CORRELATION DEGREES OF TUMOR INFILTRATING LYMPHOCYTES (TILs) WITH GLEASON SCORE IN PROSTATE ADENOCARCINOMA

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ABSTRACT

Introduction: One of the abnormalities in the prostate gland is prostate adenocarcinoma. Prostate adenocarcinoma expresses tumor antigen in the form of Prostate Specific Antigen (PSA) which will then be recognized by the immune system. The immune system then responds by infiltrating the tumor tissue. Tumor Infiltrating Lymphocytes (TILs) are defined as the infiltration of lymphocytes into the tumor microenvironment. T lymphocytes have a role in recognizing and killing tumor cells. The Gleason grading system together with serum PSA assessment and clinical staging are key in determining appropriate therapy and prognosis in prostate adenocarcinoma. The Gleason grading system is used to assess the degrees of glandular differentiation in prostate adenocarcinoma. An increase in the gleason score indicates poor gland differentiation.
Purpose: To assess the correlation between the degrees of Tumor Infiltrating Lymphocytes (TILs) with gleason score in prostate adenocarcinoma.
Method: This retrospective study used a correlation analytic method with a cross sectional study design that measured the degrees of Tumor Infiltrating Lymphocytes (TILs) in each gleason score of prostateadenocarcinoma that was observed once at a time. The research samples obtained from the patient's medical records included the gleason score and histopathological slides of the Transurethral Resection of Prostate (TURP) with hematoxylin eosin (HE) staining which were diagnosed as prostate adenocarcinoma according to the inclusion criteria using the non-probability total sampling method at Dr.RamelanNavy's Central Hospital and analyzed using SPSS version 25 application.
Result: Spearman correlation test to assess the correlation between the degree of stromal TILs with gleason score obtained p-value = 0.345 (p >0.05) which indicates there is nocorrelation.
Conclusion: There is nocorrelation between high grade stromal TILs and high Gleason Score in prostate adenocarcinoma.

Keyword: Prostate Adenocarcinoma, Tumor Infiltrating Lymphocytes, Gleason Score

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INTRODUCTION

The prostate gland is a male genital organ that functions to produce a fluid that will be expelled with semen during ejaculation. With age, some elderly men experience problems with the prostate gland and one of them is prostate adenocarcinoma. (Drake, Vogl and Mitchell, 2015; Purnomo, 2016)

Adenocarcinoma of the prostate is a cancer or malignant tumor that develops in the prostate gland in men with an incidence of more than 1.4 million new cases diagnosed in 2020 worldwide and is 7.3% of all cancer cases. (World Health Organization, 2020) Based on data from Globocan2020, prostate adenocarcinoma cases in Asia are in the second highest rank among five other continents. (World Heath Organization, 2020)

The Gleason grading system together with serum Prostate Specific Antigen (PSA) assessment and clinical staging are key in determining appropriate therapy and prognosis in prostate adenocarcinoma. The Gleason grading system is used to assess the degree of glandular differentiation in prostate adenocarcinoma. Increased gleason score indicates poor gland differentiation. (Kumar, Vinay; Abbas, Abul; Aster, 2013; Chen and Zhou, 2016; Purnomo, 2016) The association between the degree of Tumor Infiltrating Lymphocytes (TILs) and the gleason score is suspected in prostate adenocarcinoma.

Prostate adenocarcinoma expresses tumor antigen in the form of PSA which is then recognized by the immune system. (Duarsa, 2020) The immune system then responds by infiltrating the tumor tissue. Lymphocyte infiltration in the tumor microenvironment, Tumor Infiltrating Lymphocytes (TILs), is mostly mediated by T cells. T lymphocytes have a role in recognizing and killing tumor cells. (Blankensteinet al., 2012) The purpose of this study was to determine the correlation between the degree of Tumor Infiltrating Lymphocytes (TILs) and the gleason score in prostate adenocarcinoma.

METHOD

This retrospective study used a correlation analytic method with a cross sectional study design that measured the degree of Tumor Infiltrating Lymphocytes (TILs) in each gleason score of prostate adenocarcinoma at the Dr.Ramelan Navy's Central Hospital from July to September 2021. The sample in this study were 24 patient medical records from January 2017 to September 2021 including gleason scores and histopathological slides of Transurethral Resection of Prostate (TURP) preparations with hematoxylin eosin (HE) staining which were diagnosed as prostate adenocarcinoma according to the inclusion criteria by the non-probability total sampling method and analyzed using the Spearson correlation test.

RESULTS

Table5.1 - Distribution of samples based on age, stromal degree of TILs, Gleason's Pattern and Gleason Grade.

Characteristics	Prostate Adenocarcinoma	
	Amount (n)	Percentage (%)
Age (years)		
<50	2	8,33
50-59	5	20,83
60-69	4	16,67
70-79	10	41,67
>80	3	12,5
Degrees of TILs(Yang et al., 2021)		
Low (<25%)	9	37,5
High (≥25%)	15	62,5
Gleason's Primary Pattern		
Gleason Score 1		
Gleason Score 2		
Gleason Score 3	2	8,33
Gleason Score 4	12	50
Gleason Score 5	10	41,67
Gleason's Secondary Pattern		
Gleason Score 1		
Gleason Score 2	1	4,17
Gleason Score 3	12	50
Gleason Score 4	11	45,83
Gleason Score 5		
Combined Gleason Score (Purnomo, 2016; Duarsa, 2020)		
Gleason Score 6	1	4,17
Gleason Score 7	1	4,17
Gleason Score 8	2	8,33
Gleason Score 9	19	79,16
Gleason Score 10	1	4,17
Total	24	100%

The highest grade group of stromal TILs in prostate adenocarcinoma was high grade (≥25%) in 15 cases (62.5%) and the lowest was low grade (<25%) in 9 cases (37.5%). The group with the highest combined gleason score on prostate adenocarcinoma was gleason score 9 of 19 cases (79.16%) and the smallest group was gleason score of 6, 7, and 10 of 1 case (4.17%).

Table 5.2 - Sample characteristics based on degrees ofstromalTILs.

Characteristics		Degrees ofstromal TILs onGleason's Primary Pattern(%)	Degrees ofstromal TILs onGleason's Secondary Pattern(%)
Gleason Score	3	6,7	10
	4	20,35	34,37
	5	49,42	36,33
p-value*		0,007	0,537

* Kruskal-Wallis H Comparative Test

Table 5.3 - Sample characteristics based on degrees ofstromalTILs.

Variable		Degrees of TILs (%)
Combined Gleason Score	6	10
	7	7,7
	8	34
	9	33,96
	10	56
p-value*		0,335

* Kruskal-Wallis H Comparative Test

After the Kruskal-Wallis H Comparative Test was carried out to assess the difference in the degree of stromal TILs in the gleason's primary pattern between the gleason scores, it was obtainedp-value = 0,007 ($p < 0,05$)which shows that there is a significant difference. While the Kruskal-Wallis H Comparative Test to assess the difference in the degree of stromal TILs on the gleason's secondary pattern between gleason scores(p-value = 0,537)and the degree of stromal TILs between the combined gleason scores (p-value = 0,335) showed that there was no significant difference.

Table 5.4 - Correlation between the degree of stromal TILs and the Gleason Score.

Variable	Correlation coefficient(ρ)	p-value*
Degrees ofstromal TILs onGleason's Primary Pattern	0,537	0,007
Degrees of stromal TILs onGleason's Secondary Pattern	0,173	0,418
Degrees ofstromal TILs on CombinedGleason Score	0,201	0,345

* Spearman Correlation Test

The results of the analysis of the correlation between the degree of stromal TILs in the gleason's primary pattern and the gleason score of prostate adenocarcinoma were obtained p-value = 0,007 (p < 0,05)which shows a significant correlation. The correlation between the degree of stromal TILs in the gleason's secondary pattern and the gleason score of prostate adenocarcinoma was obtainedp-value = 0,418 (p > 0,05) which shows that there is no significant correlation. Meanwhile, the correlation between the degree of stromal TILs and the combined gleason score of prostate adenocarcinoma was obtainedp-value = 0,345 (p < 0,05) which shows that there is no significant correlation.

DISCUSSION

In this study the mean age for prostate adenocarcinoma was 67.58 years. The incidence of prostate cancer increases with age. The results obtained from this study are in accordance with the research conducted by Prashanth Rawla, where the most prostate cancer patients were detected at the age of > 50 years. Based on data from Globocan 2018, almost 60% of men in the world experience prostate cancer at the age of > 65 years. (Rawla, 2019)

Prostate adenocarcinoma has a differentiation scoring system that has been shown to be associated with prognosis, known as the gleason score. (Epstein et al., 2005) This study has similar results with research conducted by M Taufik Siregar to see the correlation between the degree of stromal TILs and the combined gleason score and the results obtained that there is no significant correlation (p-value = 0,083).

This could be due to several factors, including the unbalanced distribution of the number of samples for each gleason score. Most of the samples are cases with gleason score 9 (79,16%). Another factor is that prostate cells that undergo neoplastic changes to become malignant in prostate adenocarcinoma have the ability to inhibit MHC class 1 expression so as to suppress the immune response, including lymphocyte infiltration. (Mao et al., 2019) Tumor antigens together with MHC class 1 form a complex that activates CD8+ T lymphocytes. Activated CD8+ T lymphocytes are also known as T-cytotoxic (Tc) lymphocytes, which act as effectors to lyse tumor cells. (Siregar, Delyuzar and Laksmi, 2019; Diana and Kusmardi, 2020) So that the decrease in MHC class 1 expression causes a decrease in the activation of effector T cells that infiltrate tumor tissue.

Prostate adenocarcinoma cells are also able to increase the expression of immune system inhibitory molecules such as PD-L1. (Sharma et al., 2019) PD-1 has two ligands, namely PD-L1 and PD-L2. PD-1 binds to PD-L1 inhibiting T cell activation and converting effector T cells into regulatory T cells to keep the immune system from destroying normal cells excessively in response to tumor antigens. (Venkatachalam et al., 2021) Therefore, increased expression of PD-L1 results in excess regulatory T cells resulting in suppression of the immune system.

CONCLUSIONS

The study was conducted on 24 prostate adenocarcinoma patients at Dr. Ramelan Navy's Central Hospital on January 2017 – September 2021 can be concluded as follows: There is a significant relationship between the degree of stromal Tumor Infiltrating Lymphocytes (TILs) in gleason's primary pattern and

gleason grade adenocarcinoma of the prostate. There was no significant relationship between the degree of stromal Tumor Infiltrating Lymphocytes (TILs) in the gleason's secondary pattern and gleason grade adenocarcinoma of the prostate. There was no significant relationship between the degree of stromal Tumor Infiltrating Lymphocytes (TILs) and the gleason score of prostate adenocarcinoma

REFERENCES

1. Blankenstein, T. et al. (2012) 'The determinants of tumour immunogenicity', Nature Reviews Cancer. Nat Rev Cancer, pp. 307–313. doi: 10.1038/nrc3246.
2. Chen, N. and Zhou, Q. (2016) 'The evolving Gleason grading system', Chinese Journal of Cancer Research, 28(1), p. 58. doi: 10.3978/J.ISSN.1000-9604.2016.02.04.
3. Diana, D. and Kusmardi (2020) 'Tumor-infiltrating lymphocytes dan Peranannya pada Karsinoma Payudara', Maj Patol Indones, 29(1), pp. 30–40.
4. Drake, R. L., Vogl, A. W. and Mitchell, A. W. M. (2015) Gray Dasar-Dasar Anatomi. Elsevier.
5. Duarsa, G. W. K. (2020) Luts, Prostatitis, BPH Dan Kanker Prostat. Airlangga University Press.
6. Epstein, J. I. et al. (2005) 'The 2005 International Society of Urological Pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma', American Journal of Surgical Pathology, 29(9), pp. 1228–1242. doi: 10.1097/01.PAS.0000173646.99337.B1.
7. Kumar, Vinay; Abbas, Abul; Aster, J. (2013) Buku Ajar Patologi Robbins. 9th edn. Elsevier.
8. Mao, W. et al. (2019) 'Immunogenicity of prostate cancer is augmented by BET bromodomain inhibition', Journal for ImmunoTherapy of Cancer, 7(1), pp. 1–14. doi: 10.1186/s40425-019-0758-y.
9. Purnomo, B. B. (2016) Dasar-dasar Urologi. 3rd edn. CV Sagung Seto.
10. Rawla, P. (2019) 'Epidemiology of Prostate Cancer', World Journal of Oncology, 10(2), p. 63. doi: 10.14740/WJON1191.
11. Sharma, M. et al. (2019) 'Immunohistochemistry of immune checkpoint markers PD-1 and PD-L1 in prostate cancer', Medicine, 98(38). doi: 10.1097/MD.0000000000017257.
12. Siregar, M. T., Delyuzar and Laksmi, L. I. (2019) 'Correlation of Stromal Tumor-Infiltrating Lymphocytes (TILs) Degrees with Total Prostate Specific Antigen (PSA) in Benign Prostate Hyperplasia and Prostate Adenocarcinoma', International Journal of Scientific and Research Publications (IJSRP), 9(12), p. p9658. doi: 10.29322/ijsrp.9.12.2019.p9658.
13. Venkatachalam, S. et al. (2021) 'Immune Checkpoint Inhibitors in Prostate Cancer', Cancers, 13(9). doi: 10.3390/CANCERS13092187.
14. World Health Organization (2020) Global Cancer Profile 2020. Available at: https://www.who.int/cancer/country-profiles/Global_Cancer_Profile_2020.pdf?ua=1 (Accessed: 16 April 2021).
15. World Heath Organization (2020) Indonesia Source: Globocan 2020. Available at: https://gco.iarc.fr/today/ (Accessed: 16 April 2021). Yang, Y. et al. (2021) 'High intratumoral CD8+ T-cell infiltration is associated with improved survival in prostate cancer patients undergoing radical prostatectomy', Prostate, 81(1), pp. 20–28. doi: 10.1002/pros.24068.