

# Correlation of Stromal Tumor-Infiltrating Lymphocytes (TILs) Degrees with Total Prostate Specific Antigen (PSA) in Benign Prostate Hyperplasia and Prostate Adenocarcinoma

M Taufik Siregar\*, Delyuzar, Lidya Imelda Laksmi

Department of Anatomical Pathology, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia. \*Corresponding Author

DOI: 10.29322/IJSRP.9.12.2019.p9658

<http://dx.doi.org/10.29322/IJSRP.9.12.2019.p9658>

**Abstract-** Prostate disorders are one of the main causes of quality of life disorders in men. Since 1994, the total PSA value has been approved by the United States Food and Drug Administration (FDA) as a marker of early detection, determining the stage and prognosis in prostate cancer. Many studies have reported the benefits of tumor-infiltrating lymphocytes (TILs) in tumor cells, where TILs are effective in slowing tumor progression, although the mechanism is still the opposite. This study uses tissue samples of Benign Prostate Hyperplasia (BPH) and Prostate Adenocarcinoma (BPH) to assess the correlation between the degree of Stromal Tumor-Infiltrating Lymphocytes (TILs) with Total Prostate Specific Antigen (PSA) in Benign Prostate Hyperplasia (BPH) and Prostate Adenocarcinoma. A total of 32 histopathological slides for patients with BPH and prostate adenocarcinoma were examined to assess the degree of stromal TILs. Age characteristics and Total PSA values were obtained through medical records. The relationship of the degree of Stromal Tumor-Infiltrating Lymphocytes (TILs) with Total Prostate Specific Antigen (PSA) was analyzed using SPSS version 22. The results of the analysis showed that there was a significant correlation between the degree of Stromal Tumor-Infiltrating Lymphocytes (TILs) and Total Prostate Specific Antigen (PSA) on BPH and Prostate adenocarcinoma.

**Index Terms-** benign prostate hyperplasia, adenokarsinoma prostat, stromal TILs, total PSA.

## I. INTRODUCTION

Prostate disorders are one of the main causes of quality of life disorders in men throughout the world. This disease ranks second most often appears in men after respiratory disorders. The most common prostate disorders are benign prostate enlargement and prostate cancer. Benign prostate hyperplasia (BPH) or benign prostate enlargement is the most common type of tumor and occurs in about 70% of men over the age of 60 years. Worldwide, around 30 million men had symptoms related to BPH in 2013. At Cipto Mangunkusumo Hospital in Jakarta, from 1994-2013, 3804 cases were found with an average age of sufferers of 66.61 years. At Adam Malik Hospital in Medan during 2015-2016, there were 23 cases diagnosed with BPH with

an average age of 65.61 years.<sup>1</sup> Prostate cancer currently ranks second in malignancies in men and often appears asymptomatic. From the data of the Indonesian Society of Urologic Oncology (ISUO) 2011, there were 971 prostate cancer patients in Indonesia from 2006 - 2010, where the most cases were prostate adenocarcinoma with stage 4 (50.5%).<sup>2,3</sup> In 2015- 2016 found as many as 39 cases diagnosed as prostate adenocarcinoma in Adam Malik Hospital Medan.

Since 1994, the total PSA value has been approved by the United States Food and Drug Administration (FDA) as a marker for early detection, to determine the stage and prognosis in prostate cancer. The PSA screening application has succeeded in reducing mortality. Most prostate cancers occur at stage T1c with a PSA level between 2.5 ng / mL to 10 ng / mL.<sup>4-6</sup> In the United States the 5-year survival rate in prostate cancer diagnosed at an early and regional stage is near 100%.<sup>4,7,8</sup> Over the past 20 years, although not yet absolutely proven, PSA examination has significantly reduced mortality and metastatic events.<sup>3,4</sup> The role of the immune system in regulating the level of malignancy has increased significantly.<sup>9,10</sup> Many studies have reported the benefits of Tumor-Infiltrating Lymphocytes (TILs) in tumor cells, where TILs are effective at slowing tumor progression, although the mechanism is still contradictory. Histopathological measurement of TILs was performed to see an increase in immunological reactions to tumors, where an increase in prognosis in various types of cancer can affect the stage and grading of the tumor.<sup>11</sup>

## II. MATERIAL AND METHODS

### Sample selection

This study was selected cross-sectionally at H. Adam Malik General Hospital Medan consisting of 15 cases of BPH and 17 cases of prostate adenocarcinoma, which aims to assess whether there is a correlation between the stromal degree of TILs with the total PSA in BPH and prostate adenocarcinoma. All samples were obtained through TUR-P. Inclusion criteria were slides diagnosed with BPH and prostatic adenocarcinoma by histopathology and total PSA value data obtained from medical records. The assessment of TILs was carried out independently

by the researchers through examination of hematoxylin-eosin slides.

**Prostate-Specific Antigen (PSA)**

Prostate-Specific Antigen (PSA) is a protein produced by prostate cells to regulate the viscosity of semen. This protein is produced in large quantities by prostate cells and this test is used as prostate neoplasm screening. Total PSA value, categorized as:

1. Normal = PSA value ≤ 4,0 ng/ml
2. Medium = PSA value 4,1-10 ng/ml
3. High = PSA value > 10 ng/ml.<sup>12</sup>

**Stromal Tumor-Infiltrating Lymphocytes (TILs)**

Stromal Tumor-Infiltrating Lymphocytes (TILs) are defined as mononuclear inflammatory cells that are in the stromal tissue between the nests of cancer cells, and are not directly related to cancer cells. TILs are assessed at 400x magnification, and assess the percentage of stromal area alone without including calculations in tumor cells. For example, a score of 50% stromal TILs means that 50% of the surface area of the stroma and not 50% of the stroma plus epithelial cell area. The assessment is based on the focus of the most dense lymphocyte infiltration, divided by TILs working group 2013:

1. Mild : 0-10 % stromal TILs (HPFs 400x)
2. Moderate : 11-49 % stromal TILs (HPFs 400x)
3. Severe : ≥ 50 % stromal TILs (HPFs 400x).<sup>13</sup>

**Grading**

Histopathological grading of prostate adenocarcinoma is a scale for determining the prognosis of a prostate adenocarcinoma seen based on histopathological assessment based on the Gleason scale (WHO, 2016) which is categorized as:

1. Grade group 1, Gleason score ≤ 6 : consists of a combination of glands with well differentiation.
2. Grade group 2, Gleason score 3+4=7: More well differentiation glands, followed by fusion of glands.
3. Grade group 3, Gleason score 4+3=7: More fusion/ciribriform glands, followed well-differentiated glands.
4. Grade group 4, Gleason score 4+4=8, 3+5=8, 5+3=8: Consists of both poorly differentiation and fusion gland patterns, well differentiation followed by poorly differentiation gland, or more poorly differentiation glands followed by well differentiation.
5. Grade group 5, Gleason score 9-10: poorly differentiation gland forms with or without necrosis or both poorly / solid differentiation.<sup>4</sup>

**Statistical analysis**

Statistical analysis was performed using SPSS software version 22.0 (SPSS Inc., Chicago). To analyze data on the relationship of the stromal degree of TILs to the Total PSA on BPH and prostate adenocarcinoma researchers used the Spearman correlation test p-value> 0.05 was considered not significant.

III. RESULT

From 15 BPH samples and 17 prostate adenocarcinoma samples, there was no difference in age characteristics between BPH and

prostate adenocarcinoma, p-value = 0.899 (p> 0.05). There are differences in the characteristics of the Total PSA level between BPH and prostate adenocarcinoma, p-value = 0.002 (p <0.05). There was a difference in the percentage of stromal TILs between BPH and prostate adenocarcinoma, p-value = 0.0001 (p <0.05).

**Table 1. Characteristics of the sample based on the type of lesion.**

No	Characteristics	Benign Prostate Hyperplasia (n=15)			Prostate Adenocarcinoma (n=17)			P-value
		Median	Mean	SD	Median	Mean	SD	
1.	Age (year)	63	64,7	7,3	63	64,4	6,9	0,899*
2.	TotalPSA (ng/mL)	6,7	9,7	8,1	39	57,2	59,7	0,002**
3.	Percentage Stromal TILs	35	32,7	21,7	5	5,8	3,5	0,0001**

\* T Independent test \*\* Mann-Whitney U Test

There was a significant correlation between degrees of stromal TILs and total PSA in 32 samples (BPH and prostate adenocarcinoma), p-value = 0.011 (p <0.05). Whereas in each sample, BPH (p-value = 0.225) and prostate adenocarcinoma (p-value = 0.355), did not show a significant relationship (p> 0.05).

**Table 2. Correlation of degrees Stromal TILs and Total PSA.**

No.	Lesion	Correlation coefficient (p)	P-value*
1.	BPH and Prostate Adenocarcinoma	-0,445	0,011
2.	BPH	0,333	0,225
3.	Prostate Adenocarcinoma	-0,239	0,355

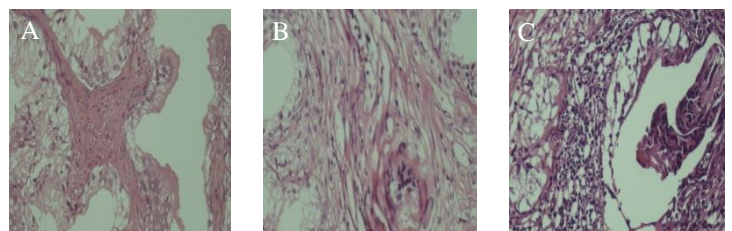
\* Correlation Spearman Test

There was no significant correlation between the degree of stromal TILs with Gleason score of prostate adenocarcinoma, p-value = 0.083 (p> 0.05). While the relationship of the total PSA value with the Gleason score in prostate adenocarcinoma obtained p-value = 0.006 (p <0.05), which shows a significant correlation.

**Table 3. Correlation between stromal TILs and Total PSA with Gleason score of prostate adenocarcinoma.**

No.	Variable	Correlation coefficient(p)	P-value*
1.	Stromal TILs Percentage	-0,398	0,083
2.	Value of Total PSA (ng/mL)	0,802	0,0001

\* Correlation Spearman Test



**Figure.** Infiltration degrees stromal TILs of BPH. A. Mild 0-10%, B. Moderate 11-49%, C. Severe > 50%.

#### IV. DISCUSSION

Inflammatory cells are commonly associated with neoplasms, where TILs play a role as a tumor cell defense factor, which often appears in solid tumors, including the prostate. The prostate is considered immunologically special because of the immunosuppressive properties of semen. Research on local immunosuppression of the prostate has been carried out on BPH, prostate intraepithelial neoplasia and prostate cancer.<sup>9</sup> The role of the immune system in the prostate has increased recently, where the development of immunotherapy is used as a new paradigm.<sup>10</sup>

In this study, the mean age for BPH was 64.7 years and for prostate adenocarcinoma 64.4 years. The data obtained in this study are in accordance with previous studies by Andreas M I (2017), who found that almost 90% of sufferers were aged over 60 years, and two to thirds died over 75 years. The risk of being diagnosed with prostate carcinoma is very closely related to the age factor, where in men aged 70-79 years have almost 7 times higher risk than men aged 50-59 years and the risk of death also increases to 21 times higher.<sup>14</sup> According to WHO the patient's age closely related to the incidence of prostate cancer, and most detected at age > 60 years. Only 1% of prostate cancer is detected when clinical examination aged <50 years.<sup>4</sup>

There are differences in the total PSA level between BPH and prostate adenocarcinoma, where the higher the total PSA level, the possibility of suspicion of the occurrence of a prostate malignancy will be even greater. This is consistent with the research of Prcic et al., Which obtained a Total PSA value statistically having a significant correlation between BPH and prostate cancer, where the Total PSA is very high in prostate cancer, and lower in BPH.<sup>15</sup> Observation of PSA levels is moderate (4- 10 ng / ml), it is still difficult to predict as a possibility of prostate cancer, which often results in about 75% of negative biopsy results. Therefore, besides using Total PSA, it can also be compared by using free PSA measurement. Free PSA was reported to have a more significant proportion of BPH patients than prostate cancer ( $p < 0.00001$ ).<sup>16</sup>

In this study, there were differences in the Total PSA is very high in prostate cancer, and lower in BPH Total PSA is very high in prostate cancer, and lower in BPH. The presence of T cells in BPH is induced by co-inhibitory receptors, co-stimulatory and regulatory T cells which cause epithelial cells and BPH stroma to produce cytokines and proinflammatory chemokines.<sup>11</sup> Whereas in prostate cancer the number of T cells decreases, and T cells that increase are memory T cells. Some findings reveal that the immunomodulatory effect of tumors affects the development of organs. Another thing that is also related is the interaction of T cell phenotypes with tumor cells.<sup>17</sup> Several studies have determined the type of T cell subset that plays a role in BPH and prostate adenocarcinoma, for the continuity of treatment in the future.<sup>18,19</sup>

There is a correlation between the stromal degree of TILs and the total PSA in BPH and adenocarcinoma, where an increase in the total PSA value is followed by a decrease in the degree of stromal TILs. There is no correlation between the degree of stromal TILs and total PSA in BPH ( $p$ -value = 0.225) and

prostate adenocarcinoma ( $p$ -value = 0.355). This is because the distribution of the total PSA value in each sample is not evenly distributed.

There is no significant correlation between the degree of stromal tumor-infiltrating lymphocytes (TILs) with Gleason score in prostate adenocarcinoma. This study is different from that obtained by Nardone et al., where they get TILs correlated with different grades and PSA values. Diagnostic index based on Gleason score can direct the diagnosis of prostate cancer.<sup>20</sup> There was a significant correlation between total PSA and Gleason score in prostate adenocarcinoma ( $p = 0.0001$ ), where an increase in total PSA was followed by an increase in Gleason score. An increased total PSA value can indicate a positive tendency for cancer, high grade, and possibly bone metastasis.<sup>21</sup> About 50% of cancer positive biopsy results have been obtained for a total PSA value of more than 20 ng / mL.<sup>22</sup>

#### V. CONCLUSION

There is a correlation between the degree of stromal TILs and total PSA in BPH and prostate adenocarcinoma

#### COMPETING INTERESTS

The author has no financial interests relevant to the product or company described in this article.

#### ACKNOWLEDGMENT

We would like to thank all staff of the Anatomical Pathology Department University of North Sumatra, H. Adam Malik Central General Hospital, Medan, Indonesia for all their assistance and cooperation.

#### ETHICAL APPROVAL

Health Research Ethical Committee, University of Sumatera Utara, Medan, Indonesia approved this study.

#### REFERENCES

- [1] Mochtar CA, Umbas R, Soebadi DM, Rasyid N, Noegroho BS, Poernomo BB dkk. Panduan Penatalaksanaan Klinis Pembesaran Prostat Jinak. Ikatan Ahli Urologi Indonesia. 2015.
- [2] Umbas R, Hardjowinoto S, Mochtar CA, Safriadi F, Soesanto WD, Soedarso MA, Danarto dkk. Pedoman Nasional Pelayanan Kanker Prostat. Kementerian Kesehatan Republik Indonesia. Ikatan Ahli Urologi Indonesia 2015.
- [3] Merani S, Payne J, Padwal R, Hudson D, Widder S, Khadaroo R. Predictors of in-hospital mortality and complications in very elderly patients undergoing emergency surgery. *World J Emerg Surg.* 2014;9(1): pp 43.
- [4] Humprey PA, Amin MB, Berney DM, Billis A, Cao D, Cheng L, Delahunt B, et al. Acinar Adenocarcinoma. In: Moch H, Humphrey PA, Ulbright TM, Reuter VE (eds). WHO Classification of Tumours of the Urinary System and Male Genital Organs 4th Edition. Lyon: IARC; 2016. p 138-180.
- [5] Huang Y, Li ZZ, Huang YL, Song HJ, Wang YJ. Value of free/total prostate-specific antigen (f/t PSA) ratios for prostate cancer detection in patients with total serum prostate-specific antigen between 4 and 10ng/mL. *Systematic Review and Meta-Analysis. Medicine* (2018) 97:13 pp 249.
- [6] Koo K, Brackett CD, Eisenberg EH, Kieffer KA, Hyams ES. Impact of numeracy on understanding of prostate cancer risk reduction in PSA screening. *PLoS ONE.* 2017. 12(12).

- [7] Sadii MV. PSA screening for prostate cancer. *Rev Assoc Med Bras* 2017; 63(8): p 722-725.
- [8] Heo JE, Koo KC, Hong SJ, Park SU, Chung BH, Lee KS. Prostate-Specific Antigen Kinetics Following 5 $\alpha$ -Reductase Inhibitor Treatment May Be a Useful Indicator for Repeat Prostate Biopsy. *Yonsei Med J.* 2018; 59(2): p 219-225.
- [9] Woo JR, Liss MA, Muldong MT, Palazzi K, Strasners A, Ammirante M et al., Tumor-infiltrating B-cells are increased in prostate cancer tissue. *Journal of Translational Medicine.* 2014 12. p 1-9.
- [10] Karja V, Altomaa S, Lipponen P, Isotalo T, Talja M, Risto Mokka. Tumor-infiltrating Lymphocytes: A Prognostic Factor of PSA-free Survival in Patients with Local Prostate Carcinoma Treated by Radical Prostatectomy. *Anticancer Research.* 2005. p 4435-4438.
- [11] Gooden MJ, De Bock GH, Leffers N, Daemen T, Nijman HW. The prognostic influence of tumor-infiltrating lymphocytes in cancer: a systematic review with meta-analysis *British Journal of Cancer.* 2011. p 93-103.
- [12] Epstein JI. Chapter 21 The Lower Urinary Tract and Male Genital System. In: Kumar V, Abbas AK, Fausto N, Aster JC. *Robbin and Cotran Pathologic Basis of Disease.* China: Saunders Elsevier; 2010. p 993-1001.
- [13] Salgado R, Denkert C, Demaria S, Sirtane N, Klauschen F. The evaluation of tumor-infiltrating lymphocytes (TILs) in breast cancer: recommendations by an International TILs Working Group 2014. *Ann Oncol.* 2015; 26(2) : p 259-271.
- [14] Andreas MI, Alvarino, Hilbertina N. Gambaran Karsinoma Prostat di RSUP Dr. M. Djamil Padang tahun 2010-2013. *Jurnal Kesehatan Andalas.* 2017; 6(2).
- [15] Prcic A, Begic E, and Hiros M. Usefulness of Total PSA Value in Prostate Diseases Diagnosis. *Acta Inform Med.* 2016 jun; 24(3): p 156-161
- [16] Diagnostic BPH : Ultrasound versus Multiparametric MRI. Sperlmg Prostate Cancer. Available at: <https://sperlingprostatecenter.com/diagnosing-bph-ultrasound-vs-multiparametric-mri.2015>.
- [17] Radestad E, Egevad L, Jorns C, Mattsson J, Sunberg B, Nava S et al., Characterization of infiltrating lymphocytes in human benign and malignant prostate tissue. *Oncotarget,* 2017, pp: 60257-60269
- [18] Yao W, He JC, Yang Y, Wang JM, Qian YW, Yang T, Ji L. The Prognostic Value of Tumor-infiltrating Lymphocytes in Hepatocellular Carcinoma: a Systematic Review and Metaanalysis. *Scientific report.* 2017.
- [19] Strasner A and Karin M. Immune infiltration and prostate cancer. *Front. Oncol.* 2015, 5:128.
- [20] Nardone V, Botta C, Carglia M, Martino EC, Ambrosia MR, Carfagno T. Tumor-infiltrating T lymphocytes expressing FoxP3, CCR7 or PD-1 predict the outcome of prostate cancer patients subjected to salvage radiotherapy after biochemical relapse. *Cancer Biology & Therapy.* 2016. p 1213–1220.
- [21] Lojanapiwat B, Anutrakulchai W, Chongruksut W, Udomphot W. 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. p 133-139.
- [22] Total PSA. Architect, AxSYM, Chemiflex and Master Check are trademarks of Abbott Laboratories in various jurisdictions. 2012.

#### AUTHORS

**First Author** – dr. M.Taufik Siregar, Resident of Department of Anatomical Pathology, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia, **email ID:** [tdrsiregar@gmail.com](mailto:tdrsiregar@gmail.com)

**Second Author** – DR. dr. Delyuzar, M.Ked(PA), Sp.PA(K), Department of Anatomical Pathology, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia.

**Third Author** – DR. dr. Lidya Imelda Laksmi, M.Ked(PA), Sp.PA, Department of Anatomical Pathology, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia.

**Correspondence Author** – dr. M.Taufik Siregar, Resident of Department of Anatomical Pathology, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia, **email ID:** [tdrsiregar@gmail.com](mailto:tdrsiregar@gmail.com)