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The correlation of Alkaline Phosphatase, lactate dehydrogenase, C-Reactive protein, erythrocyte sedimentation rate, and apparent diffusion coefficient values with Enneking staging and osteosarcoma subtypes

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Abstract: Apparent diffusion coefficient (ADC) values obtained from Magnetic Resonance Imaging (MRI) have shown potential as predictors of osteosarcoma staging and subtype, along with laboratory results for alkaline phosphatase (ALP), lactate dehydrogenase (LDH), c-reactive protein (CRP), and erythrocyte sedimentation rate (ESR). However, studies investigating this correlation are still relatively limited. These tests may be an alternative for osteosarcoma staging and subtyping, especially in low-resource settings. This study aims to investigate the correlation between the ADC value and laboratory findings with the staging and subtype of osteosarcoma. This retrospective study analyzed data from osteosarcoma patients from August 2021 to August 2023, including serum levels of ALP, LDH, CRP, ESR, and ADC values from MRI. A study of 39 osteosarcoma patients found that most were male (61.5%), with an average age of 19. The distal femur was the most common tumor location (33.3%), and osteosarcoma chondroblast type was the predominant subtype (30.8%). Enneking stage IIB was the most prevalent (79.5%). ALP, LDH, CRP, and ESR biomarkers significantly correlated with Enneking staging ($p<0.05$). However, no correlations were found between these biomarkers and osteosarcoma subtype ($p>0.1$). Additionally, no significant correlations were observed between the mean ADC and Enneking staging ($p=0.061$) or osteosarcoma subtype ($p=0.084$). ALP, LDH, CRP, and ESR levels have a strong and significant correlation to the staging of Enneking osteosarcoma. However, the mean ADC values on MRI do not have a significant correlation to the osteosarcoma subtype based on histopathology.

Keywords: *Alkaline phosphatase, Apparent diffusion coefficient, Enneking stage, Lactate dehydrogenase, Osteosarcoma subtype.*

1. Introduction

Osteosarcoma is a malignant tumor in the bone that spreads rapidly beyond the periosteum and surrounding tissues. Osteosarcoma originates from primitive cells (poorly differentiated cells) in the metaphyseal region of long bones and is often found in children whose epiphyseal growth plates are highly active (1). According to the research conducted by Novariyanto et al., osteoblastic osteosarcoma is the most prevalent type of osteosarcoma in terms of epidemiological distribution (2). There are various subtypes of osteosarcoma, including osteoblastic osteosarcoma, chondroblasts osteosarcoma,

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small cell osteosarcoma, telangiectatic osteosarcoma, and giant cell-rich osteosarcoma (3). Among the five subtypes of osteosarcoma mentioned above, chondroblastic osteosarcoma has the highest apparent diffusion coefficient (ADC) value, while small cell osteosarcoma is the subtype with the lowest ADC value (2).

The measurement of the ADC in magnetic resonance imaging (MRI) is a method used to quantify water diffusion and tends to have lower values in tissues with high cellularity (2,4). The study by Hassanien et al. reveals that the average values for ADC in benign soft tissue neoplasms are significantly higher than those in malignant neoplasms, with the average values for all benign tumors being $1.53 \pm 0.81 \times 10^{-3}$ mm2/s. In contrast, the average values for all malignant tumors are $0.84 \pm 0.33 \times 10^{-3}$ mm^2/s. There is a significant difference in the average ADC values between the two (2,5).

In recent years, the integration of various biomarkers has played a crucial role in enhancing the critical understanding of the pathophysiology of osteosarcoma and improving the quality of patient care. Among these biomarkers, alkaline phosphatase (ALP), lactate dehydrogenase (LDH), c-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) have emerged as crucial components in diagnostic modalities, providing insights into disease progression, patient outcomes, and therapeutic strategies (4,6,7).

Based on the theory regarding ADC values and laboratory results such as ALP, LDH, CRP, and ESR, which play a crucial role in cancer pathophysiology, this study hypothesizes that similar to ADC values, these laboratory examinations can also serve as an initial step in determining the staging and subtype of osteosarcoma. However, studies investigating this correlation are still relatively limited. If a significant correlation is found, these laboratory tests may be projected as an alternative for determining the staging and subtype of osteosarcoma, especially in low-resource settings.

2. Material and Methods

This is a retrospective cross-sectional study conducted with an analytical design involving the retrospective collection of data. The study population includes all patients diagnosed with osteosarcoma from August 2021 to August 2023 who meet the inclusion criteria. The inclusion criteria for this study are 1) patients with a diagnosis of osteosarcoma based on post-operative histopathological examination (resection or amputation), 2) patients with a history of undergoing serum ALP, LDH, CRP, ESR examinations, as well as preoperative MRI with ADC values, and 3) patients diagnosed with osteosarcoma with Enneking staging.

The exclusion criteria for this study are 1) patients with osteosarcoma whose diagnosis is confirmed through FNAB/core biopsy or without post-operative histopathological examination, 2) patients with osteosarcoma who did not undergo serum ALP, LDH, CRP, ESR examinations, as well as preoperative MRI with ADC values, and 3) patients diagnosed with osteosarcoma not staged according to Enneking classification.

The independent variables in this study are patients diagnosed with osteosarcoma who undergo examinations for serum levels of ALP, LDH, CRP, ESR, and MRI with ADC values. The collected data include age, gender, diagnosis, and the date and year of treatment. The dependent variables assessed in this study are patients diagnosed with osteosarcoma who have been staged and undergone post-operative histopathological examinations. ALP, LDH, CRP, and ESR data were collected during preoperative lab sampling, while ADC data were obtained from the preoperative MRI results. The examination of osteosarcoma subtypes was conducted postoperatively.

Data collection was conducted at the medical records department by documenting patients diagnosed with osteosarcoma staged according to Enneking and who had undergone post-operative histopathological examinations. Furthermore, preoperative data collection was conducted on ALP, LDH, CRP, ESR, and MRI with ADC values. The gathered data will be processed using SPSS. SPSS version 25 will be employed for testing, using Pearson correlation to assess the relationship between parameters and osteosarcoma subtypes. Meanwhile, the lambda correlation test will be applied to evaluate the relationship between parameters and Enneking staging.

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3. Results

From the evaluation results of osteosarcoma patients between August 2021 – August 2023 who underwent laboratory tests for ALP, LDH, CRP, ESR, and MRI with ADC values, a total of 39 patients were identified. There was a male predominance (n=24; 61.5%), with an average age of 19 ± 12.0 years. Examining the tumor locations, the majority of samples had tumors located in the distal femur (n=13; 33.3%), proximal tibia (n=10; 25.6%), and proximal humerus (n=8; 20.5%). In this study's samples, the majority were classified as Enneking stage IIB (n=31; 79.5%), with the remaining being stage III. For each patient, ALP, LDH, CRP, ESR, ADC, histopathological evaluation results, and Enneking stage values were recorded.

The tumor subtypes of all patients are detailed in Table 1. From the total samples obtained, the chondroblastic type of osteosarcoma (n=12; 30.8%) is the predominant subtype. The least common subtypes are telangiectatic osteosarcoma (n=2; 5.2%) and small cell type osteosarcoma (n=1; 2.6%).

Table 1.
Demographic data.

Information	Variable	Sample (n =39)
Gender	Man	24 (61.5 %)
	Woman	15 (38.5 %)
Age	0-10	7 (17.9%)
	11-20	19 (48,7 %)
	21-30	9 (2 3.1 %)
	31-40	1 (2.6%)
	41-50	2 (5.1%)
	>50	1 (2.6%)
Osteosarcoma subtypes	Chondroblastic	12 (30.8%)
	Osteoblastic	11 (28.2%)
	Fibroblastic	8 (20.5%)
	Giant cell rich	5 (12.8%)
	Telangiectatic	2 (5.1%)
	Small cell	1 (2.6%)
Location	Distal Femur	13 (33.3%)
	Proximal Tibia	10 (25.6%)
	Proximal Humerus	8 (20.5%)
	Proximal Femur	2 (5.1%)
	Scapula	1 (2.6%)
	Proximal Fibula	1 (2.6%)
	Proximal Ulna	1 (2.6%)
	Pelvis	1 (2.6%)
	Digit	1 (2.6%)
	Distal Ulna	1 (2.6%)
Stage Enneking	IIB	31 (79%)
	III	8 (21%)

Based on the evaluation results, we conducted a correlation test between each parameter and the osteosarcoma subtype based on histopathological examination using the Pearson correlation test. According to the Pearson correlation test results, no correlation was found between ALP, LDH, CRP, ESR, and osteosarcoma subtype based on histopathological examination (Table 2).

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Table 2.
Correlation between osteosarcoma subtype and Enneking with ALP, LDH, CRP, ESR, and ADC mean.

Variable	Osteosarcoma subtype**	Enneking staging***
ALP	0.137	0.002*
LDH	0.231	0.002*
CRP	0.397	0.024*
ESR	0.539	0.047*
ADC_Mean		0.084

Note: *Significant correlation
**Pearson correlation
***Lambda correlation

From the lambda correlation test, a significant correlation was found between ALP (p=0.002), LDH (p=0.002), CRP (p=0.024), and ESR (p=0.047) with Enneking staging of patients. From the correlation values, a perfect relationship between ALP and LDH and a very strong relationship between CRP and ESR with Enneking staging were observed (Table 2). The mean ADC value does not correlate with the Osteosarcoma subtype or Enneking staging (p= 0,061; p= 0,084). Also, in Table 3, it is shown that the mean ADC value does not differ significantly between osteosarcoma subtypes and enneking staging. The highest mean ALP and LDH values were found in telangiectatic osteosarcoma. However, there were only two samples in our study, which resulted in an uneven distribution of the number of subtypes. In conventional osteosarcoma, the mean ALP, LDH, CRP, and ESR values were higher in osteoblastic osteosarcoma compared to chondroblastic osteosarcoma, which had almost the same sample size.

Table 3.
The distribution of mean values for ALP, LDH, CRP, ESR, and ADC in osteosarcoma subtypes and Enneking staging.

Variable		Mean ALP ± SD	Mean LDH ± SD	Mean CRP ± SD	Mean ESR ± SD	Mean ADC ± SD
Subtype osteosarcoma						
	Osteosarcoma Chondroblastic type	226.25 ± 178.18	217.33 ± 36.02	1.36 ± 2.28	42.25 ± 28.2	0.80 ± 0.164
	Osteosarcoma osteoblastic type	336.09 ± 206.57	391.09 ± 164.97	9.41 ± 16.8	56 ± 32.6	0.87 ± 0.285
	Osteosarcoma fibroblastic type	321.75 ± 273.3	210.12 ± 74.31	5.29 ± 10.68	54.875 ± 44.8	0.81 ± 0.118
	Osteosarcoma giant cell-rich type	309 ± 422.81	419.6 ± 540.96	2.72 ± 4.14	71.8 ± 43.1	0.73 ± 0.192
	Osteosarcoma telangiectatic type	559 ± 82.04	559.5 ± 91.21	3.4 ± 0.56	28.5 ± 2.12	0.60
	Osteosarcoma small cell type	169.00	330.00	1.10	132.00	0.75
Enneking staging						
	Enneking IIB	301.0 ± 263.77	277.5 ± 145.10	5.1 ± 11.59	51.5 ± 35.33	0.78 ± 0.20
	Enneking III	310.8 ± 154.73	442 ± 403.62	3.2 ± 4.03	64 ± 43.48	0.85 ± 0.14

4. Discussion

Osteosarcoma is a primary malignant tumor of the bone. This tumor is characterized by the direct formation of immature bone or osteoid by tumor cells. In this study, the evaluated parameters are ALP, CRP, LDH, ESR, and the ADC value from patients' MRI. The analysis results indicate that ALP and LDH have a strong correlation with tumor staging, while the ADC value is strongly associated with the subtype of osteosarcoma (8).

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In the musculoskeletal context, ALP is abundant in osteoblasts and plays a crucial role in the mineralization of new bone. Given its function, an increase in ALP can occur when there is the formation and mineralization of new bone. Osteoblasts transformed in osteosarcoma can disrupt proliferation control and activate the expression of genes related to cell differentiation, increasing ALP (7).

A study conducted by Agustina et al. found that ALP has a sensitivity rate of 96%, specificity of 80%, positive predictive value of 82.7%, and negative predictive value of 95.2%, with an overall accuracy of 88% (9). Besides being a diagnostic auxiliary parameter, ALP has also been identified as a prognostic factor for osteosarcoma. The increase in ALP values in our study reached (mean=303 ± 243 U/L).

The increase in ALP is also known to occur in patients with Ewing sarcoma. Baptista et al. (10) explained that the increase in ALP in Ewing sarcoma patients was (mean=171.85 ± 88.62 U/L). When compared to our research data, although similar increases in ALP values were found in osteosarcoma cases, the ALP values tended to be higher than in Ewing sarcoma. Keller et al. explained that ALP values in osteosarcoma increased significantly (median, 355.0 U/L; range, 161–4730 U/L) compared to GCT (median, 252.0 U/L; range, 148–351 U/L). This study also found an increase in ALP (mean=303 ± 243 U/L) that aligns with the increased ALP values (11). This indicates that ALP values in osteosarcoma cases are higher than in GCT. This information can aid in the diagnosis of patients with primary bone tumors.

In this study, it was found that LDH is strongly associated with the staging of osteosarcoma but not with its subtypes. This is reasonable, considering that the heavier the formed tumor, the greater the activity of tumor cells. LDH can increase due to inflammation resulting from the malignancy process. Its specificity makes LDH not suitable as a single parameter but requires a combination with other supportive laboratory evaluations. In the study by Marais et al., an LDH value exceeding 849 IU/L is considered a threshold for the presence of metastasis in patients (12). The analysis of 18 studies revealed that an increase in LDH is strongly correlated with the deterioration of Overall Survival (OS) and Event-Free Survival (EFS) in osteosarcoma patients. This prognostic predictive ability applies to all subtypes and stages of osteosarcoma patients (6,12).

The increase in LDH in our study was found to be a mean of 311 ± 226 U/L. This increase is also known to occur in patients with Ewing sarcoma. Baptista et al. explained that patients with Ewing sarcoma experience a significant increase in LDH (mean=884.54 ± 983.29 U/L) (10). When compared to the data in this study, although similar increases in LDH values were found, in osteosarcoma cases, LDH values tend to be lower than in Ewing sarcoma. In a study by Keller et al. on LDH in Giant Cell Tumor (GCT), it was explained that there was no increase in LDH (mean 170.5 U/L; range, 131–223 U/L) (11).

In this study, it was found that CRP is significantly associated with the staging of osteosarcoma, where the higher the staging of osteosarcoma, the lower the CRP tends to be. This can be due to the chronic condition of the tumor, leading to a decrease in CRP at the time of examination. Furthermore, the patients included in this study are at an advanced stage of cancer, which means the inflammatory response caused by the tumor has subsided. As a result, CRP levels are significantly lower compared to earlier stages (13).

The increase in CRP in our study was found to be a mean of 4.76 mg/dL. This increase is also known to occur in patients with Ewing sarcoma, explaining that patients with Ewing sarcoma experience an increase in CRP (mean=1.6 mg/dL) (14). When compared to the data in this study, although similar increases in CRP values were found, in osteosarcoma cases, CRP values tend to be higher than in Ewing sarcoma. In a study by Keller et al. on GCT cases, there was no increase in CRP values (mean=0.81 mg/dL) (11).

In this research, it was found that the ESR increases significantly as the tumor staging becomes higher. ESR is a classical inflammatory marker and has been used for a long time. ESR increases infections, malignancies, and autoimmune diseases (15).

Similar to the previous study, the earlier research found that ESR can serve as a diagnostic and prognostic marker for malignant tumors. ESR was found to increase osteosarcoma and Ewing sarcoma

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significantly. Consistent with the previous study, it was discovered that ESR can function as both a diagnostic and prognostic marker for malignant tumors (13,16).

The ESR values were found to significantly increase in osteosarcoma and Ewing sarcoma (13,16). This is consistent with our research, where increased ESR values were found in osteosarcoma cases, with a mean of 54.1 mm/h. A study from Keller et al. explained that in GCT cases, there is an increase in ESR values (mean=17 mm/h), although not as high as the ESR values in osteosarcoma cases (11).

In this study, ADC values were used to compare the degree of malignancy among malignant tumors, namely osteosarcoma. It was found that there was no relationship between ADC values and the staging of osteosarcoma patients or with the evaluated osteosarcoma subtypes. This is in contrast to previous research that found a significant relationship and high sensitivity in predicting osteosarcoma subtypes based on ADC values. The ability to distinguish each osteosarcoma subtype is reasonable, considering that each subtype has its uniqueness and characteristics. Previous studies have found that each osteosarcoma subtype has different average ADC values compared to other subtypes (17,18).

The average ADC value of osteosarcoma in our study was 0.800 ± 0.19 x10-3mm^2/s. When ranked from the most malignant to the least, they were osteosarcoma telangiectatic, osteosarcoma giant cell-rich type, osteosarcoma small cell type, osteosarcoma chondroblastic, osteosarcoma fibroblastic, and lastly osteosarcoma osteoblastic. Among the conventional osteosarcoma types, the ADC values from low to high were as follows: chondroblastic type 0.800 x$10^{-3}$$mm^2$/s, followed by fibroblastic type 0.809 x$10^{-3}$$mm^2$/s, and osteoblastic type 0.867 x$10^{-3}$$mm^2$/s. These findings differ from previous research showing that the average ADC value for chondroblastic osteosarcoma was the highest (1.470 x$10^{-3}$$mm^2$/s), and osteoblastic osteosarcoma was the lowest (0.994 x$10^{-3}$$mm^2$/s) (4). The increase in the cellular matrix of osteoid leads to low ADC values and is found in osteoblastic osteosarcoma. Another study by Setiawati et al., stated that an increase in the osteoid matrix compared to the chondroid matrix would enhance diffusion-weighted imaging (DWI) restriction and decrease ADC values. The highest average ADC values were found in the chondroblastic subtype (4).

The cause of these different ADC values can be attributed to the heterogeneity of components within the tumor, and it is a natural occurrence. Within these tumor components, solid, cystic, necrotic, or hemorrhagic tissues can be found, making it challenging to determine the appropriate points for measuring ADC values that reflect the tumor's characteristics. The homogeneity of tumor tissue is also inherently uncontrolled due to processes like apoptosis, proliferation, and both small and large necrosis occurring during the tumor's development, which cannot be regulated. Necrosis does not always signify a favorable condition; in large and aggressive tumors with extensive necrosis, it can lead to high ADC values, resembling less malignant tumors.

5. Conclusion

The ALP, LDH, CRP, and ESR levels are strongly and significantly associated with the staging of Enneking osteosarcoma. ADC values are not significant in both Enneking staging and tumor subtypes. In the advancement of radiology, the development of technology related to volumetric ADC is expected to provide a solution to the heterogeneity issues in tumors, especially osteosarcoma. Thus, imaging modalities can serve as accurate references in establishing the diagnosis of osteosarcoma subtypes. Plans for therapy and education related to the prognosis of each osteosarcoma subtype can also be provided to patients as early as possible.

Ethical Informations:

This study was approved by the ethics committee of Dr. Soetomo General Academic Hospital Surabaya, Indonesia (Ethical Clearance No. 0880/KEPK/I/2024).

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