The Role of Lymphocyte-to-Monocyte Ratio (LMR) as a Prognostic Factor of Life Expectancy of Osteosarcoma Patients at H. Adam Malik Hospital Medan 2012 – 2017

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ABSTRACT

Background: Five-year relative survival rate in cases of osteosarcoma is below 20%. Some scientific evidence suggests that there is a significant association between inflammatory markers and poor prognosis in some tumor types. This study aims to determine the role of the preoperative lymphocyte-to-monocyte ratio (LMR) as a prognostic factor in the life expectancy of osteosarcoma patients at Haji Adam Malik General Hospital (RSUP HAM) Medan.
Methods: This study is a retrospective cohort study conducted from January 2019 to February 2020. Samples were taken consecutively on osteosarcoma patients treated at the HAM Hospital from January 2013 to December 2018, whether or not undergoing postoperative adjuvant chemotherapy, with a minimum of total of 24 samples. LMR is classified categorically with the cuff value obtained from the receiver operating characteristic (ROC) curve. Both variables were statistically analyzed using the Kaplan Meier survival curve.
Results: The total number of subjects in this study was 45 samples. There were 35 male samples (77.8%) and 10 female samples (22.2%) with the mean age of 21.18 ± 12.381 years. The age group at the time of diagnosis was mostly 11-20 years old, with a total of 23 samples (51.1%). Based on the location, the highest number was found in the distal femur of 17 samples (37.8%). The minimum lymphocyte value was 0.66, and the maximum value was 17.20, with a mean of 3.51±4.36. The minimum monocyte value was 0.36, the maximum value was 15.30, with a mean of 8.34 ± 3.72. The minimum LMR value is 0.36, and the maximum is 15.30 with an average of 8.34 ± 3.73. The cut off value obtained is 0.384. The number of patients with high LMR was 11 samples, with 3 alive samples and 8 deceased samples, while at low LMR there were 34 people with 1 alive sample and 33 deceased samples. Based on the Kaplan Meier survival curve, the log rank value was 0.004 with a hazard ratio of 3.143.
Conclusion: High preoperative LMR was significantly associated as a prognostic factor of life expectancy in osteosarcoma patients as a good prognostic value in patients
Keywords: Osteosarcoma, Lymphocyte-monocyte ratio, Prognostic factors

Background

Osteosarcoma is a primary malignant tumor of the skeleton characterized by the direct formation of immature bone or osteoid tissue by the tumor cells. World Health Organization (WHO) histologic classification of bone tumors divides osteosarcomas into central and surface tumors, and recognizes a number of subtypes within each group.(Picci, 2007)

Osteosarcoma is the most common primary malignant bone tumor in childhood and adolescence, with an overall annual incidence of 5.6 cases per million children under 15 years of age. The peak incidence occurs in the second decade of life, and male are more frequently affected than female. 5-year survival rate in cases of osteosarcoma is below 20%. Along with chemotherapy, life expectancy increases and there is a shift in the type of surgical procedure, namely from ablation (amputation / disarticulation) to salvage (limb rescue surgery).(Czerniak, 2016; Picci, 2007)

Several scientific evidence shows that there is a significant relationship between inflammatory markers and poor prognosis in several tumor types, including thrombocytosis, leukocytosis, high neutrophil to lymphocyte ratio or platelet-to-lymphocyte ratio, but no further studies have been conducted on LMR.(Nielsen & Rosenberg, 2017)

Based on this, a study was conducted to determine the role of preoperative LMR as a prognostic factor in life expectancy of osteosarcoma patients at HAM Hospital Medan.

Method

This study is a retrospective cohort study to determine the role of preoperative LMR as a prognostic factor in life expectancy of osteosarcoma patients at HAM Hospital Medan. This study was conducted from January 2019 to February 2020. Samples were taken consecutively from osteosarcoma patients who were treated at HAM Hospital from January 2013 to December 2018, both patients who underwent postoperative adjuvant chemotherapy and those who did not, with a minimum of 24 samples. The inclusion criteria in this study were patients diagnosed with osteosarcoma with the presence or absence of pulmonary metastases, whether or not undergoing adjuvant chemotherapy, while the exclusion criteria were patients with incomplete medical record data and patients who refused to follow-up.

Osteosarcoma is defined as a malignant bone tumor in which malignant tumor cells have the ability to produce osteoid or immature bone.(Picci, 2007) Amputation is the cutting of a body part aimed at controlling disease, wide margin resection with tumor removal until the free of tumor (normal) tissue 2 cm and 3-5 cm in the involved bone.(Durfee et al., 2016) Postoperative chemotherapy (adjuvant) is the administration of a postoperative chemotherapy regimen to reach tumor cells to prevent micro-metastases to other sites(Meazza & Scanagatta, 2016). Pulmonary metastases are conditions where at the time of diagnosis of bone tumor cells has spread to other areas of the body (lungs).(Durfee et al., 2016)

Data on age, sex, tumor location, and type of surgery were presented descriptively. The values of lymphocytes and monocytes were obtained from the patient's laboratory examination report, then calculated to obtain the LMR value. LMR is classified categorically with the cuff off value obtained from the ROC curve. Survival data were obtained through follow-up interviews. Both variables were statistically analyzed using the Kaplan Meier survival curve. The study was conducted after obtaining approval from the Ethics Commission.

Result

The number of subjects in this study were 45 samples. Based on gender, there were 35 males (77.8%) and 10 females (22.2%) with a mean age of 21.18 ± 12.381 years. The age group at the time of diagnosis was mostly 11-20 years old, with a total of 23 samples (51.1%). Based on the location, the highest number was found in the distal femur of 17 samples (37.8%), followed by the proximal tibia with 13 samples (28.9%). The distribution of samples by location of osteosarcoma is presented in Table 1. below.

Table 1. Distribution of Samples by Location of Osteosarcoma

Location	n	%
Distal femur	17	37.8%
Proximal tibia	13	28.9%
Proximal femur	8	17.8%
Proximal humerus	4	8.9%
Proximal fibula	3	6.7%
Total	45	100.0%

The minimum lymphocyte value was 0.66 and the maximum value was 17.20, with a mean of 3.51±4.36. The minimum monocyte value was 0.36, the maximum value was 15.30, with a mean of 8.34 ± 3.72. The minimum monocyte value was 0.36, the maximum value was 15.30, with a mean of 8.34 ± 3.72. The minimum LMR value is 0.36, and the maximum is 15.30 with an average of 8.34 ± 3.73. The cut value obtained is 0.384, with a sensitivity of 75% and specificity of 80.48% with a positive predictive value (PPV) of 27.27% and a negative predictive value (NPV) of 97% and an odds ratio (OR) of 12.37. This is shown in Figure 1. and Table 2. below.

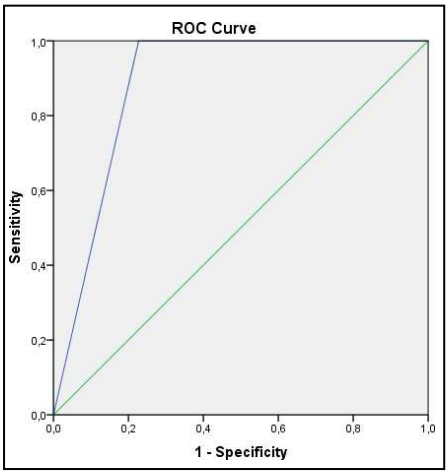

Figure 1. ROC LMR curve

Table 2. Analysis of the LMR ROC Curve

AUC	n	Cut off	Sensitivity	Specificity	95% CI
40,2%	45	0.3840	75%	80.48%	0.094 – 0.711

There were 41 patients who later died (91.1%). At the cut-off value, where the parameters must have good sensitivity and specificity, it was found at 0.3840, so that a high LMR number was obtained in 11 samples, with 3 alive samples and 8 deceased samples, while a low LMR was found in 34 samples with alive 1 sample and 33 deceased samples. Based on the analysis of the data on the Kaplan Meier curve, the log rank value was 0.004 with a hazard ratio of 3.143. This is presented in Table 3. and Figure 2. below.

Table 3. Cross Table of LMR Parameters

LMR Categories	Alive	Dead	Total
High LMR values	3	8	11
Low LMR values	1	33	34
Total	4	41	45
OR		12.37	

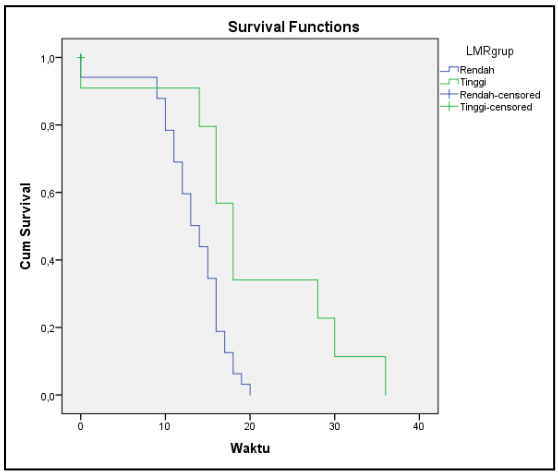

Figure 2. Life Expectancy Chart by LMR Comparison

Discussion

In this study, the average age of the research subjects was 21.18 ± 12.381 years, with the highest proportion aged less than 20 years. This is in accordance with the theory presented by other researchers such as Abbas et al. and also Errol who stated that the age in the second and third decades was the most frequent age in patients with osteosarcoma.(Hutagalung et al., 2005; MASHHADI ABBAS et al., 2009)

Based on the location of the osteosarcoma, in this study it was found that the proximal tibia was the most common location. This study found 34 people with high preoperative LMR values, and 11 people with low preoperative LMR values. Of the 11 people with high preoperative LMR values, 3 people were still alive, and out of 34 people with low LMR, 1 person was still alive. Based on Kaplan Meier curve analysis, it was found that patients with high preoperative LMR had a better life expectancy than patients who had low preoperative LMR, although at 50% the frequency of patients there was not too much difference. In patients with a high preoperative LMR it can reach more than 30 months. Based on the statistical results, it was also found that the logrank number was 0.004 which means that this

examination was statistically significant. Based on the data, the hazard ratio was found to be 3.143, which means that patients with low LMR are statistically 3 times more prone to death than patients with high preoperative LMR.

In similar studies abroad, one of which was in a study conducted by Tao Liu, where the 5-year survival rate in 327 patients with osteosarcoma was significantly higher in patients with high preoperative LMR compared to low LMR.(Liu et al., 2015)

In another study by Soon Teck Seo et al in 2019 it was also found that a low monocyte lymphocyte ratio value gave a worse prognosis than a high monocyte lymphocyte ratio value.(Teck Seo et al., 2019)

Conclusion

In this study, it was found that the age group of 11-20 years was the age group most diagnosed with osteosarcoma, with the most frequent location in the distal femur, and a high preoperative LMR was significantly associated as a prognostic factor for life expectancy of osteosarcoma patients as a good prognostic value in patients with osteosarcoma.

Suggestion

It is advisable to improve education and knowledge of osteosarcoma patients so that early detection can be faster so that treatment can be carried out at an earlier stage. Research can be developed with the assessment of other laboratory parameters, and compared with each choice of therapy and the course of the patient's disease, it is advisable to combine the studies conducted into a multicenter study.

References

Czerniak, B. (2016). Dorfman and *Czerniak's* Bone Tumors. Elsevier. https://books.google.co.id/books?id=vJOjAQAACAAJ

Durfee, R. A., Mohammed, M., & Luu, H. H. (2016). Review of Osteosarcoma and Current Management. Rheumatology and Therapy, 3(2), 221–243. https://doi.org/10.1007/s40744-016-0046-y

Hutagalung, E., Gumay, S., & Budiatmoko, B. (2005). Neoplasma Tulang: Diagnosis dan Terapi. Galaxy Puspa Mega, 26–34.

Liu, T., Fang, X.-C., Ding, Z., Sun, Z.-G., Sun, L.-M., & Wang, Y.-L. (2015). Pre-operative lymphocyte-to-monocyte ratio as a predictor of overall survival in patients suffering from osteosarcoma. FEBS Open Bio, 5(1), 682–687. https://doi.org/10.1016/j.fob.2015.08.002

MASHHADI ABBAS, F., MOSHREF, M., HOUSHMAND, B., SARGOLZAEI, S., BAGHERI, A. A. F., MASHHADI, A., & RAHIMI, H. (2009). FIBROBLASTIC OSTEOSARCOMA IN MANDIBLE: A RARE CASE REPORT AND REVIEW OF LITERATURE. JOURNAL OF DENTAL SCHOOL SHAHID BEHESHTI UNIVERSITY OF MEDICAL SCIENCE, 26(4 (78)), 403–411. https://www.sid.ir/en/Journal/ViewPaper.aspx?ID=154611

Meazza, C., & Scanagatta, P. (2016). Metastatic osteosarcoma: a challenging multidisciplinary treatment. Expert Review of Anticancer Therapy, 16(5), 543–556. https://doi.org/10.1586/14737140.2016.1168697

Nielsen, G. P., & Rosenberg, A. E. (2017). Diagnostic Pathology: Bone. Elsevier Health Sciences. https://books.google.co.id/books?id=3ngEDgAAQBAJ

Picci, P. (2007). Osteosarcoma (Osteogenic sarcoma). Orphanet Journal of Rare Diseases, 2(1), 6. https://doi.org/10.1186/1750-1172-2-6

Teck Seo, S., Singh, V. A., & Yasin, N. F. (2019). Preoperative lymphocyte count in relation to sarcoma prognosis. Journal of Orthopaedic Surgery, 27(2), 230949901985495. https://doi.org/10.1177/2309499019854957