ORIGINAL RESEARCH REPORT

Differences in monocyte-to-lymphocyte ratio of patients with cervical cancer at dr. Ramelan Central Naval Hospital, Surabaya before and after chemoradiation therapy from January 2020 to July 2023

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Article Info	ABSTRACT
	Background: Cervical cancer is a gynecological malignancy resulting from abnormal and unregulated proliferation of cells, which impairs growth, differentiation, and apoptosis of the cells. Cervical cancer is the second most prevalent disease and is responsible for approximately 10 million deaths in 2020. A number of studies have reported that the monocyte-to-lymphocyte ratio (MLR) may be a useful indicator of the prognosis of patients diagnosed with cervical cancer. **Objective**: This study aims to determine the differences in monocyte-to-lymphocyte ratio of patients with cervical cancer before and after chemoradiation therapy. **Materials and Methods**: This study used an analytical observational design with secondary data from 62 patients at dr. Ramelan Central Naval Hospital, Surabaya between January 2020 and July 2023. The sample was taken using a consecutive sampling technique. The variables included patients with stage IIB cervical cancer stage and higher who underwent chemoradiation therapy as well as the monocyte-to-lymphocyte ratio (MLR) of the patients before and after chemoradiation therapy. **Results**: The results of the Wilcoxon signed-rank test indicated that the therapy had an effect on the MLR of patients with stage IIB cervical cancer and higher, with a p-value of less than 0.001. **Conclusion**: Significant differences were observed in the MLR of patients with cervical cancer before and after chemoradiation therapy.

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Highlights

1. MLR and monocyte levels tended to increase after chemoradiation, while leukocyte levels tended to decrease after chemoradiation.
2. The differences in MLR before and after chemoradiation were found to be statistically significant.

BACKGROUND

Cervical cancer is the fourth most common primary gynecologic cancer among women globally. It is characterized by abnormal and unregulated proliferation of cells due to genetic changes that regulate growth, differentiation and apoptosis of the cells, as well as the invasion of cervical tissue (Dasari et al., 2015). According to the World Health Organization (WHO), approximately 19.2 million cases of cancer were diagnosed globally in 2020, resulting in nearly 10 million deaths. Approximately 90% of new cases and deaths occur in countries with a low-to-middle income level (Zhang et al., 2021). The significant occurrence of cancer in Indonesia is a matter of considerable concern, as evidenced by a rise in prevalence from 1.4 to 1.79 per 1,000 population between 2013 and 2018, as reported by the Basic Health Research. The Global Cancer Observatory (GLOBOCAN) revealed that in 2020, Indonesia had a total of 396,914 incidences of cancer and 234,511 fatalities. Among the cases, cervical cancer accounted for 9.2% of the overall cancer diagnoses, ranking second in prevalence (Aulia and Hartanti, 2023).

Immune status is a fundamental biological indicator and plays a key role in the development and progression of cancer (Zhao et al., 2020). Immune cells initiate an inflammatory response, which stimulates the production of inflammatory substances to enhance the survival and growth of malignant cells (Bashir et al., 2020; Li et al., 2021). The immune cells consist of mononuclear phagocyte system (MPS) with a specialized function as phagocytes. The MPS is comprised of two essential components: monocyte (Mo) and macrophages (MΦ). Both of them play a central role in the MPS, including innate immune function, adaptive immune function, and tissue homeostasis (Richards et al., 2013). Monocytes play a dual role in cancer development. They can exert a beneficial effect by inhibiting the proliferation of cancer cells as well as a detrimental effect by promoting the migration of cancer cells and suppressing the immune response to tumors (Abu-Shawer et al., 2019). This is due to the ability of tumor cells to modify numerous inflammatory substrates, as monocytes are able to suppress lymphocyte activation (Xu et al., 2021).

Lymphocytes and other immune cells are surrounding tumor cells, which exhibit distinct characteristics from those of healthy cells due to the presence of tumor antigens. These tumor antigens result in an immunological stimulus. Lymphocytes act as apoptosis inducers, suppressing the proliferation and migration of tumor cells (Zhao et al., 2020). Lymphocytes play a crucial role in regulating tumor growth, tumor spread, and deterioration of unfavorable prognosis by producing cytokines, such as IFN-γ and TNF-α. The monocyte-to-lymphocyte ratio (MLR) may serve as a prognostic indicator for cancer patients, aiding in survival prediction and prognosis assessment (Huang et al., 2019). A number of studies have investigated the use of MLR to predict the prognosis of hepatoma (Wang et al., 2022), stage IIB cervical cancer (Li et al., 2021), prostate cancer (Xu et al., 2021), and ovarian cancer (Xiang et al., 2017). A recent study highlighted the significance of inflammation associated with cancer in tumor development and progression. MLR and other systemic inflammatory response indicators have been validated as novel inflammatory markers for the diagnosis and prognosis of malignancies, including cervical cancer (Ye et al., 2023).

OBJECTIVE

This study aims to determine the differences in monocyte-to-lymphocyte ratio (MLR) of patients diagnosed with cervical cancer before and after chemoradiation therapy.

MATERIAL AND METHODS

Study design

This study used an analytical observational design and was conducted from January 2020 until July 2023 at dr. Ramelan Central Naval Hospital, Surabaya, Indonesia. The sample was taken from patients diagnosed with stage IIB cervical cancer and higher who underwent chemoradiation therapy between January 2020 and July 2023. The inclusion criteria were inpatients or outpatients with stage IIB cervical cancer and higher who underwent chemoradiation therapy and had comprehensive laboratory test results of basic hematology. This study included all medical records of 64 patients who fulfilled the specified inclusion criteria.

Data collection

This study collected data on patient age and monocyte and lymphocyte levels before and after chemoradiation. The MLR was estimated using both datasets. The results were compiled in Microsoft Excel.

Data analysis

The statistical analysis of the MLR results was conducted using the Statistical Package for the Social Sciences (SPSS) 25, specifically a paired t-test if the data were normally distributed or the Wilcoxon signed-rank test if the data were not normally distributed.

RESULTS

A total of 62 samples of patients with stage IIB cervical cancer and higher who underwent chemoradiation therapy at dr. Ramelan Central Naval Hospital, Surabaya from 2020 to 2023 were included in this study. The samples were selected based on certain inclusion and exclusion criteria from a total of 327 patients with stage IIB cervical cancer and higher.

Table 1. Characteristics of the patients (n = 62)

Characteristic	Frequency	Percentage (%)
Age		
1. 26-45 years	15	24,19%
2. 46-65 years	41	66.13%
3. >65 years	6	9.685

Characteristic	Mean ± SD
Monocyte before chemoradiation	0.5745 ± 0.34440
Monocyte after chemoradiation	0.6603 ± 0.64673
Lymphocyte before chemoradiation	2.2381 ± 0.83680
Lymphocyte after chemoradiation	1.1913 ± 0.79192
MLR before chemoradiation	0.2903 ± 0.17477
MLR after chemoradiation	0.9236 ± 1.04677

Table 1 shows that the majority of patients diagnosed with stage IIB cervical cancer and higher were between the ages of 46 and 65 years. In addition, the table indicates an increase in monocytes and MLR as well as a decrease in lymphocytes following chemoradiation therapy.

Table 2 shows that no significant difference in monocyte levels before and after chemoradiation was observed (p = 0.466). In comparison the table shows a significant difference between lymphocyte levels and MLR before and after chemoradiation with p-levels of less than 0.001 for both.

Table 2. Differences between monocyte, lymphocyte, and MLR levels before and after chemoradiation (n = 62)

Parameter	Phase	Mean	p-Value
Monocyte	Before chemoradiation	26.38	0.466*
	After chemoradiation	36.10	
Lymphocyte	Before chemoradiation	33.73	<0.001*
	After chemoradiation	14.00	
MLR	Before chemoradiation	15,00	<0.001*
	After chemoradiation	17.83	

*Wilcoxon signed-rank test

DISCUSSION

Monocytes are mononuclear cells that represent the innate immune system of the body and regulate the development of cancer, including tumor-associated macrophages (TAM), dendritic cell (DC), and myeloid-derived suppressor cell (MDSC). Monocytes contribute to the development of protumor and antitumor immunity. In addition, monocytes can directly eliminate cancer cells via phagocytosis, which is mediated by proinflammatory cytokines (IFN-g) which stimulate TNF-related apoptotic-inducing ligand (TRAIL) proteins. However, numerous cancer cells can protect themselves from phagocytosis and are resistant to TRAIL proteins, which in turn stimulates the secretion of protumor cytokines (CCL2, IL-8) (Olingy et al., 2019). Therefore, the primary objective of antitumor therapy is to prevent metastasis (Schegoleva et al., 2022).

A number of studies showed that following the administration of chemoradiation therapy, TAM can persist in the tumor, causing tumor recurrence which suppresses T-cell immunity and increases the activation and survival of tumor cells, especially in patients with stage III or IV tumors (Patysheva et al., 2022). This study showed an increase in the average number of monocytes in patients with cervical cancer after chemoradiation therapy. This is associated with an inflammatory response, including cancer cells resistant to the TRAIL proteins, and the presence of TAM, ultimately leading to a poor prognosis. An increase in the number of monocytes is associated with a poor prognosis for patients with cervical cancer (Feng et al., 2018). TAM are recruited mature macrophages in the tumor microenvironment, with the primary function of engulfing and digesting foreign substances, including cellular debris and tumor cells, which is known as clearance (Moeini and Niedźwiedzka-Rystwej, 2021).

On the other hand, lymphocytes represent the immune system of the body that exhibit a robust antitumor immune function, thereby enabling them to inhibit tumor development and progression (Chen et al., 2015; Trinh et al., 2020). Lymphocytes can produce cytotoxic cytokines, which inhibit the proliferation and metastasis of cancer cells (Jain et al., 2016; Tan et al., 2018). A high lymphocyte count is associated with a good prognosis for patients with cervical cancer. A decrease in lymphocytes may be attributed to chemotherapy agents, infection, and a decline in nutrition, thereby affecting the overall condition of the patient (Feng et al., 2018). The specific type of lymphocyte that is isolated from areas of inflammatory infiltration found in and around the tumor is referred to as tumor infiltrating lymphocyte (TIL). The presence of a local lymphocyte response is a sign of the recognition and resistance process of the immune system against cancer cells (Bagheri et al., 2019; Whiteside, 2022). Significant lymphocyte changes occur in patients with stage II cervical cancer and higher (Ao et al., 2023). The results of this study indicated that the mean value of patients with stage IIB cervical cancer and above obtained before chemoradiation was 2.2381, which was higher than the value obtained after chemoradiation therapy (1.1913). Therefore, it can be concluded that a decrease in the number of lymphocytes may contribute to a poorer prognosis of patients with cervical cancer.

MLR is calculated by dividing the absolute monocyte count by the absolute lymphocyte count (Prabawa et al., 2019; Zhu et al., 2018). The results of the MLR calculation are classified into mild, moderate, and severe. The normal range is between 0.15 and 0.3. MLR of 0.3 is considered to be severe. A high MLR is associated with inflammation, thereby increasing the risk of cancer recurrence and negatively affecting the cancer prognosis (Li et al., 2021). In addition, increased MLR is associated with the size and stage of cancer, as well as the treatment of each patient. Therefore, it serves as a predictor of the prognosis or survival of the patient. Treatment for cancer patients can include chemotherapy,

radiotherapy, blood transfusions, and the like. The higher the stage and the bigger the size of the cancer, the more unfavorable the prognosis of the patient (Tan et al., 2018). The results of this study indicated that the mean value for patients with stage IIB cervical cancer and higher obtained before chemoradiation therapy was 0.2903, which was lower than the value obtained after chemoradiation therapy (0.9236). This finding is consistent with those of other studies indicating that the higher the MLR, the more unfavorable the prognosis will be.

Limitations

This study did not consider additional factors other than MLR that may contribute to the effectiveness of chemoradiation therapy for patients with stage IIB cervical cancer and higher. Therefore, further research is necessary.

CONCLUSION

The results of this study revealed no significant change in the number of monocytes in patients with stage IIB and higher after chemoradiation therapy. However, the average data showed an increase in the number of monocytes in patients with stage IIB cervical cancer and above after chemoradiation therapy, which may be attributed to an inflammatory response from the immune system. Furthermore, the results of this study revealed a significant change in the number of lymphocytes in patients with stage IIB cervical cancer and above after chemoradiation therapy, as well as a significant difference in the MLR in patients with stage IIB cervical cancer and above after chemoradiation therapy.

Acknowledgment

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Conflict of Interest

All authors have no conflict of interest.

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None.

Ethical Clearance

This study received ethical approval from the Research Ethics Committee of Dr. Ramelan Central Naval Hospital with a certificate number 101/EC/KEP/2023.

Author Contribution

SYH: sample preparation, data collection and analysis, manuscript writing, and manuscript editing.

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