

Neutrophil-lymphocyte Ration Difference in Squamous Cell Carcinoma and Adenocarcinoma of Cervical Cancer

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Abstract

Introduction: Cervical cancer is the most commonly found malignancy in female reproductive system. There are two most found types of this cancer based on histopathologic finding, adenocarcinoma and squamous cell carcinoma (SCC). Each type has different outcome, especially in later stages. Neutrophil-lymphocyte ratio (NLR) is an indicator that can pinpoint the inflammation severity level, hence able to predict outcome and prognosis in malignancy, including cervical cancer.

Objective: This study aimed to determine the difference of NLR in both types of cervical cancer

Methods: This study used retrospective analytic observational with cross-sectional design. Data was sampled from Prof. dr. Margono Soekarjo General Regional Hospital medical record from patients diagnosed with cervical cancer of both types during January to December 2022. Mann-Whitney test was performed to determine the difference of NLR value between both types of cervical cancer.

Result: Between January and December 2022, 68 patients were diagnosed with cervical cancer. Of these, 37 (54.41%) had squamous cell carcinoma (SCC) and 31 (45.59%) had adenocarcinoma. The neutrophil-to-lymphocyte ratio (NLR) ranged from 1.55 to 25.99 in SCC patients, with a mean value of [insert mean value here]. For adenocarcinoma patients, the NLR ranged from 1.32 to 11.99.

Conclusion: Neutrophil-lymphocyte ratio can't differentiate squamous cell carcinoma and adenocarcinoma of cervical cancer.

Keywords : Adenocarcinoma, Cervical Cancer, Neutrophil-Lymphocyte Ratio,

Perbedaan Rasio Neutrofil Limfosit pada Kanker Serviks Tipe Karsinoma Sel Skuamosa dan Tipe Adenokarsinoma

Abstrak

Pendahuluan: Kanker serviks merupakan keganasan yang paling banyak ditemukan pada sistem reproduksi wanita. Berdasarkan temuan histopatologi, terdapat dua jenis kanker serviks yang paling banyak ditemukan, yaitu adenokarsinoma dan karsinoma sel skuamosa (SCC). Setiap jenis memiliki hasil yang berbeda, terutama pada tahap selanjutnya. Rasio neutrofil-limfosit (NLR) merupakan salah satu indikator yang dapat digunakan untuk mengetahui tingkat keparahan inflamasi sehingga dapat memprediksi outcome dan prognosis pada suatu keganasan, termasuk kanker serviks.

Tujuan: Penelitian ini bertujuan untuk mengetahui perbedaan NLR pada kedua jenis kanker serviks

Metode: Penelitian ini menggunakan metode observasional analitik retrospektif dengan desain cross-sectional. Data diambil dari rekam medis RSUD Prof. dr. Margono Soekarjo mengenai pasien yang terdiagnosis kanker serviks kedua jenis tersebut selama bulan Januari hingga Desember 2022. Uji Mann-Whitney dilakukan untuk mengetahui perbedaan nilai NLR antara kedua jenis kanker serviks tersebut.

Hasil: Antara Januari dan Desember 2022, terdapat 68 pasien yang terdiagnosis kanker serviks. Dari jumlah tersebut, 37 (54,41%) menderita karsinoma sel skuamosa (SCC) dan 31 (45,59%) menderita adenokarsinoma. Rasio neutrofil terhadap limfosit (NLR) berkisar antara 1,55 hingga 25,99 pada pasien SCC, dengan nilai rata-rata [masukkan nilai rata-rata di sini]. Untuk pasien adenokarsinoma, NLR berkisar antara 1,32 hingga 11,99.

Kesimpulan: Rasio neutrofil-limfosit tidak dapat membedakan karsinoma sel skuamosa dan adenokarsinoma kanker serviks.

Kata kunci: Adenokarsinoma, Kanker Serviks, Rasio Neutrofil-Limfosit,

Introduction

Cervical carcinoma is the most frequently encountered malignant tumor in the female reproductive system. In 2020, it was estimated that 604,237 women were diagnosed with cervical cancer globally, representing 6.5% of all cancers in women.¹ Approximately 200,000 deaths related to cervical cancer were recorded, with 46,000 of them being women aged 15-49 years living in developing countries. According to GLOBOCAN 2020, cervical cancer ranks 6th globally in terms of incidence and 7th as a cause of death.² According to data from Infodatin Kemenkes RI, the incidence of cervical cancer in Indonesia in 2018 was 10.69%, following breast cancer. Therefore, increasing efforts in handling cervical cancer, particularly in the fields of prevention and early detection, are urgently needed by all involved parties.³

There are various types of cervical cancer, but the most common are adenocarcinoma and squamous cell carcinoma (SCC). According to previous research, adenocarcinoma of the cervix has a worse outcome compared to squamous cell carcinoma.^{4,5}

Previous studies have found a prognostic indicator that can be assessed without invasive procedures and before starting treatment, which is the neutrophil-lymphocyte ratio (NLR). The NLR is an indicator that signifies the severity of the inflammatory process and has been widely used in predicting prognosis and outcomes in cases of sepsis, respiratory distress syndrome, fibrotic liver disease, cardiovascular disease, and malignancies.⁶⁻⁹ Previous research has also examined the relationship between cervical cancer outcomes and the NLR, finding that this ratio can predict the prognosis, cancer invasion, and recurrence of cervical cancer.¹⁰⁻¹³ The NLR can also predict treatment response in cervical cancer, including chemotherapy response and the likelihood of progression after completing chemotherapy.¹¹ Therefore,

the researchers aimed to determine the NLR values in adenocarcinoma and squamous cell carcinoma (SCC) types of cervical cancer and compare the differences in the NLR between these two types.

Methods

This study is a retrospective analytical observational study with a cross-sectional design. The research subjects are data from patients aged ≥ 18 years who were initially diagnosed with cervical cancer through anamnesis and physical examination, and subsequently confirmed by histopathological examination at Prof. Dr. Margono Soekarjo Regional General Hospital in Purwokerto during the period of January–December 2022. Patients with incomplete data, comorbidities that could affect the NLR values, those undergoing chemotherapy or chemoradiation cycles, using steroid medications, and patients who have undergone lymphatic tissue removal surgery will be excluded from this study. Data collection was done using purposive sampling techniques. Data processing was conducted by performing normality tests with the Shapiro-Wilk test, followed by Mann-Whitney statistical tests to determine the differences in NLR values between adenocarcinoma and SCC types.

Results

A total of 69 patients were diagnosed with cervical carcinoma based on anatomical pathology. One patient was excluded due to incomplete medical records. Therefore, the total number of cases in this study is 68. There are 37 cases (54.41%) of squamous cell carcinoma and 31 cases (45.59%) of adenocarcinoma. The basic characteristics of the respondents can be seen in Table 1.

Table 1 Baseline Characteristics of Study

Characteristics	Total
Age (Years)	
≥ 50	42 (61,7%)
45 – 49	16 (23,5%)
40 – 44	8 (11,7%)
35 – 39	0
< 35	2 (3,1%)
Mean (SD)	53,3 (9,34)
Stage, FIGO	
I	0
IA	1 (1,4%)
IB	4 (5,9%)
II	0
IIA	14 (20,8%)
IIB	20 (29,4%)
III	0
IIIA	3 (4,4%)
IIIB	19 (27,9%)
IIIC	6 (8,8%)
IV	0
IVA	1 (1,4%)
IVB	0
Cervical carcinoma type	
Adenocarsinoma, n (%)	31 (45,59%)
Squamous cell carcinoma, n (%)	37 (54,41%)
Characteristics	Total
Age (Year)	
Mean (SD)	53,3 (9,34)
Cervical carcinoma type	
Adenocarsinoma, n (%)	31 (45,59%)
Squamous cell carcinoma, n (%)	37 (54,41%)

Data processing was first conducted by performing a normality test using the Shapiro-Wilk test. The p-values for the normality test were 0.003 for the adenocarcinoma type and 0.000 for the squamous cell carcinoma type. With p-values <0.05, the data distribution is considered non-normal. (Table 2).

After conducting the analysis of NLR value differences using the Mann-Whitney

test on the two types of cervical cancer, a p-value of 0.645 was obtained (Table 3). With a p-value > 0.05, it can be concluded that there is no statistically significant difference in NLR values between the two types of cervical cancer.

Table 3 Results of Statistical Test for Differences in Neutrophil-Lymphocyte Ratio Based on Cervical Cancer Type

	Results
Mann-Whitney	518,500
Wilcoxon W	983.500
Z	-0.460
Asym. Sig. (2 tailed)	0.645

Discussion

Cervical cancer begins with an HPV infection. Generally, women can eradicate HPV through their immune system, but in cases of persistent infection, it can develop into preinvasive dysplastic lesions. HPV oncoproteins are crucial in the uncontrolled proliferation of cancer cells.^{4,14}

In its development, inflammation is a key characteristic of the tumor microenvironment and plays a central role in the processes of tumor initiation, promotion, progression, invasion, and metastasis.¹⁵ Neutrophils contribute by providing angiogenic, epithelial, and stromal growth factors, as well as matrix remodeling enzymes that are beneficial to the neoplastic process. In contrast, in situations of lymphopenia, the effectiveness of the host-tumor immune response decreases due to an imbalance

Table 2 Neutrophil-Lymphocyte Ratio Values Based on Cervical Cancer Type

Cervical Carcinoma Type	Neutrophil-Lymphocyte Ratio		
	Minimum	Maximum	Median
Adenocarsinoma	1,32	11,99	3,245
Squamous cell carcinoma	1,55	25,99	3,3

between the innate and adaptive immune systems. Based on the roles of neutrophils and lymphocytes where neutrophils increase with inflammation and lymphocytes generally decrease as inflammation progresses the neutrophil-lymphocyte ratio (NLR) can be used to predict prognosis and the severity progression of patients, including in malignancies. Research in Bali, Indonesia, found a cutoff NLR value of 3.38 with 82% sensitivity and 71% specificity in predicting the degree of invasion in cervical cancer.¹⁰

An increased NLR may indicate a decline in antitumor immune capability and an increase in pro-tumor inflammation. Higher NLR is associated with more advanced disease stages in younger patients. Other findings also report that pretreatment NLR values are associated with survival in patients with other malignancies as well as cervical cancer, particularly those with advanced stages.¹⁶ In this study, 61.2% of cases showed an increased NLR. Zou et al. (2020) noted that a higher NLR value is associated with a lower likelihood of survival in cervical cancer cases. Similarly, Han et al. (2021) reported that a high NLR is linked to poorer prognosis in cervical cancer patients and may serve as a precise biomarker for predicting prognosis in patients with stages I-III cervical cancer.¹⁷

In inflammatory conditions, the release of neutrophil precursors, such as myelocytes and promyelocytes, occurs. An increased number of neutrophils can stimulate the release of nitric oxide (NO), arginase, and reactive oxygen species (ROS) in large quantities, leading to impaired T lymphocyte activation and increased production of Vascular Endothelial Growth Factor (VEGF). This, in turn, causes tumor neovascularization. Thus, measuring neutrophil counts, either independently or as part of the NLR, can predict patient prognosis in various cancers, including cervical cancer.¹⁸

Meanwhile, HPV infection, as a major risk factor in the development of

cervical cancer, can produce two types of oncoproteins (i.e., E6 and E7) that affect the cell cycle and inhibit cell apoptosis. E6 and E7 are closely associated with tumor origin and development. When these oncoproteins are recognized, specific T-cell immunity will inhibit their expression, making T-cell immunity known as an antitumor immune response.¹⁹ Wang et al. (2017) found that lymphocyte counts decrease dramatically in patients with stage IV cervical cancer, indicating a dysfunction in the antitumor immune response in the body. Another study demonstrated a significant imbalance in T-cell regulation, particularly the Th17 subtype, and higher levels of inflammatory cytokines such as TNF- α , IL-2, and IL-6 in the blood of cervical cancer patients.¹⁹ Thus, pretreatment NLR values may help in determining the presence of lymph node metastasis or distant metastasis in cervical cancer.¹⁵

There are various types of cervical cancer based on histology, but the most commonly found are adenocarcinoma and squamous cell carcinoma. For patients with small tumors, <2 cm and without lymphovascular space invasion, the difference in survival rates between adenocarcinoma and squamous cell carcinoma is not significant. For tumors > 4 cm, the rate of distant failure (spread of cancer cells to distant organs) is higher in adenocarcinoma.⁵

Previous studies have found that the NLR is a predictive biomarker that can estimate prognosis, cancer invasion, and recurrence of cervical cancer. In this study, no statistically significant difference was found between the NLR values in adenocarcinoma and squamous cell carcinoma types of cervical cancer, with a p-value of 0.645, although in higher stages, adenocarcinoma tends to have worse outcomes compared to squamous cell carcinoma.⁵ Similar results were found in the study by Fachir et al. (2019), which also reported no significant difference in NLR values between adenocarcinoma and

squamous cell carcinoma types of cervical cancer.

To date, the prognosis of cervical cancer is based on the FIGO cancer staging system, expressed as a 5-year survival rate. Besides staging, there are also differences in prognosis between squamous cell carcinoma and adenocarcinoma. Adenocarcinoma has a lower survival rate compared to squamous cell carcinoma.^{4,5} Additionally, cervical cancer of the adenocarcinoma type at stages IIB-IVA has a worse response to radical radiotherapy and chemotherapy compared to the response in squamous cell carcinoma.²⁰

Conclusion

There is an increase in both types of cervical cancer, whether adenocarcinoma or squamous cell carcinoma (SCC). There is no statistically significant difference in NLR values between adenocarcinoma and squamous cell carcinoma types of cervical cancer.

Conflict of Interest

There was no competing interest to be declared.

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