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Research Article

Association between Serum Alp Levels and Pre- Operative LDH towards Clinical Prognosis of Osteosarcoma Patients in H. Adam Malik Hospital, Medan

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Abstract
Background: Osteosarcoma remains a challenging disease, especially for young patients, due to its tendency to spread to the lungs and resist treatment. Identifying reliable markers at diagnosis could help doctors start more effective treatment earlier and improve patient outcomes. Two blood markers, ALP and LDH, may offer insight into a patient's prognosis. **Objective:** This study explored whether pre-surgery levels of ALP and LDH could predict survival in osteosarcoma patients. **Methods:** Researchers reviewed medical records of patients diagnosed with osteosarcoma at RSUP Haji Adam Malik Medan from 2015 to 2017. This retrospective study included those who met the necessary criteria and had complete data. **Results:** The study found no strong evidence linking ALP or LDH levels to five-year survival. ALP had a very weak negative correlation with survival (r = -0.019), while LDH showed a weak positive correlation (r = 0.093). Median ALP was 212 U/L; LDH was 489 U/L. Sensitivity and specificity were moderate for both markers. **Conclusion:** There is no significant relationship between ALP and LDH with five-year survival.

Keywords: ALP, LDH, prognosis, osteosarcoma

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1. Introduction

Osteosarcoma is the most common primary malignant bone tumor [1]. Epidemiological data show a high incidence of osteosarcoma in ages 15-19 years and >40 years [1, 2]. Osteosarcoma is the eighth malignancy with the highest incidence of 4.4 per million [1]. In addition to improving the diagnosis and treatment of osteosarcoma, the 5-year survival rate is still very low with many local and metastatic recurrences [1, 4].

Osteosarcoma commonly occurs in children and young adolescents, but can occur at any age [1]. The two peak incidence of osteosarcoma are first in young adolescents in the 10-14 year age group and the second increases in the age of the eighth decade [3]. Nearly 20% of patients are diagnosed with metastases, the most common site of metastases being lung metastases. Several molecular serological markers such as serum alkaline phosphatase (ALP), lactate dehydrogenase (LDH), survivin, and ezrin levels have been investigated as prognostic markers in determining the survival of patients with osteosarcoma [5, 8].

Osteosarcoma prognosis is very unsatisfactory due to frequent tumor metastases to the lung or resistance to chemotherapy [7, 8]. Therefore, markers are needed to identify the prognosis of patients with osteosarcoma when diagnosed with the aim of being able to receive cancer treatment as soon as possible to improve a better prognosis. Some studies suggest that patients with high LDH have poor outcomes [9, 10,

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12]. A study conducted by Jia Chen et al stated that high serum LDL levels were closely associated with lower overall survival (OS) rates of patients with osteosarcoma. It is effective to serve as a biomarker of prognosis [12, 15].

It is known that patients with osteosarcoma are generally detected with elevated serum alkaline phosphatase (SALP) levels [15, 17]. The relationship between SALP activity and clinical outcome in osteosarcoma patients has been investigated by several studies for more than 50 years [17]. The meta-analysis study conducted by Hai-Yong Ren et al. concluded that high SALP levels were associated with poor OS and metastatic state at diagnosis [17, 18]. Therefore, the researchers were interested in seeing the relationship between preoperative serum ALP and LDH levels on the clinical prognosis of osteosarcoma patients.

2. Methods

This research is a retrospective analytic study with the data source is the medical records of patients who have been diagnosed with Osteosarcoma at Haji Adam Malik General Hospital Medan. The research was conducted at the Department of Surgery, FK-USU / Haji Adam Malik Hospital, Medan. This research was started after the proposal was approved by the research ethics committee of Universitas Sumatera Utara, with the research code of ethics no. 426/KEPK/USU/2022. The subjects of this study were patients with osteosarcoma who were treated at SMF Orthopedic Surgery at Haji Adam Malik Hospital Medan from January 2015-December 2017 who met the inclusion criteria.

Inclusion criteria in this study were no preoperative cancer therapy such as radiotherapy, and blood transfusion, all patients with osteosarcoma had undergone surgery, no haematological disease/disorder, and no infection and hyperpyrexia were found. The exclusion criteria for this study were incomplete patient medical records. This study uses a minimum total sampling as the basis for calculating the sample size, where a minimum sample of 50 people is obtained.

The flow of the study started from collecting data on patients with osteosarcoma, then assessed by the Enneking Criteria and histology that confirmed positive osteosarcoma. Then assessed by inclusion criteria to see the examination of preoperative biomarkers to obtain data related to preoperative serum ALP and LDH levels, as well as patient follow-up. Overall Survival (OS) of the patient was then monitored with the follow-up range to see the patient's outcome.

To describe the demographic characteristics of patients with osteosarcoma who were treated at SMF Orthopedic Surgery, Haji Adam Malik Hospital, Medan, it was presented in tabulated form and described. To evaluate the sensitivity and specificity of the 5 Years Overall Survival rate, the ROC curve was used. Comparison between categorical variables was carried out using the Chi-Square test, if the conditions were not met then the Fisher's exact test was used. Survival curves were constructed using the Kaplan-Meier curve and significance was calculated using the log-rank test. Predictor significance for OS was used multivariate analysis using Cox proportional hazards.

3. Results

This study is a retrospective analytic study with medical records of patients diagnosed with Osteosarcoma at Haji Adam Malik General Hospital Medan. The study was conducted at the Department of Surgery, FK-USU/RSUP Haji Adam Malik Medan on patients with osteosarcoma who were treated at SMF Orthopedic Surgery, RSUP Haji Adam Malik Medan from January 2015-December 2017. The median (min-max) of the age was 17 year (1-70 Years), ALP level was 212 U/L (49-1431 U/L), and LDH level was 489 U/L (280-865 U/L).

Table 1. Research Demographic Characteristics

Variable	Frequency (n)	Percentage (%)
Gender		
Male	36	67.9%
Female	17	32.1%
Patient Group		
Surgery	49	92.5%
Surgery+Neoadjuvan	1	1.9%
Surgery+Adjuvan	3	5.7%
Metastases		
Found	0	0%
Not Found	100	100%

Table 1 shows the demographic characteristics of the study where the male gender was found at most as many as 36 people (67.9%), and women as many as 17 people (32.1%). The most common patient group found was the surgery group as many as 49 people (92.5%), the surgery + neoadjuvant group as many as 1 person (1.9%), and the surgery + adjuvant group as many as 3 people (5.7%). In the metastatic group, all respondents did not find metastases, as many as 100 people (100%). Regarding the age variable, the median age of the respondents was 17 years with a range from 1-70 years. The ALP value in this study had a median value of 212 U/L (49-1431 U/L) and an LDH value of 489 U/L (280-865 U/L). The relationship between ALP and five-year survival is shown in Table 2.

Table 2. ALP Relationship with Five-Year Survival

ALP	Five Year Survival		p Value	r Value
	Survive	Non-Survive		
<98 U/L	5	3	0.557[a]	-0.019[b]
>98 U/L	30	15		
Total	35	18		

[a]Fisher Test [b]Spearman Test

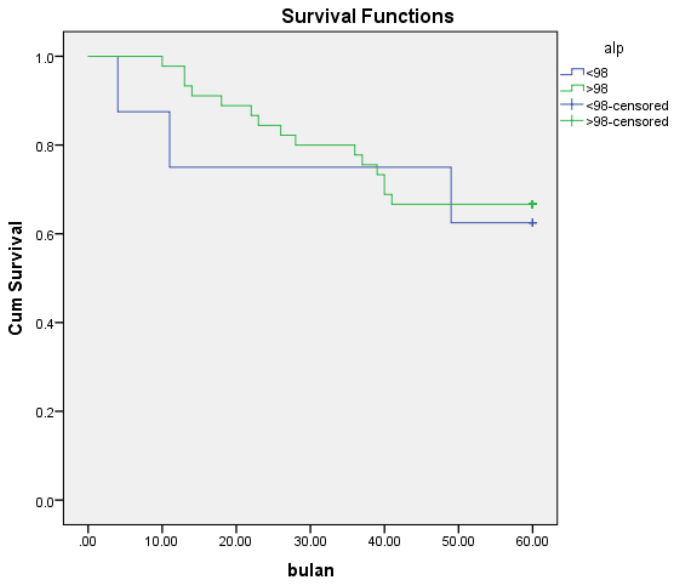

Figure 1. Kaplan Meier on the Relationship of ALP with Five-Year Survival

Regarding the relationship of ALP with five-year survival, the ALP category <98 U/L with five-year survival with a survival category of 5 people, and 3 people died. In the ALP category >98 U/L, 30 people were found alive and 15 people died with a p value of 0.057 indicating no significant relationship between

ALP and five-year survival and r value of -0.019 which means ALP and five year survival has weak correlation, with a different way, that means the higher ALP, the lower the five-year survival of the patient.

Table 3. Relationship of LDH with Five-Year Survival

LDH	Five Year Survival		p Value	r Value
	Survive	Non-Survive		
<300 U/L	4	0	0.179[a]	0.093[b]
>300 U/L	31	18		
Total	35	18		

[a]Fisher Test [b]Spearman Test

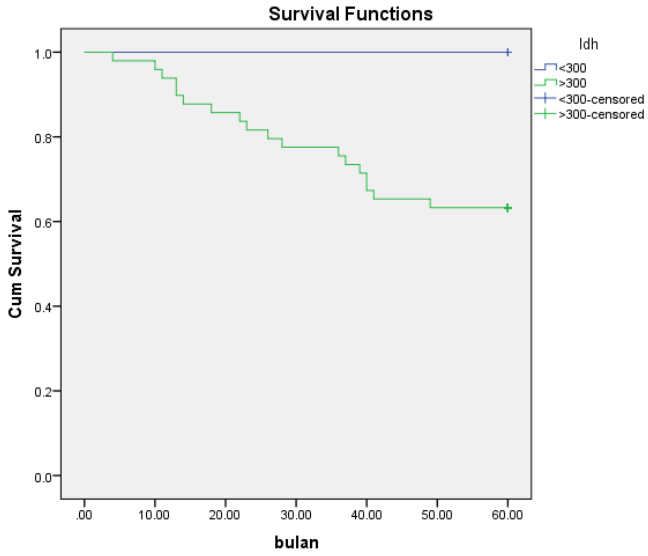

Figure 2. Kaplan Meier diagram on the Relationship of LDH with Five-Year Survival

Related to Table 3 regarding the relationship of LDH with five-year survival, the LDH category <300 U/L with five-year survival with 4 people living category, and 0 people dying. In the LDH category >300 U/L, 31 people were found alive and 18 people died where the p value of 0.179 showed no significant relationship between LDH and five-year survival, r value of 0.093 which means has weak correlation between LDH and five year survival.

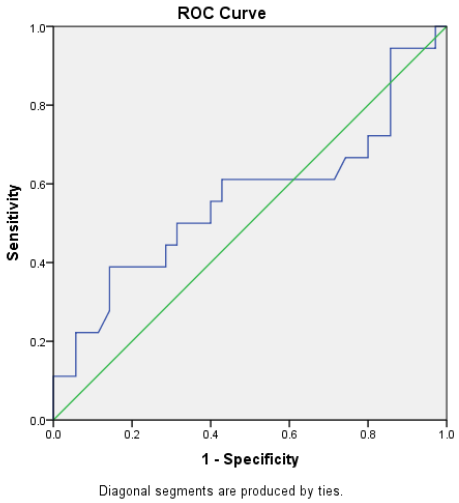

Figure 3. Diagram ROC ALP curve
Sensitivity: 61.1% Specifity: 57.1%

Based on Figure 3 related to the ROC ALP curve, the ALP sensitivity is 61.1% and ALP specificity is 57.1% with a cut-off of 217.5 U/L. Regarding the sensitivity and specificity of LDH, it is shown in Diagram 4.

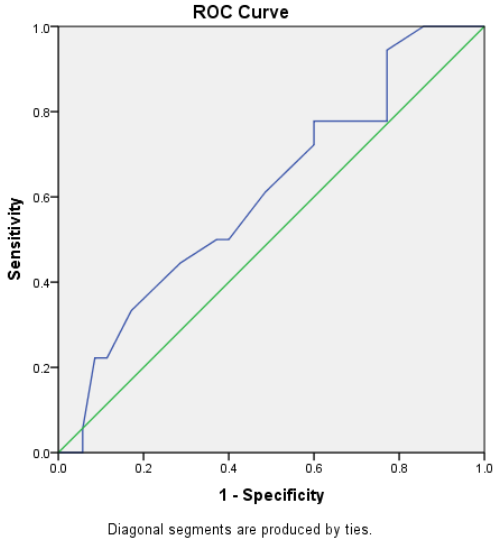

Figure 4. Diagram ROC LDH Curve
Sensitivity: 61.2% Specifity: 51.4%

Based on Figure 4 related to the ROC LDH curve, the LDH sensitivity was 61.2% and the LDH specificity was 51.4% with a cut-off of 488.5 U/L. Associated with multiple linear regression on the variables ALP and LDH on five-year survival of osteosarcoma patients in this study, the researchers used regression analysis technique which is a research hypothesis analysis method or technique to test whether there is an influence between one variable and another variable which is expressed in the form of mathematical equations (regression). Multiple linear regression analysis serves to find the effect of two or more independent variables (independent variable or X) on the dependent variable (dependent variable or Y) (Figure 5).

Coefficients

Model		Unstandardized Coefficients		Standardized Coefficients			95.0% Confidence Interval for B	
		B	Std. Error	Beta	t	Sig.	Lower Bound	Upper Bound
1	(Constant)	1.021	.202		5.056	.000	.621	1.422
	Nilai ALP	.000	.000	.110	1.140	.257	.000	.001
	Nilai LDH	.001	.000	.125	1.289	.200	.000	.001

Figure 5. Coefficient of ALP and LDH on Five-Year Survival of Osteosarcoma

The r value obtained in this study was 0.165, which means that preoperative serum ALP and LDH levels can be independent prognostic predictors with weak correlation in osteosarcoma patients with the following mathematical equation:

$$Y = \alpha + \beta 1X1 + \beta 2X2$$

There are three values that can be seen in the table above, namely constant with a value of 1.021, ALP with a value of 0.0001 and LDH with a value of 0.001. Constant is the alpha value of the regression equation Y = + 1X1 + 2X2. As for the lines ALP and LDH are the regression coefficients of each independent variable (β1 and 2 in the linear regression equation) so that the regression model in this example is as follows:

$$Y = 1.021 + 0.0001X1 + 0.001X2.$$

This means that if ALP and LDH are 0, then five-year survival will increase by 1,021 times. This result is significant at 5% alpha. β_2 is 0.0001. This means that assuming the LDH is fixed (unchanged), then every 1 unit increase in ALP will increase the LDH by 0.0001. This result is significant at 5% alpha of the t test results. β_2 is 0.350, it means that assuming the ALP is fixed (unchanged), then every 1 unit increase in LDH

will increase ALP by 0.001. This result is significant at Alpha 5% of the test results.

4. Discussion

Osteosarcoma is the most common malignant bone tumor in many patients. Several prognostic factors have been proposed including detectable metastases, advanced age, non-extremity location, large tumor volume, elevated LDH or ALP, and poor histologic response to chemotherapy [16, 19, 20] Of these, metastatic disease, large tumor size and poor response to neoadjuvant chemotherapy were consistently associated with poor outcome [17]. Tumor size may reflect tumor burden and/or extent of disease [17]. Large primary tumors are more likely to be associated with distant metastases. In addition, tumor size has been associated with an increased risk of death. Patients with tumors >15 cm in diameter had a threefold higher risk of death, whereas those with tumors <15 cm in diameter had better survival [21].

In this study found that the male sex was found at most as many as 36 people (67.9%), and women as many as 17 people (32.1%). This study is in line with research conducted by Kamal in 2021 which found that in 58 samples of osteosarcoma, 38 were male and 20 female. Research by Prabowo in 2021 also found that osteosarcoma patients were dominated by 40 men (62.5%) and 24 women (37.5%) [21, 22, 23].

In age-related variables, the median age of the respondents was 17 years with a range from 1-70 years. This study is in line with research conducted by Kamal in 2021 which found that in 58 samples of osteosarcoma, the average age was 5–67 years with an average of 16 years. Regarding patient characteristics and demographic data in this study, these findings are consistent with previous studies in which the prevalence of osteosarcoma was reported to be higher in men than women. In addition, osteosarcoma is also most common in the second decade of life, with the distal femur and proximal tibia being the most affected sites. Age distribution can be associated with the presence of a rapid bone growth (growth spurt) in men, especially in men, second decade of life, whereas women experience it at an earlier time. Most of the patients with osteosarcoma who visited the research facility presented with long-standing symptoms or complaints and a large tumor size [21-22, 23].

In another study, based on data analysis using logistic regression, female gender, age over 20 years, duration of symptoms 12 weeks, and tumor enlargement after neoadjuvant chemotherapy were significant variables that correlated with poor chemotherapy response. The significance of female gender as a predictor of poor Huvos response in this study may be due to the non-standardization of both sexes, with 21 of 24 female patients having an initial tumor diameter of >10 cm, and 20 females. The patient is in the second decade of life. In contrast, the research of Prabowo et al. demonstrated that male gender, tumor diameter >10 cm at diagnosis, and 12-week duration of symptoms were significantly correlated with poor chemotherapy response. A study by Bacci et al. reported a complete chemotherapy response, which was found in cases of local tumors without metastases. In addition, they also demonstrated that tumor cell and tissue type, as well as serum methotrexate concentration, were major determinants of chemotherapy response [21-23].

The most common patient group found was the surgery group as many as 49 people (92.5%), surgery + neoadjuvant group as many as 1 person (1.9%), and surgery + adjuvant group as many as 3 people (5.7%). This study is in line with Kamal's study in 2021 which found that 58 patients underwent neoadjuvant chemotherapy with a CAI regimen, while 13 (36.2%) of 58 patients underwent neoadjuvant chemotherapy [21-23]. Another study by Bacci also found that chemotherapy was adjuvant in 240 patients (29.0%) and neoadjuvant in 620 (71%). Neoadjuvant chemotherapy was started in 620 patients, but 3 patients had to discontinue preoperative treatment because of toxicity [20].

In the metastatic group, all respondents did not find metastases, as many as 100 people (100%). The results of this study are explained by previous studies showing that increased post-chemotherapy ALP correlates with shorter survival and a greater incidence of pulmonary metastases, as well as poor response to chemotherapy. A decrease in ALP levels during clinical therapy may be a symptom of a positive response to treatment [19].

The ALP value in this study had a median value of 212 U/L (49-1431 U/L) and an LDH value of 489 U/L (280-865 U/L). Research by Kamal in 2021 found a preoperative ALP value of 229 U/L (51-3354 U/L), where the LDH value showed a value of 404 U/L (60-2225). Another study by Bacci found the mean LDH value in osteosarcoma patients was 489 U/L [22-23].

Regarding the relationship between ALP and five-year survival, the ALP category <98 U/L with five-year survival with 5 people living and 3 people died. In the ALP category >98 U/L, 30 people were found alive and 15 people died with a p value of 0.057 indicating no significant relationship between ALP and five-year survival. The results of this study are in line with research by Kamal in 2021 which found that the ALP value did not have a significant relationship with five-year survival with a p value of 0.918 [19-23].

Regarding the ROC ALP curve, the ALP sensitivity was 61.1% and ALP specificity was 57.1% with a

cut-off of 217.5 U/L. Meanwhile, the ROC LDH curve showed that the LDH sensitivity was 61.2% and the LDH specificity was 51.4% with a cut-off of 488.5 U/L. Previous studies showed that the sensitivity of ALP in metastases was 53.2% (95% CI: 0.431-0.624), and specificity was 78.2% (95% CI: 0.720–0.839) at 15 months postoperatively and 90.0% (95% CI: 0.824-0.952) at 3 years postoperatively. Serum ALP was found to be a valuable tumor marker with high specificity in osteosarcoma. In LDH, previous studies showed that although a high LDH level was able to predict the presence of metastases with a high specificity of 81%, the sensitivity was found to be low at 38% [8].

The specificity of ALP in the diagnosis of osteosarcoma has not been previously reported. Compared with 899 other primary bone lesions, ALP showed an excellent specificity of 90.1% in this study; 88.9% among malignant lesions and 90.4% among benign lesions. The sensitivity and specificity of ALP on metastases during postoperative surveillance are other important characteristics of tumor markers. The sensitivity of ALP in the first metastases was 53.2% and the specificity was 78.2% in the early metastatic-prone stage and 90.0% in the late stable stage [13].

Regarding the relationship between LDH and five-year survival, the LDH category <300 U/L with five-year survival includes 4 people living and 0 people dying. In the LDH category >300 U/L, 31 people were found alive and 18 people died, where the p value of 0.179 showed no significant relationship between LDH and five-year survival. The results of this study are not in line with research by Kamal in 2021 which found that the LDH value had a significant relationship with five-year survival with a p value of 0.046 [15, 16. 21-23].

LDH was reported to be the strongest predictor of disease-free survival and an important predictive indicator in osteosarcoma. Ferry et al. reported that patients with serum LDH less than 460 U/L had better disease-free survival than those with higher LDH levels. Baseline serum level of LDH showed independent prognostic significance for DFS; and patients with normal LDH levels had 55% DFS, whereas patients with higher levels had 29% DFS. It was also confirmed by the meta-analysis reported by Fu et al. and Chen et al. concluded that significantly increased serum LDH values correlated with reduced disease-free survival and lower survival rates. Meanwhile, other studies reported that LDH is not a prognostic indicator for osteosarcoma [16-17].

The weakness of this study is that many samples are excluded, the risk of bias, the type of surgical technique data was not included. The sample size is too small due to the large number of excluded samples, reducing the power of the study and increasing the margin of error. Moreover, the cause of death due to primary or metastatic tumors or other diseases. Another weakness found is that the research method is retrospective, only single center, where it is suggested that other prognostic variables need to be added. There was no significant relationship between ALP and LDH with five-year survival with p-values of 0.557 and 0.179 ($p>0.05$). ALP has a weak correlation with five-year survival with an r value of -0.019 which means the higher the ALP, the lower the five-year survival of the patient. Meanwhile, LDH has a weak correlation with an r value of 0.093, which means the higher the LDH, the higher the patient's five-year survival. ALP Value in this study have mean value 212 U/L and LDH Value with 489 U/L. ALP had sensitivity of 61.1% and specificity of 57.1% with a cut-off of 217.5 U/L. Meanwhile, LDH had sensitivity 61.2% and specificity was 51.4% with a cut-off of 488.5 U/L.

5. Conclusions

In this study, the demographic characteristics of the study where the male gender was found at most were young age and the most common patient group was the surgery group.

6. Data Availability Statement

The datasets generated and analyzed during the current study are not publicly available due to privacy and ethical considerations but are available from the corresponding author upon reasonable request.

7. Ethical Statement

This study was approved by the Research Ethics Committee of Universitas Sumatera Utara under approval number: 426/KEPK/USU/2022.

8. Author Contributions

All authors contributed to the design and implementation of the research, data analysis, and finalizing the manuscript.

9. Funding
No funding.

10. Conflict of Interest
Authors declares no conflict of interest.

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