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PROGNOSTIC VALUE OF SERUM LDH AT DIAGNOSIS IN PATIENTS WITH MULTIPLE MYELOMA

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ABSTRACT

Background: Multiple myeloma (MM) is a malignant disorder of clonal plasma cells. A number of biological factors influence the evolution of patients with MM. **Objective:** the present study aims to evaluate the prognostic value of serum lactate dehydrogenase (LDH) at diagnosis in terms of survival of patients with MM and response to treatment. **Materials and Methods:** This is prognostic study conducted in the Department of Oncology in Tishreen University Hospital –Lattakia- Syria between January 2006 and January 2016. Patients who newly diagnosed with MM were included in the study. **Results:** A total of 120 patients with MM were included in the study. The median age was 60.5 years and 55% were men. Arate of 48.3% of patients were in stage II, and 72.5% of cases were secreted of IgG. The response to therapy was complete in 16 % of patients with elevated level of LDH versus 44.3% in normal LDH group ($p<0.05$), and refractory to therapy was more frequently in elevated LDH group (36% vs. 2.9%, p:0.001). Median overall survival(OS), progression –free survival(PFS) were 65.3±32.9 ,36.3±21.5 months respectively in normal LDH group versus 36.7±20.4 , 16.06±17.4 months respectively in elevated LDH group (p:0.0001). High level of LDH, creatinine, and stage III were independent adverse prognostic parameters for both OS and PFS ($p<0.05$). **Conclusion:** High level of LDH is a negative prognostic factor in evolution of MM patients, adversely influencing therapeutic response rates and reducing the survival of patients with MM.

KEYWORDS: Multiple myeloma(MM), lactate dehydrogenase(LDH), survival, prognostic factor.

INTRODUCTION

Multiple myeloma(MM) accounts for 1% of all cancers and approximately 10% of all hematologic malignancy.[1] The annual incidence is 4 to 5 per 100.000 individuals worldwide.[2] It is characterized by neoplastic proliferation of a single clone of plasma cells in the bone marrow producing a monoclonal immunoglobulin and ultimately causing various complications and organ dysfunction.[3] The duration of survival of patients with MM ranges from a few months to several years.[4] Clinical and laboratory studies have determined several prognostic factors of MM including clinical stage, the level of serum beta2-microglobulin , albumin, platelet count, creatinine, and age, are important markers for survival during the course of disease.[5] Moreover , serum LDH at diagnosis is also known to be of prognostic significance in MM patients. The median OS of the patients whose LDH levels are high is shorter than those patients whose LDH levels are normal.[6] As LDH gives an idea about the level of tumor mass, the increase of LDH during the course of the disease may refer to the increased levels of tumor, relapse or the existence of extra plasmacytomas.[7] The aim of the study was to determine the prognostic role of serum LDH levels at diagnosis in MM patients.

MATERIALS AND METHODS

Study design and data collection

This study includes patients who were newly diagnosed with MM between January 2006 and January 2016 in Tishreen University Hospital – Lattakia-Syria. The following data were recorded: demographic (age, sex), laboratory parameters including plasma cells of bone marrow, hemoglobin, platelets, serum albumin, calcium, creatinine, lactate dehydrogenase (LDH) and β2

microglobulin. Clinical stages were determined based on the ISS staging system and response rates to treatment were recorded. Exclusion criteria were patients with elevated level of LDH due to other causes (hepatic diseases, hemolysis) and who discontinued treatment.

Definitions

Overall survival (OS): It was defined as time from commencement of induction therapy to death or last follow-up.[8]

Progression free survival(PFS): Time from start of treatment to disease progression or death from any cause.[9]

International staging system (ISS) for MM

Stage I: B2-MG<3.5 mg/L;ALB ≥ 3.5 g/dL
Stage II: B2-MG<3.5 mg/L;ALB ≥ 3.5 g/dL;or B2-MG 3.5-5.5 mg/L.
Stage III: B2-MG>5.5 mg/L.[10]

Complete response: negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and<5% plasma cells in bone marrow aspirates.[11]

Very good partial response: serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥ 90% reduction in serum M-protein plus urine M-protein level<100 mg per 24 hours.[11]

Partial response: ≥ 50% reduction of serum M-protein plus reduction in 24 hour urinary M-protein by ≥ 90% or to <200 mg per 24 hours.[11]

Statistical Analysis

Statistical analysis was performed by using IBM SPSS version 20. Basic Descriptive statistics included means, standard deviations (SD), Frequency and percentages.

Differences among different groups were examined with using chi- square test. Independent t student test was used to compare 2 independent groups.

Survival curves were plotted by Kaplan-Meier method and compared by the log-rank test. Multifactorial analysis was done using Cox regression p<0.05 was considered as statistically significant.

RESULTS

A total of 120 patients with MM were identified. The median age was 60.5 (range, 30-87 years), and 55% were male. With the follow up time, median OS was 47 months and medial PFS was 26 months. According to ISS, 16.7, 48.3 and 35 % had stages I, II, and III, respectively. 90.8% of MM were secreted, and the type of M protein was IgG in 72.5% of the cases. The treatment which study population received was conventional therapy in 97.5% of cases, and 32.5% of patients achieved a complete response, Table(1).

Table (1). Demographic characteristics of the study population (N=120).

Variables	
Age(years)	60.5(30-87)
Sex	
Male	66(55%)
Female	54(45%)
Disease stage	
Stage I	20(16.7%)
Stage II	58(48.3%)
Stage III	42(35%)
Type of M protein, n(%)	
No secreted	11(9.2%)
Secreted	
IgG	87(72.5%)
IgA	22(18.3%)
Type of treatment regimens	
Conventional therapy	117(97.5%)
Combination Conventional therapy with immunotherapy	3(2.5%)
Response rates to treatment	
Complete response	39(32.5%)
Very good partial response	23(19.2%)
Partial response	38(31.7%)
Refractory to treatment	20(16.7%)

A total of 41.66 % (50/120) patients had a high LDH level at diagnosis. As shown below, there were no statistical differences between the two groups in patient's clinical characteristic except for response rates to treatment in which complete response was more frequently in patients with normal LDH, whereas partial response and refractory to treatment were more frequently in patients with high levels of LDH.

Table (2). Comparison between two groups of patients according to serum LDH level at diagnosis in clinical characteristic.

Variables	LDH		p-value
	Elevated(50)	Normal(70)	
Age(years)	60[36-87]	62[30-81]	0.4
Age group(years) <70 ≥70	 33(66%) 17(34%)	 50(71.4%) 20(28.6%)	0.5
Sex Male Female	 28(56%) 22(44%)	 38(54.3%) 32(45.7%)	0.8
Disease stage Stage I Stage II Stage III	 6(12%) 27(54%) 17(34%)	 14(20%) 31(44.3%) 25(35.7%)	0.4
Response rates to treatment Complete response Very good partial response Partial response Refractory to treatment	 8(16%) 3(6%) 21(42%) 18(36%)	 31(44.3%) 20(28.6%) 17(24.3%) 2(2.9%)	0.0001

There were no statistical differences between two groups in regard to laboratory parameters; p>0.05, Table (3).

Table (3). Comparison between two groups of patients in laboratory parameters according to serum LDH level at diagnosis.

Variables	LDH		p-value
	Elevated(50)	Normal(70)	
Hemoglobin(Hb)	9.65±1.5	9.69±1.8	0.9
Erythrocyte sedimentation rate(ESR)	111.9±33.4	102.7±39.2	0.1
Creatinine(Cr)	1.33±0.6	1.30±1.1	0.8
Albumin	3.17±0.5	3.27±0.7	0.4
Platelets	193.3±90.1	214±76.2	0.1
calcium	9.01±1.3	8.9±1.09	0.6
B2-MG	10.1±6.1	5.02±2.5	0.3
Uric acid	6.01±1.8	6.4±1.5	0.1
Bone marrow plasma cells 30%≤ >30%	 34(68%) 16(32%)	 52(74.3%) 18(25.7%)	0.4
Type of M protein; n(%) IgG IgA	 36(72%) 9(18%)	 51(72.8%) 13(18.6%)	0.9

In the univariable Cox analysis, the risk of death was increased for high LDH versus normal LDH (HR 5.5,95% CI 3.5-8.6, p=0.001), as well as high level of: creatinine (HR 5,95% CI 1.7-13.9, p=0.002), B2-MG (HR 2.7,95% CI 1.1-6.6, p=0.02), uric acid (HR 2.4,95% CI 0.9-5.8, p=0.03), and stage III of disease (HR 2.9,95% CI 0.6-10.3, p=0.04).

Table (4). Univariate Cox regression analyses for overall survival (OS) in patients with MM.

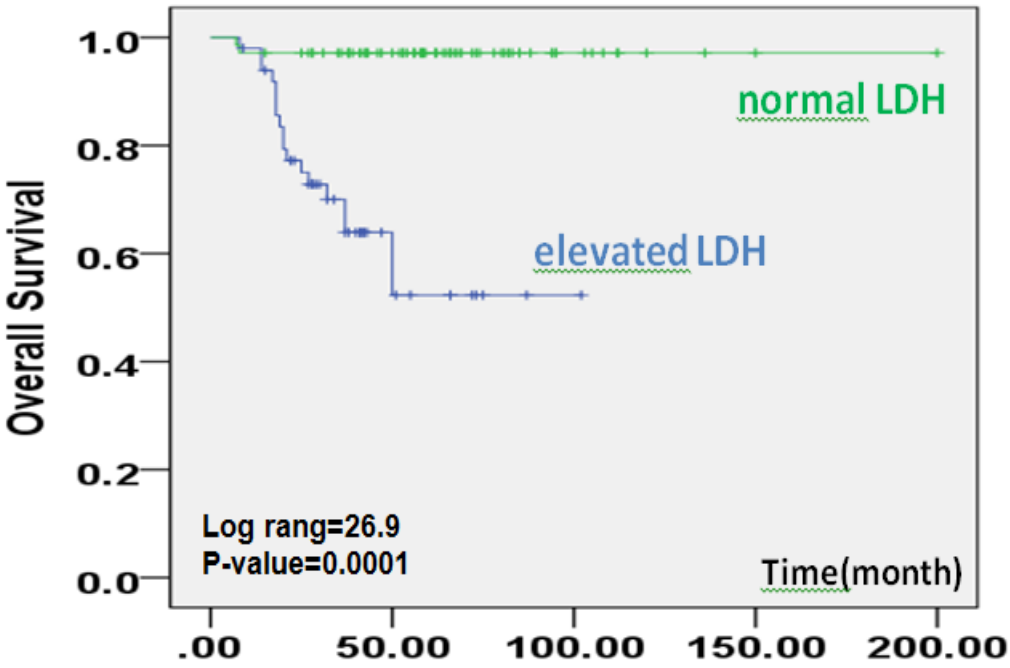
Variables	N	HR	CI	p-value	Median OS(months)
Sex					
Female	54	1			50
Male	66	1.01	[0.4-2.4]	0.9	43
Age group					
<70	83	1	[0.1-1.4]		53
70≥	37	0.4		0.1	41
LDH					
Normal	70	1	[3.5-8.6]	0.001	59
Elevated	50	5.5			32
Hb					
<10	54	1			56
10≥	66	2.6	[0.9-7.3]	0.06	41
ESR					
<20	3	1			42
20≥	117	1.9	[0.2-5.8]	0.6	47
Creatinine					
2≤	111	1			50
>2	9	5	[1.7-13.9]	0.002	32
Albumin					
3.5 ≥	38	1			56
<3.5	82	2.9	[0.7-3.9]	0.09	42
Platelets					
>100	112	1			48
100≤	8	3.1	[0.9-10.6]	0.07	34
Calcium					
<11.5	115	1		0.05	47
>11.5	5	3.01	[0.6-12.9]		29
B2-MG					
5.5≤	82	1			47
>5.5	38	2.7	[1.1-6.6]	0.02	44
Uric acid					
7≤	71	1			48
>7	49	2.4	[0.9-5.8]	0.03	42
Bone marrow plasma cells					
<30%	34	1			50
30%≥	86	0.8	[0.3-2.2]	0.7	42
Type of M protein; n(%)					
IgG	87	1			51
IgA	22	0.5	[0.2-1.7]	0.3	38
Disease stage					
Stage I	20	1			58
Stage II	58	1.04	[0.2-5.1]	0.9	48
Stage III	42	2.9	[0.6-10.3]	0.04	43

In the multivariate cox Hazard analysis, elevated level of LDH, creatinine, and Stage III of myeloma were factors predicting inferior OS, Table (5).

Table (5). Multivariate cox Hazard analysis for OS in patients with MM.

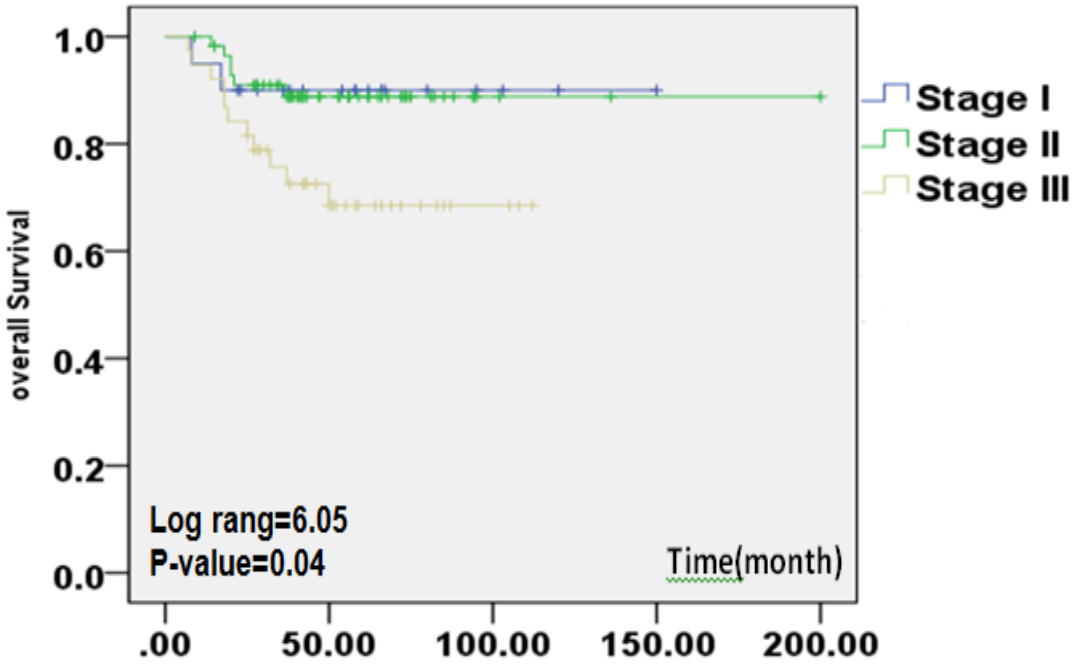
Risk factors	HR	p-value
Creatinine	3.2[1.06-8.9]	0.03
LDH	5.4[3.7-9.8]	0.002
Stage III	2.1[0.9-3.1]	0.04

Median OS was 65.3±32.9 months in normal LDH group versus 36.7±20.4 months in elevated LDH group (p:0.0001), Figure(1).



Figure(1). OS analyses between patients according to LDH level.

Median OS was 59. 6±36.3, 53.5±32.4, 50.2±28.3 months in stage I, II, III respectively; p:0.5, Figure (2).



Figure(2). OS analyses between patients according to ISS stages.

The risk of progression was increased for high LDH versus normal LDH(HR 3.3,95% CI 2.9-7.83, p=0.001), as well as high level of: creatinine(HR 4.6,95% CI 1.6-13.1, p=0.003), B2-MG(HR 2.7,95% CI 1.1-6.6, p=0.03), uric acid(HR 2.5,95% CI 0.9-6.3, p=0.04) and stage III(HR 2.1,95% CI 0.3-8.9, p=0.04), Table (6)

Table (6). Univariate analyses for progression –free survival (PFS) in patients with MM.

Variables	N	HR	CI	p-value	Median PFS(months)
Sex					
Female	54	1		0.9	26
Male	66	0.9	[0.4-2.3]		23
Age group					
<70	83	1	[0.1-1.6]	0.1	28
70≥	37	0.4			23
LDH					
Normal	70	1		0.001	38
Elevated	50	3.3	[2.9-7.8]		13
Hb					
<10	54	1		0.08	32
10≥	66	2.4	[0.8-6.8]		18
ESR					
<20	3	1		0.6	23
20≥	117	2.9	[0.3-6.3]		26
Creatinine					
2≤	111	1		0.003	26
>2	9	4.6	[1.6-13.1]		12
Albumin					
3.5 ≥	38	1		0.1	28
<3.5	82	0.3	[0.1-1.3]		23
Platelets					
>100	112	1			26
100≤	8	2.6	[0.7-9.1]	0.1	11.5
Calcium					
<11.5	115	1	[0.06-1.2]	0.1	26
>11.5	5	0.2			7.5
B2-MG					
5.5≤	82	1		0.03	26
>5.5	38	2.7	[1.1-6.6]		24
Uric acid					
7≤	71	1		0.04	27.5
>7	49	2.5	[0.9-6.3]		16.5
Bone marrow plasma cells					
<30%	34	1		0.8	26.5
30%≥	86	0.9	[0.3-2.4]		26
Type of M protein;_n(%)					
IgG	87	1	[0.2-1.8]	0.4	28
Disease stage					
Stage I	20	1			28
Stage II	58	1.04	[0.2-5.1]	0.9	26
Stage III	42	2.1	[0.3-8.9]	0.04	21

In the multivariate cox analysis, elevated LDH, creatinine, and Stage III of myeloma were factors predicting inferior PFS, Table(7).

Table (7). Multivariate cox Hazard analysis for PFS in patients with MM.

Risk factors	HR	p-value
Creatinine	2.8[1.03-8.5]	0.04
LDH	4.7[3.2-6.3]	0.001
Stage III	1.9[0.7-2.5]	0.04

Median PFS was 36.3±21.5 months in normal LDH group versus 16.06±17.4 months in elevated LDH group (p:0.0001), Figure (3).

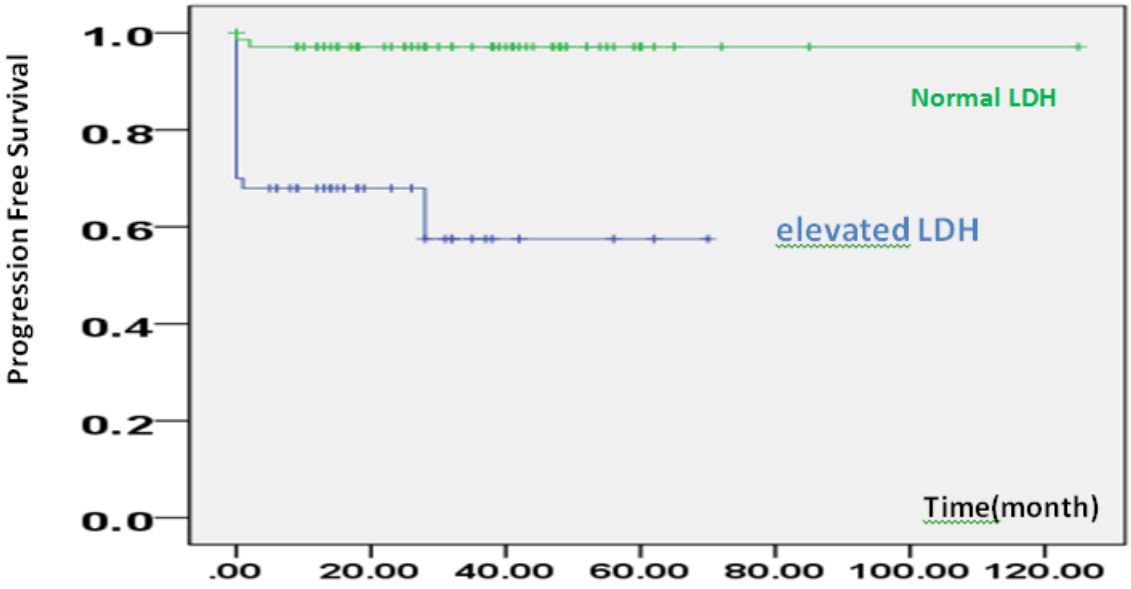


Figure (3). PFS analyses between patients according to LDH level.

Median PFS was 32.2±28.2, 28.4±21.1,24.9±20.6 months in stage I, II, III respectively; p:0.4, Figure (4).

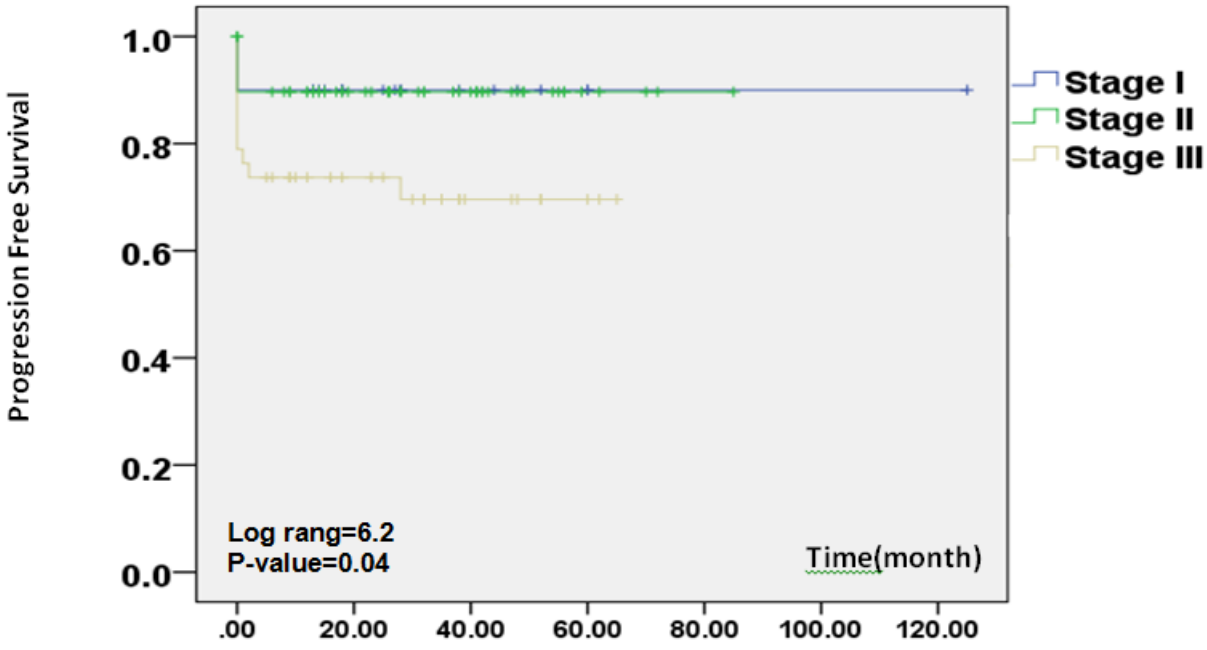


Figure (4). PFS analyses between patients according to ISS stages.

DISCUSSION

This prognostic study demonstrated that MM is largely more frequent in advanced age, slightly more frequent in men than in women. The vast majority of patients have a monoclonal protein produced and secreted by malignant plasma cells, and the most MM subtype was IgG. Elevated level of LDH was detected in 42% of the patients with statistical differences regard to response rates to treatment according to LDH levels in which partial response and refractory to treatment were more frequently in patients with high levels of LDH. Median OS and PFS were lower in elevated LDH group compared to normal LDH group (p:0.0001). High levels of LDH, creatinine, B2-MG, uric acid and stage III of disease were associated with increased risk of death and progression of disease. High level of LDH, creatinine, and stage III of myeloma were independent prognostic factors for both OS and PFS($p<0.05$).

Increased LDH is associated with worse overall survival,

progression-free survival, aggressive disease and high tumor burden. Elevated level of LDH is a marker of poor prognosis at the time of diagnosis of MM. The Revised International Scoring System(R-ISS) for myeloma, which incorporates high LDH, high beta -2 microglobulin, low albumin, and the presence of high risk chromosomal abnormalities, is an effective clinical tool to evaluate the risk and prognosis of patients with newly diagnosed MM.[12,13]

Many previous studies focused on the prognostic value of LDH levels at diagnosis in MM patients. Terpos *et al*(2010) demonstrated that LDH had an independent prognostic value for OS($p< 0.001$), and the median OS of patients with high and normal LDH was 15 vs 44 months($p<0.001$).[14]

Maria *et al*(2011) found that LDH is a simple, inexpensive, and readily available blood test that may be included among the variables that define very high risk MM. Increased LDH level was associated with a higher probability of early death.[15]

Chim et al (2014) also showed that elevated level of LDH was an independent adverse factor for OS and PFS.[16]

Gu *et al* (2017) demonstrated that high LDH was a unique independent adverse indicator for overall response rate and early death in MM patients, in which patients with high LDH group had significantly shorter OS and PFS.[17]

CONCLUSION

Serum LDH level is one of the most useful prognostic factors in patients with MM.

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REFERENCES

1. Palumbo A, Anderson K. Multiple myeloma. N Engl J Med, 2011; 364: 1046-60.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics. CA: Cancer J Clin, 2015; 65: 5-29.
3. Rajkumar SV. Multiple myeloma update on diagnosis, risk-stratification, and management, American Journal of Hematology, 2011; 86: 57-65.
4. Kumar SK, Rajkumar SV, Dispenzieri A. Improved survival in multiple myeloma and the impact of novel therapies. Blood, 2008; 111: 2516-20.
5. Kyle RA, Rajkumar SV. Criteria for diagnosis, staging, risk stratification and response assessment of multiple myelom.Leukemia, 2009; 23: 3-9.
6. Simonsson B, Brenning G, Kallander C, Ahre A. Prognostic value of serum lactic dehydrogenase (s-LDH) in multiple myeloma. Eur J Clin Invest, 1987; 17: 336-9.
7. Liu Y, Wen L, Chen H, Duan W. Serum lactate dehydrogenase can be used as a factor for re-evaluating first relapsed multiple myeloma. Acta Haematol.Doi:10.1159/000505737.
8. Chen YK,Han SM, Yang Y. Early mortality in multiple myeloma: Experiences from a single institution.Hematology, 2016; 21: 392-398.
9. Jagannath S, Roy A, Kish J,Lunacsek O. Real world treatment patterns and associated progression free survival in relapsed /refractory multiple myeloma among US community oncology practices. Expert Rev Hematol, 2016; 9(7): 707-717.
10. Greipp PR, San Migul J, Durie BG, Barlogie B. International staging system for multiple myeloma. J Clin Oncol, 2005; 23: 3412-20.
11. Durie BG, Harousseau JL, Miguel JS, Gertz M. International myeloma working group. International uniform response criteria for multiple myeloma. Leukemia, 2006; 20(9): 1467-1473.
12. Dimopoulos MA, Barlogie B, Smith TL. High serum levels of lactate dehydrogenase as a marker for drug resistance and short survival in multiple myeloma. Ann Intern Med, 1991; 115(12): 931-935.
13. Palumbo A, Avet-Loiseau H, Oliva S,Lok-horst HM. Revised International staging system for multiple myeloma: A report from International Myeloma working group.J Clin On-col, 2015; 33(26): 2863-9.
14. Terpos E,Katodritou E, Roussou M, Pouli A. High serum lactic dehydrogenase adds prognostic value to the international myeloma staging system even in the era of novel agents. Eur J Haematol, 2010; 85(2): 114-9.
15. Maria Gkotzmanidou, Efstathios Kastritis, Dimitra Gika. Increased serum lactate dehydrogenase should be included among the variables that define very high risk multiple myeloma. Clinical Lymphoma,Myeloma & Leukemia, 2011; 5: 409-13.
16. Chor Sang Chim, Joycelyn Sim, Sidney Tam, Eric Tse. LDH is an adverse prognostic factor independent of ISS in transplant-eligible myeloma patients receiving bortezomib –based induction regimens. European Journal of Haematology, 2014; 94: 330-335.
17. Yan Gu,Ya-Hui Yuan, Ji Xu,Qing-Lin hi.High serum lactate dehydrogenase predicts an unfavorable outcome in Chinese elderly patients with multiple myeloma. Oncotarget, 2017; 8(29): 48350-48361.