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Original article

Prognostic Impact of Pretreatment Serum Lactate Dehydrogenase Levels in Adult Patients with Acute Myeloid Leukemia: Single Center Experience

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Abstract

Background: Lactate Dehydrogenase (LDH) elevation is considered a poor prognostic factor for numerous neoplastic diseases, including Acute Myeloid Leukemia (AML) which denotes leukemic cell turnover and cell destruction. **Subjects and Methods**: Fifty-two patients (27 males and 25 females) with newly diagnosed AML at the Hematology unit (Mansoura University) from October 2016 to November 2019 were recruited in this cohort study. They were categorized as favorable risk (7 [13.46%], intermediate risk (35 [67.3%], and adverse risk (10 [19.2%]). The LDH levels were measured initially at presentation for the patients and control group (n=15). **Results:** The Mean LDH level was 1156 ± 744.49 U/L in the studied patients. The complete remission rate (CR) was statistically significantly higher in those with normal versus high LDH {[22 (71%) versus 9 (29%)], p value=0.003}. Cox proportional-hazards regression was used to analyze the effect of age, WBC, LDH, and adverse cytogenetics on Overall Survival (OS). Elevated LDH was found associated with shorter cumulative 3-year-OS in univariable (P value <0.001, HR: 3.17, 95%CI=1.64-5.86) as well as multivariable (P<0.001, HR: 3.97, 95%CI=1.87-8.43) analyses. **Conclusions:** Elevated LDH level is considered a predictor of dismal outcomes and overall survival for patients with AML.

Keywords: Acute Myeloid Leukemia, LDH, Prognosis, Overall Survival.

Introduction

Acute Myeloid Leukemia (AML) is a heterogeneous genetic disorder of hematopoietic stem cells. Conventional and molecular cytogenetic assessments are part of AML diagnosis and risk stratification, this is in addition to their crucial importance for the choice of target therapy.[1] Advanced age, unfavorable cytogenetics, molecular marker mutation, and measurable residual disease (MRD) are recognizable adverse risk factors for AML survival. LDH is widely distributed in human tissues including white blood cells.[2]

The pivotal role of LDH in the development of neoplastic disorders is

linked to its release from lysed malignant cells enters the bloodstream. Therefore, it reflects tissue destruction and tumor Lysis.

Given the extreme importance of LDH in the emergence and development of the disease, LDH had been involved in many prognostic models of hematologic malignancies including Non-Hodgkins Lymphoma (NHL)[3] and multiple myeloma (MM)[4] but not acute leukemias despite its association with a poorer prognosis.[5,6,7] Since the estimation of LDH level is readily available and non-expensive, this simple test can be done as a basic workup for outcome association and assessment of survival prognosis in patients with Acute Myeloid Leukemia.

Aim of the study:

This study aimed to estimate the significance of elevated serum Lactate dehydrogenase (LDH) levels on treatment response in adult AML patients and its prognostic role in survival outcomes.

Subjects and methods

The current study is a retrospective case-control study. A total of 52 adult patients with a confirmed diagnosis of de-novo non-APL acute myeloid leukemia who attended the Oncology Center, Mansoura University in the period between October 2016 & November 2019 were enrolled in the current study. The inclusion criteria for the study were normal karyotype by conventional cytogenetics on bone marrow aspiration at the time of diagnosis. Patients with acute promyelocytic leukemia and therapy-- related AML were excluded from the study. They were 27 males and 25 females. FAB and WHO criteria were used for diagnosis.[8,9] Nine patients were (M1), 12 patients were (M2), 13 patients were (M4), 16 patients were (M5) and 2 patients were (M6). The serum LDH level was measured using a Modular autoanalyzer (P-800), ROCHE company with LDH, and was considered high if it was > 480 U/L.

The treatment strategy was based on the patient's age and performance status (PS) according to the following:

I. Patients younger than 60 years and those older than 60 years with PS ≤2 received the standard-of-care '7+3' induction chemotherapy protocol followed by consolidation intermediate-dose Cytarabine chemotherapy in favorable / intermediate-risk patients while Allogenic hematopoietic stem cell transplantation (HSCT) was offered for the adverse risk group. Primary refractory and progressive cases received salvage therapy.[9]

II. The treatment of choice for patients ≥ 60 years old with PS>2: Low dose Cytarabine till progression or unacceptable toxicity.[9]

Evaluation of treatment response was assessed according to the 2003 revised criteria.[10]

Control group:

The study included 15 healthy subjects, 5 males and 10 females with ages ranging from 23-72 -year- old as a control group for complete blood picture, biochemical tests, and LDH level.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Ethical approval

The Mansoura University IRB approved the present work (R.22.12.1996) and informed consent was obtained from patients.

This article does not contain any studies with animals performed by any of the authors.

Statistical analysis

Data were analyzed by IBM-SPSS software (Version 20. Armonk, NY). Quantitative data is Mean ± SD (normally distributed) and is compared by independent-samples t-test. Qualitative data is N (%) and is compared by the Fisher-Freeman-Halton test. Time-to-event (survival distribution) was assessed by Kaplan–Meier method, log-rank test, and Cox proportional-hazards regression. Results are considered statistically significant if the p-value <0.05.

Hematology parameters:

Patients' hematological and biochemical characteristics are shown in Table (1). LDH level ranged from 363 to 3761 U/L with a mean value of 1156 ± 744.49 U/L in the studied patients, while it was 203±42.49 U/L in the control group (Table 2). Out of the 52 patients, 13.46 % of patients (7 of 52) were classified as favorable risk, 67.3% (35 patients) were intermediate risk and 19.2% (10 patients) were an adverse risk. Thirty-one patients (59.6%) out of the total 52 studied patients achieved complete remission (CR), 14 patients (26.9%) were refractory to treatment and 7 patients (13.5%) succumbed to induction death (ID). A complete remission (CR) was observed in 22 patients (71%) with normal LDH (up to 480U/L) compared to 29% in patients with high LDH (>480 U/L) (***P value*** = 0.003) (Table 3).

Results

Table (1): Patients' demographic and laboratory parameters at the time of diagnosis.

Parameter	*Minimum- Maximum*	*Mean ± SD*
Age (yrs)	18-89	46.8±17.88
WBC (x10^9/L)	3.1-435 x10^9/L	67.65±83.19
Hemoglobin (g/dl)	5.1-11.1	7.67±1.5
Platelets count (x10^9/L)	7.7-192 x10^9/L	50.38±43.68
ANC (x10^9/L)	0.05-226 x10^9/L	14.08±39.45
Peripheral blood myeloblast %	9-98%	61.88± 24.92
Bone marrow blast %	20-96%	72.25±20.39
Serum Albumin (g/dl)	2.0-5.4	3.8 ± 0.7
Total bilirubin (mg/dl)	0.1 to 1.3	0.5 ± 0.27
Serum creatinine (mg/dl)	0.5 to 5.0	1.13 ± 0.7
Serum uric acid (mg/dl)	1.9 to 22.7	6.7± 4.0
LDH (U/L)	363 to 3761	1156 ± 744.49

Table (2): LDH level in the studied AML patients and control group.

LDH (U/L) ***Mean ± SD***	**AML patients**	**Control group**	***P* value**
	1156 ± 744.49	203±42.49	**<0.001**

Notes: Data is mean ± SD. The test of significance is an independent-samples t-test.

Table (3): Effect of LDH level on treatment outcome of AML patients.

LDH level	**CR**	**RD**	**ID**	**Total**	**p-value**
Normal (Up to 480U/L)	22 (71%)	3 (21.4%)	2 (28.6%)	27 (51.9%)	**0.003**
High (>480 U/L)	9 (29%)	11 (78.6%)	5 (71.4%)	25 (48.1%)	

Notes: Data is N (%). The test of significance is the Fisher-Freeman-Halton test.

Survival analysis:

Analysis of 3-year- Overall Survival (OS) revealed statistically significant higher OS in patients with normal level LDH compared to those with high LDH (***P value*** = 0.001), likewise Disease Free Survival (DFS) showed that patients with normal level LDH have mean DFS 19 months versus 7.6 months for those with high LDH (***P value*** = 0.0003) (Table 4, Figure1&2).

Table (4): 3-year- overall survival analysis according to LDH.

3-year-Overall Survival (OS)				
LDH level	***No. of patients***	***Alive cases***	***Mean OS***	***Log-rank test***
Normal	27	8 cases	16.9 months	***P value*** = 0.001
High	25	1 case	7 months	
3-year- Disease-Free Survival (DFS)				
LDH level	***No. of patients***		***Mean DFS***	***Log-rank test***
Normal	27		19 months	***P value*** = 0.0003
High	25		7.6 months	

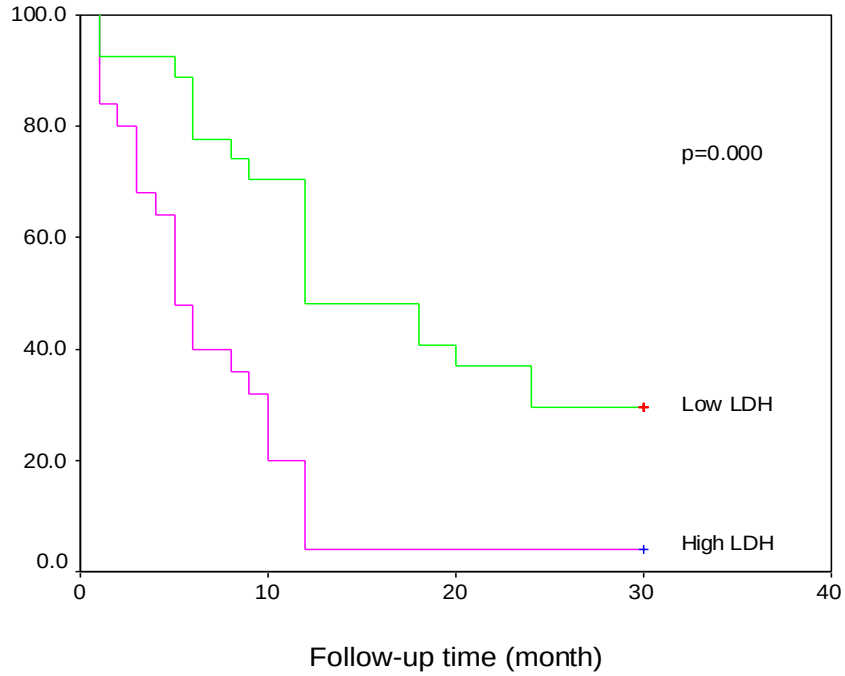

Figure 1: Kaplan-Meier curve showing 3-year overall survival (OS) for AML patients in reference to normal and high LDH levels.

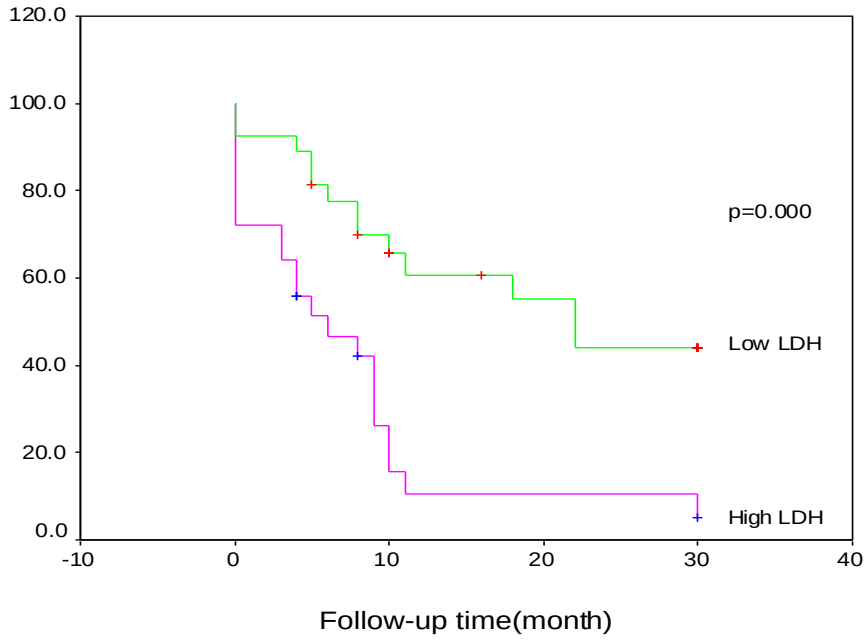

Figure 2: Kaplan-Meier curve showing Disease Free Survival (DFS) at 3 years according to LDH level.

Univariate analysis regarding the different variables and overall survival: Age ≥ 60 years, high LDH level, WBC at presentation, and adverse genetics were significant with P values: 0.03, 0.000, 0.01, 0.001, and 0.000 respectively, while in Multivariate analysis, the age, LDH level, and adverse risk genetics are the

only independent predictive factors with P values = 0.006, 0.000 and 0.000 respectively (Table 5).

Univariate analysis for Disease-free survival (DFS), high LDH level, total leucocytic count >100,000 at presentation, and adverse genetics are significant predictive factors with p value= 0.005, 0.008 and 0.008 respectively, while on Multivariate analysis adverse genetics was the independent predictive factor with P value =0.04 (Table 6).

Table 5: *Cox Regression of Overall Survival (OS) analysis.*

Univariate Analysis			
Predictive Variables		***HR(95% CI)***	***P value***
Age (yrs)		2.15(1.07-4.28)	0.03
LDH (U/L)		3.17(1.64-5.86)	0.000
WBC	20-100X10^9/L	2.7(1.95-15.91)	0.01
	>100X10^9/L	5.57(1.95-15.91)	0.001
Adverse cytogenetics		4.46(2.31-8.6)	0.000
Favorable cytogenetics		0.7(0.35-1.41)	0.32
Multivariate Analysis			
Predictive Variables		***HR (95% CI)***	***P value***
Age (yrs)		2.96(1.35-6.46)	0.006
LDH (U/L)		3.97(1.87-8.43)	0.000
WBC	20-100X10^9/L	1.33(0.55-3.20)	0.51
	>100X10^9/L	0.93(0.26-3.26)	0.91
Adverse cytogenetics		5.72(2.55-19-83)	0.000

Table 6: ***Cox Regression of Disease-Free Survival (DFS) analysis.***

Univariate Analysis			
Predictive Variables		***HR (95% CI)***	***P value***
Age (yrs)		1.14(0.48-4.19)	0.51
LDH (U/L)		3.17(1.41-7.11)	0.005
WBC	20-100X10^9/L	1.7(0.03-4.54)	0.29
	>100X10^9/L	4.45(1.47-13.46)	0.008
Adverse genetics		13.42(1.94-92.53)	0.008
Favorable genetics		0.47(0.17-1.27)	0.13
Multivariate Analysis			
Predictive variables		***HR (95% CI)***	***P value***
Age		1.69(0.45-6.35)	0.43
LDH		2.74(0.96-7.82)	0.06
WBC	20-100X10^9/L	1.33(0.47-3.78)	0.51
	>100X10^9/L	1.49(0.25-8.80)	0.56
Adverse genetics		5.72(2.55-19-83)	0.04

Discussion

Lactate dehydrogenase is an enzyme present in various body tissues. Elevated blood levels of LDH have been detected in several diseases including infections, inflammations, and malignancies. LDH is a non-specific tissue turnover marker, a normal metabolic process. Various neoplasms can lead to elevations in LDH levels or one of its isozymes.[11]

Several mechanisms have been postulated about the association between elevated LDH and its poor prognostic association in acute leukemias as acidification of the extracellular water space by lactate leads to activation of the tumor. Other proposed theories included low PH microenvironment may increase cancer cell resistance to hypoxia-induced apoptosis by protecting mitochondria from oxidative stress and overexpression of LDH reflects an upregulated hypoxia-induced Factor (HIF) pathway, which regulates glycolysis, angiogenesis, resistance to programmed cell death, and metastasis. [12-14]

A study conducted on 18 newly diagnosed AML patients with a mean age of 57.7 years showed that Log LDH significantly correlated to AML bone marrow vascularity (p = 0.007) and suggest that serum LDH can be used as a simple parameter for predicting angiogenesis in AML bone marrow which is related to poor prognosis in these patients and they also suggested that AML patients with high LDH levels could be candidates for novel anti-angiogenesis therapy.[15]

A retrospective study was conducted to evaluate the outcome of elderly AML, all treated with intensified chemotherapy, and to identify the factors predictive of complete remission (CR) and survival showed in their univariate analysis, cytogenetics, high LDH level, TLC, and performance status (PS) were significant adverse prognostic factors for OS and event-free survival (EFS). Age was not a significant prognostic factor for either CR or survival. Furthermore, in contrast to other studies, LDH levels did not show poor prognostic significance in the multivariate analysis.[16]

A previous Egyptian study assessed the prognostic value of LDH in 17 and 33 patients with ALL and AML, respectively, in addition to 20 healthy control individuals. LDH level was significantly elevated in acute leukemia patients compared to the control group, and it was elevated significantly more in ALL than in AML ($p<0.001$). Kaplan–Meier analysis showed that patients with higher LDH activity levels >350 IU/L had significantly shorter OS and DFS in the 2 studied acute leukemia groups.[17]

In agreement with our study, ***Shireen et al., (2022)*** showed that the CR rate was significantly lower in AML patients with elevated LDH ($P= 0.018$), high WBC ($P= 0.042$), and patients with advanced age ($P =0.048$), and more aggressive treatment is necessary for patients with these risk factors.[18]

Recently ***Moualla Y*** and his colleagues illustrated an inverse relationship between LDH levels and the OS duration, and therefore they concluded that LDH serum is an independent predictive marker for AML patients.[19]

Summary and conclusion:

LDH is a potent biochemical marker associated with lower response rates and poor survival in AML patients. Further studies are required to incorporate LDH in the risk stratification of the disease.

List of abbreviations

AML: Acute Myeloid Leukemia.
ALL: Acute Lymphoblastic Leukemia.
ANC: Absolute Neutrophil Count.
APL: Acute Promyelocytic Leukemia.
CR: Complete Remission.
DFD: Disease Free Survival.
ID: Induction Death.
LDH: Lactate Dehydrogenase.
MDR: minimal (measurable) residual disease.
MM: Multiple Myeloma.
NHL: Non-Hodgkins'Lymphoma.
OS: Overall Survival.
PS: Performance Status.
RD: Refractory Disease.
TLC: Total leucocytic count.

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