

## THE RELATIONSHIP OF THE NEUTROFIL LYMPHOCYTE RATIO (RNL) WITH THE GLEASON SCORE OF PROSTATE CANCER PATIENTS

Fatimah Andriyani<sup>1</sup>, Puspita Sari<sup>2</sup>, Rossa Dwi Wahyuni<sup>3</sup>, Yuli Fitriana<sup>4</sup>, Arlin Rinni Tutu<sup>5</sup>, Aristo<sup>6</sup>

<sup>1</sup>Fakultas Kedokteran Universitas Tadulako

<sup>2</sup>Departemen Patologi Anatomi, Fakultas Kedokteran Universitas Tadulako

<sup>3</sup>Departemen Patologi Klinik, Fakultas Kedokteran, Universitas Tadulako <sup>4</sup>RSUD Undata

<sup>5</sup>Departemen Histologi, Fakultas Kedokteran Universitas Tadulako

<sup>5</sup>Departemen Patologi Anatomi <sup>4</sup>RSUD Undata

<sup>6</sup>Departemen Ilmu Bedah Fakultas kedokteran, Universitas Tadulako

<sup>4</sup>RSUD Undata

e-mail: [fatimahandriyani17@gmail.com](mailto:fatimahandriyani17@gmail.com)

### ABSTRACT

One of the diseases of the prostate gland is prostate cancer. This cancer causes abnormal growth of prostate cells. Trigger factors for the emergence of this cancer are age, genetics, obesity, and a diet high in fat and animal fibre. The neutrophil-lymphocyte ratio (RNL) is recommended as a biomarker for inflammatory diseases and in several cancers, including prostate cancer. The higher of the RNL value indicates that the cancer prognosis is getting worse. This study aims to determine the relationship between RNL and Gleason score in prostate cancer patients at Undata Hospital Palu, 2019-2022. In this study, the researcher used an analytic observational research design with a cross-sectional design. Samples were taken using total sampling, with 33 samples from 2019 to 2022. Samples were taken using complete sampling, with 33 samples from 2019 to 2022. Based on the Spearman correlation test, the total significance was obtained between RNL and Gleason score ( $r=-0.105$   $P=0.562$ ). No significant relationship exists between RNL and Gleason score in prostate cancer patients.

**Keywords:** Neutrophil to lymphocyte ratio., prostate cancer., Gleason score.

### INTRODUCTION

Prostate cancer is one of the prostate diseases. This cancer affects abnormal growth of the prostate gland, which sometimes remains asymptomatic but can be painful and induce urinary retention. The older the male, the higher the risk of suffering from prostate cancer. Prostate cancer can be promoted by factors such as genetics, obesity, high fat and protein diet, and mutation. This disease is rare in men under 50 years old.<sup>1</sup>WHO in the Global Cancer Observatory (Globacan) recorded 1,276,106 new cases of global prostate cancer in 2018. The prevalence of prostate cancer is higher in developed countries. Data from the Ministry of Health of Indonesia documented that the prevalence of prostate cancer in 2013 was 25,012, or 0.2%.<sup>2</sup> Meanwhile, data by Global Burden of Disease in 2012 showed that prostate cancer is the 3rd rank with the highest incidence in males with lung cancer and colorectal cancer co-morbidities.<sup>3</sup> Prostate cancer is predicted to rise by fourfold globally in men aged 65 years or older between 2000 and 2050.<sup>4</sup> Systemic inflammation response is associated with prostate cancer growth. Inflammation is an important determinant. Oxidative compounds are released by inflammation cells, which defect cells and genes and ultimately lead to cell mutation and prostate cancer. The neutrophil-to-lymphocyte ratio is a prominent biomarker for inflammation and several cancers,

including prostate cancer. Studies showed that increased NLR can be prognostic for patients with prostate cancer.<sup>5</sup> Increased neutrophil level indicates inflammations. Proinflammatory cytokines recruit neutrophils to peripheral tissue to make phagocytes and apoptosis. Lymphocytes increase cell cytotoxic activities and cytokine production to prevent tumour proliferation and migration. Low lymphocyte levels indicate that the body is resistant to immune response and promote a worse prognosis. Thus, the neutrophil-lymphocyte ratio can suggest a balance between protumor inflammatory and antitumor immune responses. NLR indicates an inflammatory response produced by dividing neutrophils to lymphocyte levels.

### METHOD

This observational study used a cross-sectional study design. Secondary data were the patient's medical record of prostate cancer at the General Hospital of Undata Palu in 2019-2022. Samples were all 33 patients retrieved through a total sampling technique. Data were then analyzed using the rank-spearman test.

## RESULTS

**Table 1** Characteristics of Study Population

Age		Frequency	Percentage
Early adolescence	12-16 years	0	0
Late adolescence	17-25 years	0	0
Young adulthood	26-35 years	0	0
Late adulthood	36-45 years	1	3
Young elderly	46-55 years	4	12
Late elderly	56-65 years	9	27
Seniors	> 65 years	19	58
Total		33	100
Gleason score		Frequency (n)	Percentage(%)
Well differentiation	≤ 6	0	0
Moderate differentiation	7	7	21
Poorly differentiation	8-10	26	79

As shown in Table 1, the characteristics of respondents consist of age and Gleason score of prostate cancer patients. Based on age, one patient (3%) was aged 36-45 years old, four patients (12%) were aged 46-55 years old, nine patients (27%) were aged 56-65 years, and the majority, 19 patients

(58%) aged > 65 years old. Regarding the Gleason score, seven patients (21%) had moderate differentiation scores, and the remaining 26 (79%) had poorly differentiation scores. No patient had a good differentiation score.

**Table 2** Distribution of Complete Hematological Test

Neutrophil	Frequency (n)	Percentage (%)
Low (<50%)	4	12
Normal (50-70%)	21	64
High (>70%)	8	24
<b>Total</b>	<b>33</b>	<b>100</b>
Lymphocytes	Frequency (n)	Percentage(%)
Low (<20%)	11	33
Normal (20-40%)	21	64
High (>40%)	1	3
<b>Total</b>	<b>33</b>	<b>100</b>
Neutrophil to Lymphocyte Ratio	Frequency (n)	Percentage (%)
Low (<0,78)	0	0
Normal (0,78 -3,53)	22	67
High (>3,53)	11	33
<b>Total</b>	<b>33</b>	<b>100</b>

As per data on neutrophil level distribution, four patients (12%) had low neutrophil levels (<50%), 21 patients (64%) had normal neutrophils (20-70%), and eight patients (24%) had high neutrophil level (>70%). Meanwhile, the distribution of lymphocyte levels shows that 11 patients (33%) had low lymphocyte levels (<20%), 21

patients (64%) had normal lymphocytes (20-40%), and one patient (3%) had high lymphocyte level (>40%). Furthermore, the distribution of NLR shows 22 patients (67%) with a moderate NLR (0.78-3.53), and the other 11 patients (33%) had a high NLR (>3.53).

**Table 3** Rank Spearman Correlation of NLR and Clinical Stage of Patients with Prostate Cancer at Undata General Hospital of Palu in 2019-2022

			NLR
Spearman's rho	Gleason Score	Correlation Coefficient	-0,105
		Sig. (2-tailed)	0,562
		N	33

Based on the Spearman correlation result, the p-value was 0.562, indicating no significant correlation between NLR and Gleason score in prostate cancer patients.

### DISCUSSION

In this study, the dependent variable was the neutrophil-to-lymphocyte ratio, and the independent variable was the Gleason score. The majority of our samples are seniors (>65 years old). Our study is in line with a study by (Ikbal et al., 2023) showing that prostate cancer is more prevalent in seniors (> 60 years old). Ageing affects the progression of prostate cancer, and approximately 86% of prostate cancer cases were diagnosed by the age of 60 years.<sup>6</sup> Age is a significant risk factor for prostate cancer progression. This type of cancer is manifested from the accumulation of genetic and epigenetic changes leading to the transformation of normal epithelium cells into adenocarcinoma. Testosterone levels decrease due to ageing, while estrogen levels tend to elevate. Estrogen hormone regulates the proliferation of prostate cells by increasing the sensitivity of the cells to androgen stimulation, elevating androgen receptors, and suppressing apoptosis.

The Gleason scoring system analyses tumour cell differentiation in prostate cancer to promote a strong prognosis. The Gleason score is divided into five categories per the scoring system 2014, namely 1, 2, 3, 4, and 5. Tumours with well differentiation scores 2-6 indicate a better prognosis. A score of 7 indicates moderate differentiation, while a score of 8-10 indicates poorly cell differentiation with higher mortality. In this present study, the Gleason score of severe prostate cancer patients was 8-10 (poorly differentiated).<sup>7</sup> Neutrophil is immune against infection. It facilitates migration, phagocyte, and autolysis. Neutrophil enters tissue by migrating as a response to chemotactic factors, while lymphocyte is an integral part of the immune response. Lymphoid cells will differentiate and proliferate into B and T cells. Leukocyte deficit is known as leukopenia, which can be due to virus infection, prolonged stress, radiation, and chemotherapy.<sup>8</sup> The neutrophil to lymphocyte ratio is the number of neutrophils divided by lymphocyte level. Elevating neutrophil levels indicate inflammation inside the body. Proinflammatory cytokines recruit neutrophils entering peripheral tissue to make phagocytosis and apoptosis. Lymphocytes promote cytotoxic cell activities and produce cytokines, preventing tumour cell

proliferation and migration. A low lymphocyte level indicates a body that is not sensitive to immune responses and has a poor prognosis; thus, the neutrophil to lymphocyte ratio can determine the balance between protumor inflammatory and antitumor immune responses. NLR is a biomarker for inflammation, such as cancer, sepsis, pneumonia, etc. Our study, somehow, does not show any association between NLR and Gleason score in patients with prostate cancer at Undata General Hospital of Palu in 2012-2022 (p-value = 0.562). Even though it is not statistically significant, NLR and Gleason score affect theoretically and clinically and thus require further investigation. The negative r value (-0.105) showed a non-linear correlation. This finding aligns with a study by Kurnia, which found no association between NLR and the clinical stage of nasopharynx carcinoma. These results can be due to a small sample size and thus cannot be generalized.<sup>9</sup>

Furthermore, our study is also in line with a survey by Aulia that found no significant association between NLR pre-therapy and life expectancy of nasopharyngeal carcinoma patients (p = 0.495). Several factors contribute to this finding, including differences in the medication process of patients that can affect prognosis, such as different methods and duration of medication. These differences can be due to co-morbidities of nasopharyngeal carcinoma patients. Co-morbidity results in the disability of patients to receive ideal therapy and thus lead to poor prognosis.<sup>10</sup> Another study by Chua also shows no significant association. Presumably, another factor that contributes to the leukocyte level (neutrophil, lymphocyte, and monocyte) is the history of smoking. Smoking can increase systemic inflammation. Although the mechanism remains unknown, smoking elevates leukocyte levels in the peripheral system. A study made in Turkey showed the level of neutrophil increased in heavy smoker patients.<sup>11</sup>

On the other hand, our finding is contrary. A study by Widhyasih showed a significant correlation between Carcinoembryonic antigen (CEA) and Neutrophil to Leukocyte Ratio (NLR). Elevated neutrophil level is a biomarker for severe body inflammation, which is not specific, while high lymphocyte level is a biomarker for insensitive response of the immune system against pathogens. Elevated neutrophil level induces tumour progression and metastasis by re-arranging extracellular

matrix, suppressing lymphocyte and releasing reactive oxygen species (ROS).<sup>12</sup> Furthermore, a study by Rulando also found different results from our findings. This study assigned 121 samples and found a significantly positive correlation between NLR and the Gleason score of prostate adenocarcinoma biopsy patients ( $r = 0,572$ ;  $p = 0,001$ ). This study showed that high NLR was linear with a higher Gleason score. This finding supports the theory that immune response is important in patients with high Gleason scores, which indicates a higher risk of systemic metastasis. High NLR shows elevated neutrophil and decreased lymphocyte. Neutrophil responds to tumour cells' interleukin 8 (IL-8) secretion by removing enzymes that can affect the extracellular matrix. This study is not in line with our research because of the small sample size that we only included data from one institution.<sup>13</sup>

#### CONCLUSION AND RECOMMENDATION

No significant relationship exists between RNL and Gleason Score in prostate cancer patients. Further research will likely use a more significant number of samples so that the results obtained can strengthen the possibility of a correlation between RNL and Gleason score.

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