adenocarcinoma prostate case group found the majority of tumor cells moderately stained (75%), as well as the study sample for the benign prostate hyperplasia (BPH) case group, the majority of the tumor cells, were moderately stained (66.7%). Statistical analysis showed that there was no difference in cell staining (p = 0.844) between the two groups. In addition, the majority of the intensity of outward appearance in the sample group of cases of adenocarcinoma prostate > 50% with a mean of 77.0 ± 27.45% (0 – 95%), as well as the intensity of outward appearance in the sample group of cases of BPH majority > 50% with a mean of 82.2 ± 16.29% (50 – 95%). With statistical analysis, it was found that there was no difference in the mean of the polished area (p = 0.705) and the intensity of outward appearance (p = 0.134) between the two groups.

Table 2. Immunohistochemistry imaging of androgen receptor.

Variable	Case Group		P-value
	Adenocarcinoma Prostate (n = 20)	BPH (n = 18)	
Intensity of cell			
Weak	1 (5,0)	1 (5,6)	0,844[a]
Moderate	15 (75,0)	12 (66,7)	
Strong	4 (20,0)	5 (27,8)	
Intensity area, n(%)			
< 10%	2 (10,0)	0 (0)	0,134*
10 – 20%	0 (0)	0 (0)	
> 20 – 50%	0 (0)	2 (11,1)	
> 50%	18 (90,0)	16 (88,9)	
Intensity area (%)			
Average ± SD	77,0 ± 27,45	82,2 ± 16,29	0,705†
Median (Min-Max)	85 (0-95)	90 (50-95)	

*Pearson Chi-square test, p < 0.05; †Mann Whitney Test, p < 0.05.

Differences in AR (androgen receptor) expression in adenocarcinoma prostate and benign prostate hyperplasia (BPH) based on Allred score

The results of this study showed that the group of cases of prostate adenocarcinoma had positive AR expression in as many as 18 samples (90%), while in the group of cases of benign prostatic hyperplasia (BPH) it was found that all preparations had positive AR expression. However, statistical analysis showed that there was no difference in AR expression between prostate adenocarcinoma and benign prostatic hyperplasia (BPH) patients.

Table 3. Differences in AR (androgen receptor) expression.

Variable	Case Group		P-value
	Adenocarcinoma prostate (n = 20)	BPH (n = 18)	
AR Expression Average ± SD Median (Min-Max)	 4,8 ± 1,19 5 (1 – 6)	 5,17 ± 0,71 5 (3 – 6)	 0,295[b]
AR Expression Positive Negative	 18 (90,0) 2 (10,0)	 18 (100) 0 (0)	 0,488*

*Fisher exact test, p < 0.05.

Correlation of Gleason score and AR expression in adenocarcinoma prostate

Analysis using the Spearman Rho's test showed that there was a weak and insignificant negative correlation between the Gleason score and AR expression in the prostate adenocarcinoma case group (r = - 0.277; p = 0.237).

Table 4. Correlation of Gleason score and AR expression in adenocarcinoma prostate.

Variable	Variable	r	P-value
Gleason score	AR Expression	-0,277	0,237

Spearman Rho's, *p < 0,05.

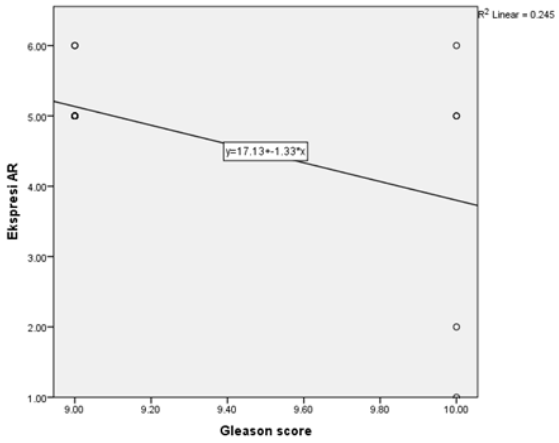

Figure 1. Gleason score correlation graph and AR expression in adenocarcinoma of the prostate.

The results of this study showed the distribution of adenocarcinoma prostate with Gleason Score in group 5 (score 9-10), as shown in the following table:

Table 5. Total cases with a Gleason score of 5.

No.	Gleason Score	Total cases
1	(<6)	0
2	(3+4=7)	0
3	(4+3=7)	0
4	4+4=8, 3+5=8, 5+3=8	0
5	(9-10)	20

4. Discussion

The prevalence of BPH was found to be 70% in those aged between 60 and 69 years and more than 80% in those aged over 70 years.[14] In this study, BPH patients had a mean age of 66.8 years with an age range of 54 to 89 years. The results of this study are in line with research conducted by Tjahjodjati et al. in Bandung in 2021, which reported that from 235 BPH patients, the median age of BPH patients was 68 years with the highest age range is 60-69 years (43.4%).[15] Another study conducted by Prasetyo et al. in 2021 in Malang reported that from 162 BPH patients, the highest age range was 61 – 70 years (39.5%).[16]

Prostate cancer is the most frequently diagnosed malignancy in elderly men. More elderly men are being diagnosed with prostate cancer due to increased life expectancy. The risk increases particularly after age 50 in white men with no family history of prostate cancer and after age 40 in black men or in men with a family history of prostate cancer.[17] The results of this study were obtained in the prostate adenocarcinoma case group, with a mean age of 63.4 years with an age range of 33 to 84 years. The results of this study are not much different from the research conducted by Safriadi et al. in Bandung in 2021, which reported that from 113 adenocarcinoma patients, the average age was 67.9 years with the highest age range is 60-69 years (46%).[18] The mean age of BPH and prostate adenocarcinoma patients in this study was not significantly different, so that age did not affect the comparison of AR gene expression in the two groups in this study.

Androgen hormones play an important role in the pathogenesis of prostate adenocarcinoma, therefore prostate adenocarcinoma never occurs in males before puberty.[9] AR functions in the growth and differentiation of male urogenital structures. Under abnormal conditions, the mechanism of this AR pathway undergoes changes in the development and progression of both benign and malignant prostate lesions.[7,10] AR expression has been shown to be associated with cell proliferation and contribute to the development of prostate cancer. These results clearly show the importance of AR expression level in regulating prostate gland growth rate, especially in aging.[19]

The assessment of AR expression in this study was carried out using the Allred[19] scoring system, which was to add up the scores of the polished area (P) with a score range of 0 to 3; and intensity (I) of coloring with a score range of 0 to 3, then AR expressions were divided into two groups, namely negative expressions if the total score was 0 – 2 and positive expressions if the scores were 3 – 6.

Histologically, there was no significant difference in cell staining and staining intensity between adenocarcinoma and BPH patients in this study. In addition, there was no difference in the mean AR expression between the two groups of patients. The majority of positive AR expression was found in both adenocarcinoma and BPH patients. Husain et al.'s 2016 study involving 25 patients supports the results of this study, which reported no statistically

significant difference in the intensity of AR staining between hyperplasia and prostate cancer patients (p = 0,143).[20]

The prostate cancer grading system used today was introduced by Dr. Donald Gleason in 1966-1974. There are two aspects of the assessment of the Gleason system, namely, the glandular architectural pattern. The resulting grade is taken from the calculation of the two most common glandular architectural patterns. The primary and secondary architectural patterns range from 1 to 5. If the tumor has only one histologic pattern, then the primary and secondary patterns are in equal numbers, then the mean Gleason score ranges from 2 (1+1) to 10 (5+5).[8] In this study, the Gleason score ranged from 9 to 10. There was a negative correlation between the Gleason score and AR expression, which means that the higher the Gleason score (severe), the lower the AR expression, but the relationship between the two variables is weak and not significant.

5. Conclusion

There are no differences in the expression of AR between the case of adenocarcinoma prostate and benign prostatic hyperplasia.

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