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The Relationship between Stromal Cell Ratio and Prostate Epithelium Against the Degree of LUTS in Benign Prostate Hyperplasia Patients at Dr. Saiful Anwar Hospital Malang

Basuki B Purnomo*, Constantino Satriono*
**Department of Urology, Faculty of Medicine, Brawijaya University - Dr. Saiful Anwar General Hospital, Malang*
***Department of Surgery, Faculty of Medicine, Brawijaya University - Dr. Saiful Anwar General Hospital, Malang*

Abstract
BPH (Benign Prostatic Hyperplasia) is the most common disease in elderly man. Prevalence of this disease related with the age, occurs in 30% man with the age between 30 – 50 years old, and reached the top at 88% in 9th decade of elderly man life. Histopathological definition of BPH is increasing of stromal and epithel of prostatic gland in periurethral area which is hyperplasia. Ethiologically, BPH occurs when the prostatic cells and the proliferation of stromal and epithel of prostatic gland are increasing or the apoptosis was decreased.
BPH was the hyperplasia process.The prostatic growth regulated by stromal and epithel interaction. Prostate epithel differentiation and growth controlled by some growth factor which is produced by stromal cells. This situation will cause urethral compression and interrupted of emptying bladder which will eventually cause lower urinary tract symptoms (LUTS).
This study aims to determine the relationship between the ratio of stromal and epithel of prostatic gland with the severity level of LUTS in BPH patient which is evaluated by IPSS score. This study hypothesis was the greater the ratio of stromal to prostatic gland epithelium with tehe level of LUTS in BPH patient. Sample obtained by random, results in 42 samples. Each sample had undergone transurethral resection and the resected tissue was processed into histopathological preparations which will be measured in stromal and epithelial area. From the study results obtained the smallest value of stromal and epitheliat prostatic gland ratio was 2.01which is not much different from normal prostate. From 42 samples, the other 39 samples shows the higher value of stromal to prostatic epithelial ratio which shows that in patient with BPH, the ratio increases.
The results of the study showed a strong correlation between the ratio of the stromal and epithelium of prostate gland to the level of LUTS in patient with BPH (r:0.859 ; p:0.000). This study also showed that the higher ratio correlated with the higher IPSS score which depicted the patient's level of LUTS
Keywords: *Stromal, epithel, BPH, LUTS, IPSS .*

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I. Introduction

Benign prostate enlargement or BPH (Benign Prostatic Hyperplasia) is the most common disease in older men. The prevalence of BPH disease is related to age, which occurs in 30% of men aged 30-50 years. The definition of BPH is a histopathological term, which is an increase in the number of stromal and epithelial cells in the prostate gland in the periurethra area which is hyperplasia. In etiology, there is an increase in the number of prostate cells, the proliferation of prostatic stromal and epithelial cells or there is a decrease in programmed prostate cell death. BPH is a pure hyperplasia process. Prostate growth is regulated by interactions between the epithelium and prostatic stroma. Prostatic epithelial cell differentiation and growth are indirectly controlled by stromal cells through a certain mediator (growth factor). The stimulation causes the proliferation of epithelial cells and prostate stromal cells. This situation will result in interference with the emih channel which is commonly known as LUTS (Lower Urinary Tract Symptomps).

The International Prostate Symptom Score (IPSS) is a WHO approved tool for assessing LUTS symptoms from BPH. The IPSS questionnaire is a valid measuring tool for the severity of BPH in a well-educated patient population. IPSS itself consists of several aspects including aspects of voiding, storage, postmission and quality of life. The aspect of voiding consists of intermittent, weak emission and straining (having to push when starting to urinate) which is thought to be caused by interference with the contraction of the smooth muscle of the prostate which is the constituent of the stroma of the prostate gland. So it is suspected

that if the stromal results are more dominant in the resection of the prostate gland, the degree of LUTS in these patients will be heavier. This study aims to determine the relationship between the ratio of the stromal and epithelial glands of the prostate gland to the LUTS degree of BPH patients who were assessed using the IPSS score.

II. Materials And Method

Research Design

The study design was observational (cross-sectional) which aims to observe the relationship between the ratio of the stromal to the epithelium of the prostate gland to the degree of LUTS in BPH patients.

Time and Place of Research

Subjects with BPH were obtained from patients of the RSSA Urological Surgery who had been diagnosed as BPH and had indications for surgery during January 2019 to December 2019. Making slides of the anatomical pathology of prostate tissue was carried out at the RSSA Anatomical Pathology Laboratory and for measuring the ratio of stromal to epithelium The prostate gland from the preparation was carried out at the Laboratory of Anatomical Pathology, Faculty of Medicine, University of Brawijaya Malang using the Olyvia program which was connected to the Olympus microscope.

Population and Research Sample

The population of this study were all patients of RSSA Urology Surgery who had been diagnosed as BPH. The sample who will be the research subjects are outpatients at the RSSA Urology Surgery Poli who have been diagnosed as BPH and have an indication for surgery. The number of research subjects was calculated using a formula in accordance with the minimum requirement for a cross-sectional research design. From the calculation results obtained a minimum sample size of 32 people.

Sample selection criteria

• Inclusion criteria: RSSA Urological Surgery patients who have been diagnosed as BPH and have an indication of surgery and are willing to undergo surgery at RSS.
• Exclusion criteria: Patients who have been diagnosed as a BPH but are not willing to undergo surgery and the result of the surgical tissue is a prostate carcinoma.

Research Variables

Independent variables: The ratio of the stromal to the epithelium of the prostate gland Dependent variable: LUTS degrees

Operational Definitions

- TUR-P surgery is the removal of prostate tissue in BPH patients by endourology by a urologist.
- The ratio of stromal to prostate gland epithelium is a microscopic image of prostate tissue specimens taken from patients after TUR-P surgery at RSSA to then compare the ratio of the area of the stromal area of the prostate to the area of the epithelial area of the prostate gland. The data scale is numeric.
- The LUTS degree is the score obtained on study subjects (covering storage and voiding) who meet the inclusion criteria. The assessment of the degree of LUTS using the IPSS score instrument was carried out at the beginning of the study before the patient received therapy from poly and emphasized more on the voiding aspect of this study. The data scale is numeric.

Research Materials and Tools Research materials:

- TUR-P scraped prostate tissue from BPH patients who met the inclusion criteria
- The scraped prostate tissue is washed with 0.9% NaCl solution to clean it fromblood and urine and then fix it with 10% formalin. The material was then made of paraffin blocks and HE stained. HE staining of preparations that had been completed were scanned and the area of each epithelium and stromal area was measured using the Olyvia program.

Research tools:

Tool for making histopathological preparations:

- Formalin buffer 10%
- 70% alcohol
- 96% alcohol
- Absolute alcohol
- Xylol or xylol substitutes

- Paraffin with a melting point of 55-59 ° Celsius
- Hematoxylin
- Eosin
- Microtome blade
- Embedding Cassette + lid *
- Slaid
- Cover glass
- Mounting medium
- Label
- Cutter / scalpel

Research Procedures

Sampling

• Operators: Urologists and researchers

• Implementation procedures:

o Retrieval of tissue by endourology (trans urethra resection)

o Immediately after the results of the prostate tissue scrapings are taken, the blood and urine are washed with a physiological saline solution

o Then the tissue sample is inserted into the organ tube containing 10% formalin.

Preparation Slide Preparation

• Executor: Anatomical Pathology laboratory staff

• Implementation procedures:

1) Macroscopic cutting process:

• Examining specimens and taking measurements, recording macroscopic abnormalities in accordance with macroscopic cutting standards based on organs.

• Specimens are inserted into a cassette that has been given an identification number

• Soaking in 10% buffered formalin before further processing.

2) Specimen processing can take place manually or using automatic machines which include fixation, dehydration with graded alcohol, clearing with xylol or xylol substitute fluids and infiltration with liquid paraffin. The paraffin used should have a melting point

3) The process of specimen planting (embedding) to place and position the specimen in such a way as in paraffin.

4) Microtomy cutting process

o Coarse cutting (trimming) to remove excess paraffin above the specimen.

o Fine cutting (sectioning) 3 microns thick.

5) The process of developing the specimen paraffin tape using a water bath filled with warm water with a temperature of not more than 60 0 C (boiling point of paraffin - see manufacturer's instructions) and affixing it to the slaid. The slides that have been attached with paraffin tape need to be drained at an angle sufficiently to prevent air bubbles from making holes.

6) Heating process using a hotplate with a temperature according to the melting point of paraffin.

7) The network is processed using a histokinet machine which has been set automatically for 16 hours

8) Slaid staining process:Hematoxylin and eosin staining

9) The process of closing the slaid using a clean, flat, and thin cover glass with adhesive (mounting medium) with a good refractive index.

Measurement of the Prostate Gland Epithel Stromal Ratio Measurement

Implementation procedures:

The histopathology slides that have been made in the Anatomical Pathology Laboratory of RSSA are then taken to the Anatomical Pathology Laboratory, Faculty of Medicine, Brawijaya University. Using the Olyvia program, histopathology slides were scanned so that they were saved in the form of a file. Using the same program the histopathological dosage file was measured using a polygonal measuring scale so that it could follow the shape and structure of the irregular stromal and epithelium. Measurements were made by calculating the area of both epithelium and stromal in two fields of view with a magnification of 10x. In each field of view is divided into 8 field of view for easy measurement. Measurements were made using a 40x magnification because at this magnification the boundary between the epithelium and the stromal was clearly visible so that from each preparation 16 fields of view were obtained for measurement. The area of each stromal and epithelial area was summed and then manual comparisons were made.

Measurement of the IPSS Score

• Implementation procedures:

o The assessment of the IPSS score was carried out at the start of the study, when a patient with a BPH diagnosis had not undergone any therapeutic intervention from the Urology Clinic

o All BPH patients who met the inclusion criteria were assessed with one assessment modality, namely IPSS

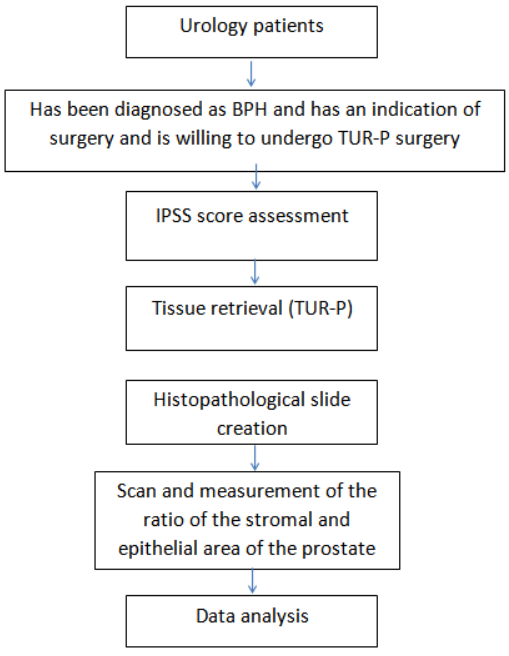
Data Analysis

• This study obtained a sample size of 42 patients, where the ratio of the number of stromal cells to epithelial cells was measured using a numerical scale, the IPSS value was also measured using a numerical scale. The results of this study then the comparison value of the number of stromal cells with epithelial cells was made into groups in order to facilitate reporting. This score is divided into 7 groups. Data in the form of IPSS scores and the ratio of stromal cells to the epithelium of the prostate gland were analyzed using different tests and correlation tests using SPSS software version 23.0. The data analysis process ($p = 0.05$) in this study was carried out in successive calculation stages: (1) normality test of sample data to determine the appropriate type of analysis to be used next, (2) comparative test, (3) correlation test. The data normality test with Shapiro-Wilk was used for a sample size of less than 50 (Sopiyudin, 2012). The data normality test is known by looking at the p value, if the p value is> 0.05, then the conclusion is that the data is normally distributed, whereas if $p < 0.05$, the data is not normally distributed. Inferential approach to parametric analysis through the paired t-test / Wilcoxon sign comparison test. If the data is not normally distributed or the variance of the data is not the same, then the data is transformed first with logarithms or other means before hypothesis testing can be carried out. If after transformation, the data is still not normally distributed, then a non-parametric statistical analysis is performed using the Wilcoxon test. Pearson and Spearman correlation test was used to determine the relationship between the ratio of stromal to prostate gland epithelium to the LUTS degree of BPH patients. The decision is based on the p value if it is less than 0.05, it can be concluded that there is a significant correlation between the 2 variables. Furthermore, the level of closeness of the relationship (correlation coefficient) can be interpreted into five levels (Arikunto, 2002), as follows:

• a. Correlation value> 0-0.25: very weak
• b. Correlation value> 0.25-0.5: sufficient
• c. Correlation value> 0.5-0.75: strong
• d. Correlation value> 0.75-0.99: very strong
• e. Correlation value = 1: perfect

Linear regression criteria are used to predict the causal relationship between numerical variables and other numerical variables, using a 95% confidence interval ($p = 0.05$) and significant if $p < 0.05$

Correlation coefficient (r)	p-value	Decision
0.859	0.000	Significant connection



Comparison of the number of stromal cells with epithelial cells (Within range)	IPSS							Average	Frequency total
	28	29	30	31	32	33	34		
0-1	0	0	0	0	0	0	0	0	0
>1-5	4	4	1	0	0	0	0	28.67	9
>5-10	0	5	9	1	0	0	0	29.73	15
>10-15	0	1	3	2	2	0	0	30.62	8
>15-20	0	0	0	1	1	0	0	31.5	2
>20	0	0	0	2	2	2	2	32.5	8
Total	4	10	13	6	5	2	2	30.604	42

III. Results

Comparison of Stromal Cells and Epithelial Cells with IPSS Score in BPH PatientsFrom the results of the study, it was found that there was a variation of the IPSS in each group of the ratio of the stromal to epithelial ratio. The first group with a comparison value of 0-1, in this group there were no samples with a comparison of stromal and epithelial cells, so it can be concluded that there was no sample that had a higher epithelial cell value than stromal cells (according to the theoretical baseline review which states that in the prostate normal stromal cell count is twice as much as epithelial cells). In the second group, namely with a value of more than one to 5. In this group, 5 samples were obtained with 4 samples having an IPSS value of 28 and 4 samples with an IPSS value of 29 and 1 sample with an IPSS value of 30. Where in this group the value was obtained IPSS average of 28.67. In the third group, namely the comparison of the value of stromal cells with epithelial cells of more than five to 10, the number of samples was 15, with 5 samples having an IPSS value of 29, 9 samples having an IPSS value of 30 and 1 sample having an IPSS value of 31. The IPSS mean score in this group was 29.73.In the fourth group, namely the group that has a comparison value of stromal cells with epithelial cells with a value of more than ten to fifteen. The number of samples in this group was 8 samples with 1 sample having an IPSS value of 29, 8 samples having an IPSS value of 30, 2 samples having an IPSS value of 31 and 2 samples having an IPSS value of 32. While the average IPSS value in this group amounting to 30.62. In the fifth group is the group with the value of stromal cells compared to epithelial cells above fifteen to twenty, in this group obtained 2 samples. Where 1 sample has an IPSS value of 31 and 1 sample again has an IPSS value of 32. The average IPSS score in this group is 31.5. In the sixth group is a group with a ratio of stromal cells to epithelial cells above 20. In this group, the number of samples is 8 where 2 samples with an IPSS value of 31, 2 samples with an IPSS value of 32, 2 samples with an IPSS value of 33 and 2 samples with an IPSS value of 34. Meanwhile, the average score in this group was 32.5. The IPSS average value for all samples was 20,604.

IV. Discussion

Prostate growth is regulated by the interaction between the epithelium and prostatic stroma. The histopathological definition of BPH is associated with an increased number of prostatic stromal and epithelial cells in the hyperplastic periurethral area. Cunha (1973) proved that the differentiation and growth of prostate epithelial cells is indirectly controlled by stromal cells through a certain mediator (growth factor). The stimulation causes the proliferation of epithelial cells and prostate stromal cells. This condition will generally cause compression of the urethra, impaired emptying of the bladder which will eventually cause urinary tract symptoms or often referred to as LUTS. In patients with BPH, smooth muscle contraction and postate tissue enlargement are due to stromal growth which contributes to urethral obstruction, urinary tract disorders and symptoms of voiding (Oelke et al., 2013; Hennenberg et al., 2014). So that these two factors greatly influence the IPSS value. In the research conducted, it was also found that the higher the IPSS value, the higher the ratio of stromal cells to epithelial cells of the prostate gland.

Research conducted by Wang et al., 2019 increased prostate size in BPH-induced mice in line with the increase in smooth muscle and stromal cells in prostate tissue. These results are also in line with the results of a study conducted, in which BPH patients obtained a greater increase in stromal cells compared to the increase in epithelial cells in the prostate gland. In a study conducted by Schaucer and Rowley, 2011, it was said that cell proliferation was greatly increased in BPH, epithelial cell proliferation was 9 times higher, while the proliferation of stromal cells was 37 times higher. The results of research conducted by Wen, S et al., 2015 stated that the indication from BPH is that there are 88.4% stromal cells with 9% epithelial cells, this indicates that stromal cells have an important role in the development of BPH. In this study, the stromal to prostate epithelium ratio was obtained with the smallest value of 2.01 while the greatest value was 57.85. If in a normal prostate the stromal to epithelial ratio is 2 to 1, then the BPH ratio can increase to 4 to 1. In the stromal to

prostate epithelial ratio with a result of about 2 it is possible that these patients do not have BPH but have clinical symptoms of LUTS.

The increased number of stromal cells causes an increase in the size of the prostate cells and prostate cells to become denser. Overall, in this study, only 3 samples had a stromal to prostate epithelium ratio of about two times while the rest had a significant stromal to epithelial ratio, these results support the hypothesis that the increasing the stromal to prostate gland ratio will increase. the value of the IPSS score in these patients. Prostate tissue that continues to experience hyperplasia will further solidify and cause symptoms so that in this situation it will increase the value of the IPSS (Partin, 2020). This is also supported by the statement of Raza et al. 2015, in a study conducted by them said that stromal cells that continue to grow will affect the volume of the prostate and the increase in volume of prostate cells will cause symptoms but an enlarged prostate size is not significantly correlated with the IPSS score

V. **Conclusion**

The results of the study showed a strong correlation between the ratio of the stromal and epithelium of prostate gland to the level of LUTS in patient with BPH (r : 0.859 ; p : 0.000). This study also showed that the higher ratio correlated with the higher IPSS score which depicted the patient's level of LUTS.

DISCLOSURE

The author declares no conflict if interest

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