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Evaluation of Factors Associated with Clinical Outcomes in Patient with Malignancy Spine Disease: A 4-Years Study of a 38 cases

Pamudji Utomo[1], **Dimas Prasetyo**[2*], **Abdaud Rasyid**[1], **R Andhi Prijosedjati**[1] and **Romaniyanto**[1]

[1]*Department of Orthopaedic and Traumatology, Orthopaedic Hospital, Surakarta, Indonesia*

[2]*Department of Orthopaedic and Traumatology, Universitas Sebelas Maret, Surakarta, Indonesia*

[*]**Corresponding author:** Dimas Prasetyo, Resident of Orthopaedic and Traumatology, Faculty of Medicine Universitas Sebelas Maret, Surakarta, Indonesia, Tel: +6281325012925; E-mail: dr_dimasprasetyo@yahoo.com

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Abstract

Background: Spinal malignancies can present as a progression of known cancer or as a primary neoplasm. Spine is the third most common organ affected by metastatic cancer, after the lungs and the liver. One of the losses incurred is spinal cord compression that can leads to permanent neurological impairment and compromised quality of life of patients. This study intends to analyze the correlation of several pre-treatment factors on the outcome of malignancy spine disease in patients which have been treated at Soeharso Orthopedic Hospital.

Methods: We retrospectively reviewed the medical records data of all patients treated for spinal metastasis between September 2015 until November 2018 in Soeharso Orthopaedic Hospital Surakarta. We supplement the data through interviews, then we analyze the data statistically Univariate data was calculated by chi square, while bivariate data was calculated by multiple logistic regression.

Results: Patients consisted of 15 male and 23 female in the most age range at 41-60 years (mean=52 years). Patients with elevated pre-treatment serum LDH level (>280 IU) were 5.89 times more likely to develop more severe neurological deficits, while the patients with high level ALP serum (>128 IU) have a mortality rate as high as 5.81 times greater.

Conclusion: Our study suggest that, gender, age, LDH and ALP baseline serum can be used as references to predict the prognosis in spine malignancy with elevated baseline serum LDH and ALP indicates a poor prognosis.

Keywords Alkaline phospatase; Lactate dehydrogenase; Clinical outcomes; Spine malignancy

Introduction

Definition

Spinal metastases are the most common type of bone metastasis and have a prevalence of 30-50% in cancer patients [1]. Spinal malignancy leads to spinal instability, pathologic fractures, neurologic deficits, and decreased quality of life [2]. Management of spinal metastases is primarily palliative and includes consideration of surgery, radiotherapy, medical management, and palliative therapy. Determination of the appropriateness of invasive management such as multi-level decompression and stabilization requires accurate pre-operative estimation of survival [2,3].

A number of prognostic factors have been identified in this population but routinely collected laboratory markers have yet to be fully understood or utilized. Serum Alkaline Phosphatase (ALP) and Lactate Dehydrogenase (LDH) are such marker that routinely collected in spinal metastatic disease patients but remains underutilized for prognostication [4-6].

Alkaline phosphatase has been well-established as a marker of hepatobiliary pathology and bone turnover and mineralization. This metalloenzyme is expressed on the cell surface of osteoblasts and serum levels of the enzyme correlate with increased osteoblastic activity [7]. In osteolytic bone metastases this enzyme is elevated secondary to a local bone formation response in an attempt to compensate for the predominant destructive lesion. In osteoblastic bone metastases, alkaline phosphatase is elevated secondary to local stimulation of osteoblasts [8].

LDH is a ubiquitous enzyme that plays a central role in anaerobic glycolysis, as it catalyzes the reversible conversion of pyruvate into lactate. It is used to maintain glycolysis as an alternative source of energy during hypoxic stress and subsequent high LDH level in cytoplasmic compartment [5]. Furthermore, higher LDH is significantly correlated with increased vascular density and decreased infiltration of lymphocytes within the tumours. Therefore, the increased LDH level reflects these alterations and suggests more severe tumour burden, tumour angiogenesis and tumour progression conditions, all of which lead to the poor prognosis of malignant tumours [9].

Aim of the study

This study intends to analyze the correlation of several pre-treatment factors on the outcome of malignancy spine disease in patients which have been treated at Soeharso Orthopedic Hospital.

Method

The patients sample consisted of patients with malignancy spine disease consecutively admitted from September 2015 until November 2018 in Soeharso Orthopaedic Hospital. The baseline data were taken and processed from the medical record data we obtained from the Soeharso Orthopedic Hospital Surakarta Medical Records Department through prior written permission. We conducted interviews at the same time (December 2019) with 44 patients that we had recapitulated. 33 patients were still alive, 5 patients have died while the remaining 7 patients cannot be contacted, and furthermore the patients who cannot be contacted are excluded. A structured questionnaire including details of the symptoms as well as back pain, paresthesia, weakness, and bladder dysfunction were asked to the remaining 38 patients. The other data, including gender, age, diagnose, treatments received, neurological deficit, level of LDH and ALP serum were recorded by supplemented from cross-checking all patient records.

Neurological status was documented and graded as follows: Motor function (0-no contraction; 1-flicker or trace of contraction; 2-active movement possible only with gravity eliminated; 3-active movement against gravity but not resistance; 4-active movement against resistance and gravity; and 5-normal power). Sensory symptoms and signs along with bladder and bowel function were also recorded. We classified these neurological deficits based on the Frankel Classification. Pulmonary metastases was defined as both parenchymal and pleural metastatic lesions. The factors of interest potentially related to the results of the correlation analysis of various pre-treatment factors both clinical and laboratories to the outcome of these patients.

Statistical Analysis

Frequencies by demographic and clinical characteristics for all patients were calculated. Descriptive analytical statistic summary measures were used to assess relevant variables. Continuous variables are reported as mean. Univariate analysis was calculated by chi square, while bivariate analysis was calculated by multiple logistic regressions. All p-values that <0.05 considered statistically significant. Statistical analyses were performed with SPSS ver. 24 for Windows.

Results

The patients consisted of 15 males and 23 females. Most of the patients were in the age group of 41-60 years old (n=17). The mean age of patients was 52 years. We summarize some of the complaints that were mostly felt by patients like pain (n=33), paresthesia (n=32), limbs weakness (n=32), sensibility loss (n=32), autonom deficit (n=31). Serum ALP and LDH, reported in International Units per Liter (IU/L). The range of values from 140 to 280 IU was set as the range of normal values for LDH, while the range of values of 53-128 IU was set as the range of normal AL p-values. The mean LDH level of patients was 235.03 and the average ALP of patients was 137.45 (Table 1). Based on the level of LDH levels, this study was dominated by patients with LDH levels of >280 (42.1%). As for ALP levels, this study was dominated by patients with ALP levels of >128 (47.4%)

The thoracal spine was the most commonly affected site (n=27), followed by lumbar spine (n=12) and cervical spine (n=4). Previous studies have suggested that malignancies found in the spine can be accompanied by signs of pulmonary metastasis. In the patient data that we reviewed, 5 out of 38 patients showed signs of involvement with pulmonary malignancy.

Independent Variable	Sensibility Lost		p-value	Odds Ratio
	No	Yes		
Age				
< 20 years old	0(0.0)	0(0.0)		
20-40 years old	0(0.0)	8(100)		
41-60 years old	5(29.4)	12(70.6)		
>60 years old	1(7.7)	12(92.3)	0.105	0.92
Gender				
Female	3(13.0)	20(87.0)		
Male	3(20.0)	12(80.0)	0.663	0.72
LDH				
<140	5(38.5)	8(61.5)		
140-280	0(0.0)	9(100)		
>280	1(6.3)	15(93.8)	0.020*	4.09
ALP				
<53	2(50.0)	2(50.0)		
53-128	3(18.8)	13(81.3)		
>128	1(5.6)	17(94.4)	0.08	4.12
Affected segment				
Cervical	0(0.0)	3(100)		
Thoracal	3(14.3)	18(85.7)		
Lumbal	3(33.3)	6(66.7)		
Thoracal and Lumbal	0(0.0)	4(100)		
Cervical and Thoracal	0(0.0)	1(100)	0.46	2.18

*Statistically significant

ALP: Alkaline Phospatase;

LDH: Lactate Dehydrogenase

Table 1: Correlation between Age, Gender, LDH, ALP, and affected segmentto the sensibility lost (Bivariate).

Based on the results of the analysis above, it was known that patients with LDH levels >280 experienced the highest sensibility lost, which was 93.8% with a p-value of 0.020, so there was a statistically significant relationship between LDH levels and the incidence of sensibility lost, where patients with LDH levels >280 have the opportunity to experience sensibility lost by 4.09 times higher when compared to patients with lower LDH levels (Table 2).

Independent Variable	Neurological Deficit	p-value	Odds Ratio

	None	Incomplete	Complete		
Age					
<20 years old	0(0.0)	0(0.0)	0(0.0)		
20-40 years old	0(0.0)	2(25.0)	6(75.0)		
41- 60 years old	5(29.4)	4(23.5)	8(47.1)		
>60 years old	1(7.7)	1(7.7)	11(84.6)	0.150	2.06
Gender					
Female	2(8.7)	6(26.1)	15(65.2)		
Male	4(26.7)	1(6.7)	10(66.7)	0.156	0.26
LDH					
<140	4(30.8)	3(23.1)	6(46.2)		
140-280	0(0.0)	1(11.1)	8(88.9)		
>280	2(12.5)	3(18.8)	11(68.8)	0.08	2.38
ALP					
<53	2(50.0)	1(25.0)	1(25.0)		
53-128	2(12.5)	3(18.8)	11(68.8)	0.331	1.49
>128	2(11.1)	3(16.7)	13(72.2)		
Affected segment					
Cervical	0(0.0)	3(100)	0(0.0)		
Thoracal	3(14.3)	1(4.8)	17(81.0)		
Lumbal	3(33.3)	1(11.1)	5(55.6)		
Thoracal and Lumbal	0(0.0)	1(25.0)	3(75.0)		
Cervical and Thoracal	0(0.0)	1(100)	0(0.0)	0.873	0.92

*Statistically significant

ALP: Alkaline Phospatase;

LDH: Lactate Dehydrogenase

Table 2: Correlation of age, gender, LDH, ALP, and affected segment to neurological deficit (Bivariate).

Based on the results of the analysis above, there are no independent variables that have a significant correlation to the neurological variable. But it can be seen that the highest risk for developing neurological deficit was in patients with LDH levels >280 with OR of 2.38 times (Table 3).

Independent Variable	Outcome		p-value	Odds Ratio
	Alive	Dead		
5Age				
<20 years old	0(0.0)	0(0.0)		
20-40 years old	8(100)	0(0.0)		
41-60 years old	14(82.4)	3(17.6)		
> 60 years old	11(84.6)	2(15.4)	0.456	-
Gender				
Female	18(78.3)	5(21.7)		
Male	15(100)	0(0.0)	0.136	-
LDH				
<140	12(92.3)	1(7.7)		
140-280	9(100)	0(0.0)		
>280	12(75.0)	4(25.0)	0.16	0.78
ALP				
<53	4(100)	0(0.0)		
53-128	15(93.8)	1(6.2)		
>128	14(77.8)	4(22.2)	0.277	0.23

Affected segment				
Cervical	2(66.7)	1(33.3)		
Thoracal	19(90.5)	2(9.5)		
Lumbal	8(88.9)	1(11.1)		
Thoracal and Lumbal	3(75.0)	1(25.0)		
Cervical and Thoracal	1(100)	0(0.0)	0.738	-
ALP: Alkaline Phospatase; LDH: Lactate Dehydrogenase				

Table 3: Correlation between Age, Gender, LDH, ALP, and Affected segment to outcomes (Bivariate).

There are no independent variables that have a significant correlation to the Outcome variable. But it can be seen that the highest risk of patients to experience death is in patients with LDH levels >280 with OR of 0.78 times (Table 4).

Independent Variable	Pulmonal Metastase		p-value	Odds Ratio
	No	Yes		
Age				
<20 years old	0(0.0)	0(0.0)		
20-40 years old	8(100)	0(0.0)		
41-60 years old	15(88.2)	2(11.8)		
>60 years old	10(76.9)	3(23.1)	0.307	0.74
Gender				
Female	21(91.3)	2(8.7)		
Male	12(80.0)	3(20.0)	0.365	2.62
LDH				
<140	12(92.3)	1(7.7)		
140-280	8(88.9)	1(11.1)		
>280	13(81.3)	3(18.8)	0.667	1.13
ALP				
<53	3(75.0)	1(25.0)		
53-128	15(93.8)	1(6.2)		
>128	15(83.3)	3(16.7)	0.508	1.15
Affected Segment				
Cervical	3(100)	0(0.0)		
Thoracal	18(85.7)	3(14.3)		
Lumbal	7(77.8)	2(22.2)		
Thoracal and Lumbal	4(100)	0(0.0)		
Cervical and Thoracal	1(100)	0(0.0)	0.757	0.93
ALP: Alkaline Phospatase; LDH: Lactate Dehydrogenase				

Table 4: Correlation between age, gender, LDH, ALP, and affected segment to pulmonary metastases (Bivariate).

Based on the results of the analysis above, there were no independent variables that had a significant relationship to the pulmonary metastases variable. However, it can be seen that the highest risk of patients to experience pulmonary metastases were male patients, with an OR of 2.62 times.

Almost of those patients were performed surgical procedure for its diseases. Patients had been performed laminectomy biopsy, 6 patients were laminotomy biopsy, 6 patients were percutaneous biopsy, 8 patients were open excise biopsy, 1 patients was performed Anterior Cervical Corpectomy and Fusion surgery, and 1 patients were only received palliative treatment due to the condition (Table 5).

Treatment Received	No. of patients (%) (n=38)
Laminectomy biopsy	19(38.0)
Open excision biopsy	7 (18.4)
Laminotomy biopsy	5 (13.1)
Percutaneus biopsy	5(13.1)
ACCF	1 (2.6)
Paliative	1 (2.6)
ACCF: Anterior Cervical Corpectomy and Fusion Multivariate Analysis Results of Multiple Logistic Regression	

Table 5: Treatment received by patient.

Following is the final model of multivariate logistic regression analysis after passing the confounding and interaction testing stages (Table 6).

Final Model:

Var Dependent: Loss of Sensibility

Independent Var: ALP, LDH, age, gender and affected segments

Independent Variable	p-value	B	AOR	95% CI	
				Lower	Upper
LDH	0.243	1.22	3.38	0.43	26.18
ALP	0.637	0.51	1.67	0.19	14.02
Age	0.798	0.19	1.22	0.27	5.55
Affected segment	0.575	-0.29	0.75	0.27	2.09
ALP: Alkaline Phospatase; LDH: Lactate Dehydrogenase					

Table 6: Multivariate analysis results of loss of sensibility.

Based on the final model above, shows that the LDH variable have the highest adjusted OR (AOR) with 3.38 times after being controlled with ALP variables, age, and affected segments (Table 7).

Final Model:

Dependent Var: Neurologic deficit

Independent Var: ALP, LDH, age, gender and affected segment

Variable Independent	p-value	B	AOR	95% CI	
				Lower	Upper
LDH	0.069	1.77	5.89	0.87	39.87
ALP	0.258	-1.61	0.19	0.01	3.27
ALP: Alkaline Phospatase; LDH: Lactate Dehydrogenase					

Table 7: Multivariate analysis results of neurologic deficit.

Based on the final model above, shows that the LDH variable have the highest adjusted OR (AOR) with5.89 times (Table 8).

Final Model:

Dependent Var: Patients Outcomes

Independent Var: ALP, LDH, age, gender and affected segments

Variable Independent	Nilai P	B	AOR	95% CI	
				Lower	Upper
ALP	0.124	1.76	5.81	0.62	54.75
Usia	0.283	0.75	2.13	0.54	8.44
ALP: Alkaline Phospatase; LDH: Lactate Dehydrogenase					

Table 8: Multivariate analysis results of patients outcomes.

Based on the final model above, shows that the ALP variable have the highest Adjusted OR (AOR) of 5.81 times after being controlled with the age variable (Table 9).

Final Model:

Dependent Var: Pulmonary Metastases

Independent Var: ALP, LDH, age, gender and affected segment

Variable Independent	Nilai P	B	AOR	95% CI	
				Lower	Upper
Gender	0.186	1.72	5.61	0.43	72.15
LDH	0.637	0.57	1.77	0.16	18.99
ALP	0.685	-0.74	0.47	0.01	17.23
ALP: Alkaline Phospatase; LDH: Lactate Dehydrogenase					

Table 9: Multivariate analysis results of pulmonary metastases.

Based on the final model above, it can be concluded that the gender variable was the highest Adjusted OR (AOR) of 5.61 times after being controlled by LDH and ALP variables.

Discussion

Spinal cord compression due to malignancy is an oncological emergency, unless early diagnosed and treated promptly, can lead to permanent neurologic impairment and can seriously affect a patient's quality of life. However, most patients report late and land up in permanent damage to the cord [10].Previous studies have reported a high incidence of neurological disorders caused by spine neoplasms [11]. In this current study, we retrospectively reviewed the clinical features and treatment outcomes of spinal cord compression due to malignancy. According to our study of 44 patients, most of them were women (n=25 (56.82%)) in the age range 41-60 years old. This was in line with previous study conducted in Northern India where many cases occur at the age of over 50 years [12], although it did not statistically significant.

In general, patients with pulmonary metastases showed a low life expectancy. In our study, we can conclude that male had a more frequent incidence of pulmonary metastases or primary lung tumor (Adjusted OR (AOR) of 5.61). That was in line with previous studies that shown that male were the most at risk [13]. LDH and ALP serum was routinely used as a laboratory examination in cases of malignancy not only in the spine but also in the other organs. Our present study showed a statistically significant result where an elevated in serum LDH levels was consistent with an increase of morbidity in spine malignancy patients, whereas a high ALP level showed a high mortality rate [14].

Elevated lactate dehydrogenase (LDH) levels are associated with poor outcomes in cancer patients. Elevated LDH levels were the product of enhanced glycolytic activity of the tumor and tumor necrosis due to hypoxia, the latter being associated with high tumor burden [15-17]. Based on the previous study, patients with elevated LDH before or after 2 months of treatment showed a significantly shorter overall survival than that of the low-low group (15.9 m vs. 52.1 m, p=0.0003) [5]. Serum alkaline phosphatase was recently studied as risk factor for 30-day postoperative mortality in spinal metastatic disease patients in the National Surgical Quality Improvement Program (NSQIP), a database of short-term postoperative outcomes in North America [7].

This study has several limitations including the absence of follow-up of each subject within a certain period of time so that it cannot be

assessed improvement in neurological conditions after surgery. Our hope for further study is to be more stringent in the follow up of each patient so that can not only present the improvement in the patient's neurological condition but also can analyze survival rate of the patients.

Conclusion

Based on this study, it can be concluded that male patients in their fifth decade of age have higher risks of suffering from spine malignancy. Serum LDH and ALP tests have been shown to be useful in predicting our patient outcomes.ALP was the most influential factor in predicting death, while LDH was the most influential factor predicting neurologic deficit.

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