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The Effect of Elevated Serum Lactate Dehydrogenase Level on Survival of Newly Diagnosed Acute Myeloid Leukemia (AML) Patients

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ABSTRACT

Background: Acute myeloid leukemia (AML) is a complex clonal malignancy that is impacted by both environmental variables and chromosomal anomalies. High tumour load and a poor prognosis are pathologically indicated by elevated white blood cell (WBC) count and lactate dehydrogenase (LDH) values.

Objective: This study aimed to assess the clinical significance and prognostic value of serum LDH levels in AML patients.

Patients and methods: At the Hematology Unit, Oncology Center, Mansoura University, we performed a retrospective analysis with 40 AML patients (19 males and 21 females) with a mean age of 44.3 ± 15.1 years. Hemoglobin was 8.5 g/dL, platelet count was 32.2 x 10^9/L, and median WBC was 31.5 x 10^9/L. Median serum LDH was 731.5 IU/L. The eligible patients had intermediate dose Cytarabine consolidation after receiving standard-intensity induction chemotherapy.

Results: AML patients exhibited significantly higher LDH levels compared to healthy controls (215 IU/L; range 107-330) (P<0.001). Higher LDH levels correlated positively with WBC count and were notably associated with age over 60 and WBC > 50×10^9/L (P < 0.05). Patients whose LDH was higher than the median had an OS of two months, which was significantly shorter (range 1-6 months) versus 6 months (range 1-9 months) for those below the median (P=0.035). Univariable and multivariable analyses confirmed elevated LDH as a poor prognostic indicator for OS (P=0.036; HR=1.007, 95% CI, 1.005-1.011).

Conclusion: High serum LDH level at diagnosis is an inexpensive, predictive marker of poor survival outcomes in patients with recently diagnosed AML, underscoring its importance in prognostic assessments.

Keywords: AML; LDH; OS.

INTRODUCTION

Acute myeloid leukemia (AML) is a malignant clonal illness marked by myeloid blast growth and proliferation, which prevents cells from differentiating into mature types of cells. This condition occurs in the setting of ineffective hematopoiesis and can lead to the development of life-threatening cytopenia and transfusion dependency. AML is a disease that can strike anyone at any age; however it is more frequently diagnosed in older people, with a median age of 68. Furthermore, patients older than 55 account for more than two thirds of AML diagnosis [1].

The accurate evaluationn of prognosis in AML is a result of a meticulous and comprehensive evaluation process involving several factors. AML prognosis estimation involves an integrated assessment of both clinical and biological factors. These clinical variables include the traits of the patient as well as any illness symptoms at the time of presentation. Evaluation is also given to biological issues, such as gene mutations and cytogenetic anomalies. Additionally, measurable residual disease (MRD) at several pre-defined time intervals during therapy is taken into account when prognostically stratifying AML patients. This tiered evaluation technique ensures appropriate patient classification according to their prognosis [2].

Recent research has suggested that genomic instability accounts for 75% of the variations in AML prognosis. The remaining 25% of variations may be influenced by clinical, treatment, and demographic variables. As such, it is imperative to conduct a comprehensive examination of all these factors to accurately determine the prognosis of AML patients [3].

An essential component of the anaerobic metabolic cycle, lactate dehydrogenase (LDH) is an oxidoreductases class enzyme. Its main job is to make it easier for lactate to be converted reversibly to pyruvate while reducing NAD+ to NADH and vice versa. It functions as a crucial gatekeeper for DNA metabolism and gluconeogenesis and is present in all tissues of a wide range of organisms, including plants and mammals [4, 5].

The role of LDH is altered in cancerous cells in contrast to healthy cells. Even when oxygen is present, cancer cells use LDH to improve aerobic metabolism, which includes lactate generation, ATP synthesis, and glycolysis. The Warburg effect is the name given to this phenomenon in general. Because of their changed metabolism, cancer cells can transition to an anaerobic metabolic phenotype, which helps them proliferate by preventing oxidative stress from being produced by the Electron Transport Chain (ETC). Moreover, cancer cells can produce lipids and nucleic acid using the metabolic

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intermediates of the tricarboxylic acid cycle, which are produced by glucose and pyruvate. This process facilitates the fast growth of cancer cells [6, 7].

Numerous medical conditions have been linked to an elevation in serum LDH levels. These ailments include anaemia, pancreatitis, cancer, muscular damage, trauma, heart attacks, liver and kidney disorders, and certain infectious infections. LDH is a well-established biomarker that holds significant prognostic value in various medical disorders [8-12]. But, it is prognostic function in AML remains inadequately defined and requires further investigations. The present study aimed to determine serum LDH level prognostic value and clinical importance in patients with AML.

PATIENTS AND METHODS

This is retrospective case-control research that involved 40 adult patients who were diagnosed with de-novo non-APL acute myeloid leukemia. The research was conducted at the Cancer Canter's Haematology Unit, Mansoura University during the period from January 2017 to December 2018.

Inclusion criteria: Patients who were diagnosed with AML and were at least 18 years old.

Exclusion criteria: Patients who were diagnosed with acute promyelocytic leukaemia (APL) or therapy-related AML.

The study consisted of a group of 40 participants, comprising 19 males (47.5%) and 21 (52.5%) females between the ages of 18 and 65 years old. The criteria for diagnosis were established using both FAB and WHO guidelines [13, 14]. 8 patients were M1, 10 were M2, 13 were M4, 7 were M5, and 2 were M6. Elevated levels of serum LDH, as determined by a Modular autoanalyzer (P-800, ROCHE) were categorised as high when they were above 480 U/L.

Performance status (PS) and age were considered as two crucial criteria in establishing the therapy plan for each patient.

1. Patients below 60 years of age or those over 60 years with PS ≤ 2 were subjected to the standard-of-care '7+3' induction chemotherapy protocol. The patients who achieved complete remission (CR) and had favourable/intermediate-risk karyotyping underwent consolidation intermediate-dose Cytarabine chemotherapy. On the contrary, patients classified as being at unfavourable risk were provided with the option of allogenic hematopoietic stem cell transplantation (HSCT), whereas salvage therapy was administered to primary resistant and progressing cases [14, 15].
2. Patients aged 60 years or above with PS > 2 were treated with Low-dose Cytarabine until progression or unacceptable toxicity [14, 15].

Control group: The control group for the study comprised 10 healthy participants, consisting of 4 females and 6 males, aged between 21 and 59 years. Their ages were recorded in the whole blood picture, biochemical profile, and LDH level.

Ethical considerations: The study was done after being accepted by the Research Ethics Committee, Mansoura University (approval number: R.24.04.2570). All patients provided written informed consents prior to their enrolment. The participants' decision to partake in the research and contribute data was clearly delineated in the consent form, so guaranteeing the preservation of their privacy and confidentiality. Regarding research involving human subjects, this investigation was conducted in adherence to The Code of Ethics of the World Medical Association (Declaration of Helsinki).

Statistical analysis

The data was evaluated utilizing IBM-SPSS programme (Version 20. Armonk, NY). Mann-Whitney U test was utilized to compare quantitative data, which was presented as Median (Range). To compare qualitative data, N (%) values were utilized in conjunction with Fisher-Freeman-Halton test. The time-to-event (survival distribution) was analysed utilizing Cox proportional-hazards regression, log-rank test, and Kaplan–Meier technique. Statistical significance was deemed to have been attained when p-value ≤ 0.05.

RESULTS

The following study provided an overview of key metrics related to AML cases, including peripheral blood counts, bone marrow examination results, liver and kidney functions testing, karyotype analysis, and risk assessment. Bone marrow examination at diagnosis revealed that 25% were normocellular, 12.5% were hypocellular, and 62.5% were hypercellular BM. Median blasts in the bone marrow were 77.5%. Median LDH was 731.5 IU/L ranged from 188-6292 IU/L, while it was 215 IU/L ranged from 107-330 in the control group. Karyotype analysis identified that 77.5% had normal karyotype, while 22.5% had abnormal karyotype. Of those with abnormal karyotype, One instance exhibited t(8;21), 1 case 11q23, 4 cases inv16, 1 case t(6;9), 1 case monosomy 7, 1 case trisomy 8, and 1 case del1 (p33). Notably, one case was classified as FAB M4 and possessing both inv16 and t(6;9). The risk assessment was conducted for all cases, with 10% classified as favourable risk, 82.5% as intermediate risk, and 7.5% as poor risk (Table 1).

Table (1): Demographic and laboratory data of the patients at time of diagnosis

Parameters	**AML (No =40)**	
Laboratory characteristics	**Median**	**Minimum-Maximum**
TLC (x10^9/L)	31.5	1.7-300
Hemoglobin (g/dL)	8.5	2.8-14.2
Platelets count (x10^9/L)	32.2	7-320
ANC (x10^9/L)	1.4	0-90.5
Peripheral blood blasts (%)	66	23-100
Bone Marrow (BM) Blast (%)	77.5	20-97
ALT (U/L)	23.5	10-234
AST (U/L)	30	12-277
Bilirubin (mg/dL)	0.7	0.1-3
Albumin (g/dL)	3.3	2-4.6
Creatinine (mg/dL)	0.9	0.6-2.5
Uric acid (mg/dL)	5	1.4-17.2
LDH (U/L)	731.5	188-6292
ESR 1st hour (mm/h)	82.5	10-150
	No	**%**
• **FAB subtypes**		
M1	8	20
M2	10	25
M4	13	32.5
M5	7	17.5
M6	2	5
• **Bone Marrow cellularity**		
Hypocellular	5	12.5
Normocellular	10	25
Hypercellular	25	62.5
• **Cytogenetics**		
t(8;21)	1	2.5
11q23	1	2.5
Inv 16	4	10
t(6;9)	1	2.5
Monosomy 7	1	2.5
Trisomy 8	1	2.5
del 1 (P33)	1	2.5
Normal karyotype	31	77.5
• **Risk stratification**		
Favorable	4	10
Intermediate	33	82.5
Poor	3	7.5

AML: Acute Myeloid Leukemia, TLC: Total Leukocyte Count, ANC: Absolute Neutrophil Count, BM: Bone Marrow, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, LDH: Lactate Dehydrogenase, ESR: Erythrocyte Sedimentation Rate, FAB: French-American-British.

Of the cases studied, 24 achieved complete remission (60%), while 16 failed to achieve complete remission (40%). Induction therapy was associated with 13 fatalities (32.5 %) and three refractory patients (7.5 %). A total of 29 patients (72.5 %) perished during the research period, whilst 11 survivors remained (27.5 %). A total of 24 % of patients achieved a one-year survival, with a median OS of five months. 39.3 % of patients achieved one year of disease-free survival (DFS), with a median DFS of eight months (Table 2).

Table (2): Response rate and Survival in AML patients

Response rate		N	%
Complete remission (CR)		24	60
Failure of CR	**Induction death**	13	32.5
	Refractory disease	3	7.5
Fate			
Alive		11	27.5
Dead		29	72.5
1 year Cumulative OS (%)			24
Median OS (95 % CI) (months)		5	(1.9-8)
1 year Cumulative DFS (%)			39.3
Median OS (95 % CI) (months)		8	(3.3-12.7)

AML: Acute Myeloid Leukemia, CR: Complete Remission, OS: Overall Survival, CI: Confidence Interval, DFS: Disease-Free Survival.

Based on the findings, the levels of LDH were significantly elevated in the group with AML in comparison to the control group ($p<0.001$), as evidenced in table (3) & figure (1).

Table (3): Comparison of LDH level between AML and control groups

	Control (No=10)		AML (No = 40)		*P value*
	Median	**Minimum-Maximum**	**Median**	**Minimum-Maximum**	
LDH Level	215	107-330	731.5	188-6292	<0.001

AML: Acute Myeloid Leukemia, LDH: lactate dehydrogenase.

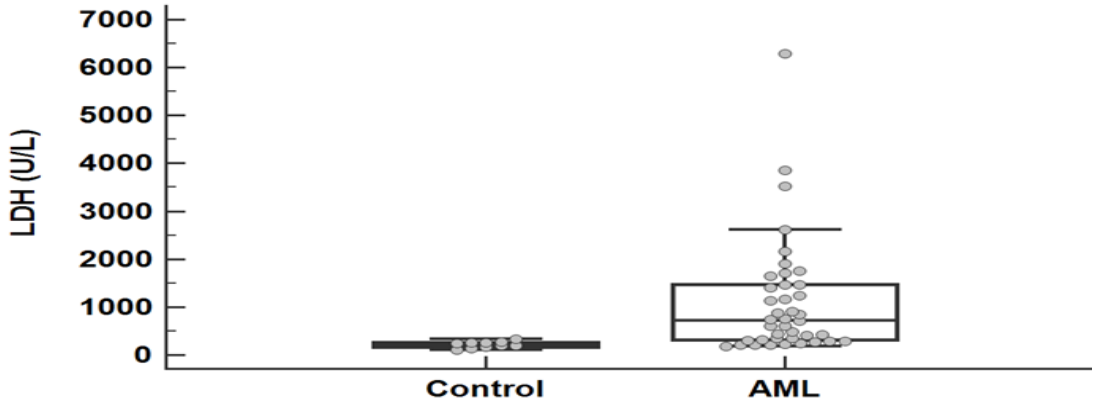

Figure (1): LDH level among AML and control groups.

The study findings indicated a statistically significant positive correlation between LDH and total leukocyte count (TLC). Conversely, no significant associations were seen between LDH levels and the remaining factors such as age, hemoglobin level (Hb), platelets count, absolute neutrophil count (ANC), blast cells in peripheral blood (PB), blast cells in bone marrow (BM), and uric acid (Table 4).

Table (4): Correlation between LDH level and other studied parameters

	LDH level	
	rs	***P value***
Age	0.258	0.108
TLC	0.362	0.022
Hemoglobin	0.081	0.621
Platelets count	-0.069	0.670
Absolute neutrophil count (ANC)	0.305	0.056
Peripheral Blood Blast	0.133	0.412
BM blast	-0.059	0.717
Uric Acid	0.045	0.784

rs, Spearman's correlation coefficient.

The study findings suggested that there was a significant connection between higher LDH levels and advanced age (> 60) as well as elevated TLC levels (>50x10^9/L). However, the analysis revealed no significant differences in LDH levels based on factors such as FAB, karyotyping, risk categories, response rate, and mortality as shown in table (5).

Table (5): Comparison of LDH level between different studied subgroups

		LDH level			*p*
		Median	Minimum- Maximum		
Age	**≤60 years**	478	188	3860	0.008
	>60 years	1645	412	6292	
WBC	**≤50x10^9/L**	417	188	6292	0.003
	>50 x10^9/L	1465	246	3860	
FAB subtype	**M1**	363	206	6292	0.144
	M2	1033	215	3526	
	M4	853	290	2164	
	M5	1235	220	3860	
	M6	250	188	311	
Karyotyping	**Normal Karyotyping**	715	188	6292	0.884
	Abnormal Karyotyping	907	275	1470	
Risk categories	**Favorable**	693	290	1134	0.451
	Intermediate	601	188	6292	
	Poor	1235	1158	1470	
Response	**CR**	732	188	2615	0.825
	Failure of CR	676	215	6292	
Status	**Alive**	599	275	1715	0.555
	Dead	750	188	6292	

LDH: Lactate Dehydrogenase, WBC: White Blood Cell, FAB: French-American-British, CR: Complete Remission.

The present study revealed that LDH levels exceeding the median subgroup were significantly linked to reduced OS when contrasted with LDH levels below the median subgroup. Conversely, LDH levels surpassing the median subgroup were non-significantly linked to a decreased DFS when contrasted with LDH levels below the median subgroup (Table 6 & figure 2).

Table (6): Comparison of survival times between below and above median LDH subgroups in all studied AML cases

		LDH below median N=20	LDH above median N=20	*P* value
OS	**1-year Cumulative OS (%)**	41.7	6.7	0.035
	Median OS (95 % CI) (months)	6 (1-9)	2 (1-6)	
DFS	**1-year Cumulative DFS (%)**	46.2	31.3	0.493
	Median DFS (95 % CI) (months)	9 (4-9)	5 (4-9)	

OS: Overall Survival; DFS: Disease Free Survival; CI: Confidence Interval, LDH: Lactate Dehydrogenase.

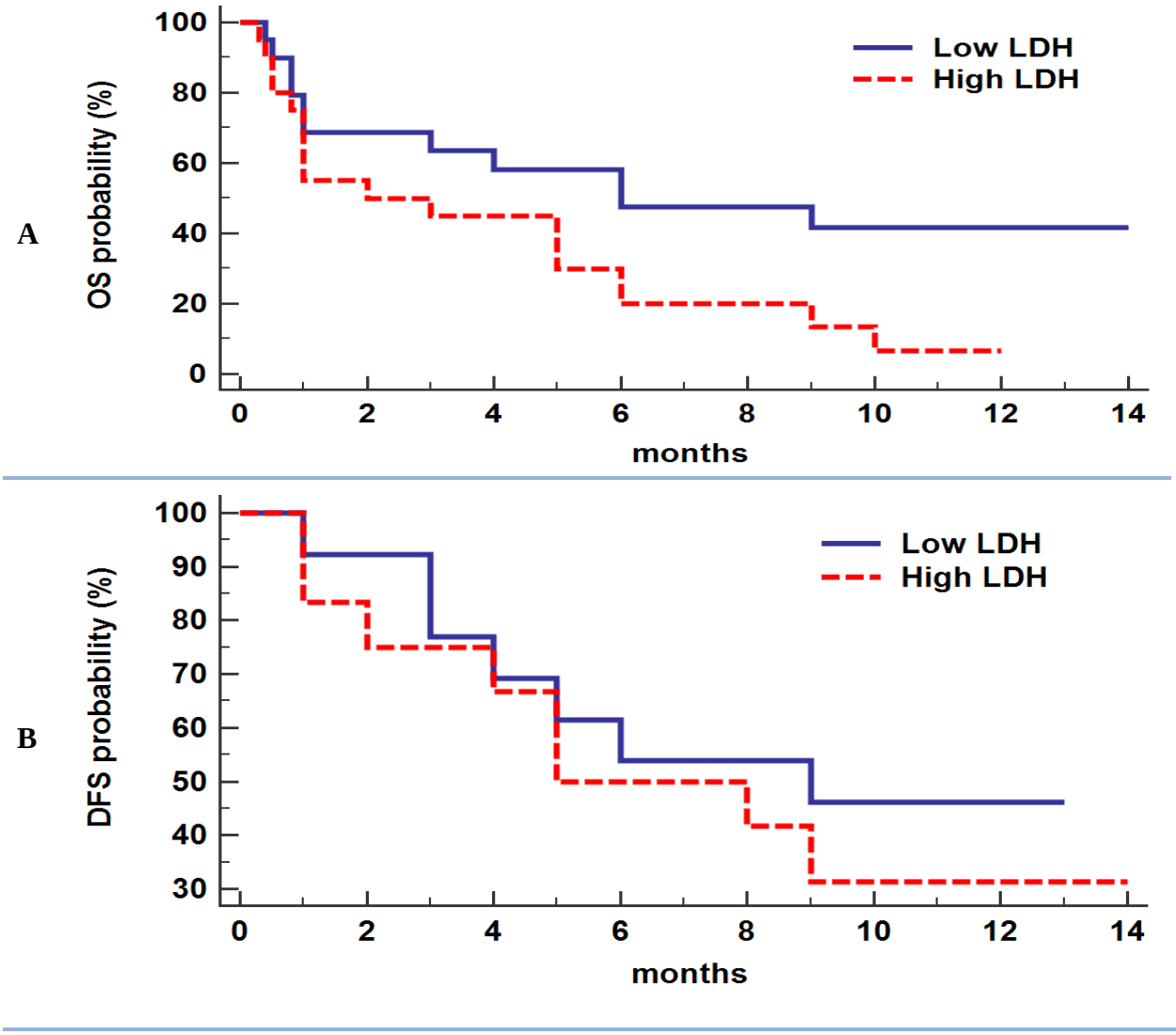

Figure (2): Survival times. (A) OS, (B) DFS according to LDH level among AML cases.

Cox regression analysis was executed to predict OS of patients with AML based on covariates such as age, laboratory results, karyotyping, and LDH levels. Univariable analysis revealed that high TLC and LDH levels were connected to shorter OS, however, the multivariable analysis specifically singled out LDH as a key factor contributing to poor prognosis among AML patients in terms of shorter OS (Table 7).

Table (7): Cox regression analysis for prediction of OS of studied AML cases

	OS					
	Univariable			Multivariable		
	p	HR	95% CI	P value	HR	95% CI
Age	0.920	1.001	0.976-1.027			
TLC	0.041	1.006	1.002-1.011	0.318	1.003	0.997-1.010
ANC	0.928	0.999	0.981-1.018			
Peripheral blasts	0.993	1.002	0.985-1.015			
BM Blast	0.280	1.010	0.992-1.029			
Abnormal Karyotyping	0.784	0.888	0.378-2.082			
LDH	0.018	1.012	1.005-1.071	0.036	1.007	1.001-1.011

OS: Overall Survival, HR: Hazard Ratio, CI: Confidence Interval, TLC:Total Leukocyte Count, ANC: Absolute Neutrophil Count, BM:Bone Marrow, LDH: Lactate Dehydrogenase.

A Cox regression analysis was conducted to predict DFS among patients with AML. The analysis utilized age, laboratory results, karyotyping, and LDH levels as covariates. In this study, none of the factors were identified as a poor prognostic factor for predicting shorter DFS in AML patients (Table 8).

Table (8): Cox regression analysis for prediction of DFS of studied AML cases

	DFS		
	P value	**HR**	**95% CI**
Age	0.962	1.001	0.964-1.039
TLC	0.188	1.006	0.997-1.015
ANC	0.806	1.003	0.982-1.024
Peripheral blood blasts	0.812	1.002	0.982-1.023
BM Blast	0.305	1.014	0.987-1.041
Abnormal Karyotyping	0.687	1.267	0.402-3.995
LDH	0.364	1.023	1.010-1.099

TLC:Total Leukocyte Count, ANC:Absolute Neutrophil Count, BM: Bone Marrow, LDH:Lactate Dehydrogenase, DFS: Disease Free Survival.

DISCUSSION

Human LDH, a glycolytic enzyme that facilitates the oxidation of NADH to NAD+ and the conversion of pyruvate to lactate, is essential for invasive tumour cells to promote glycolysis. [16]. In reaction to cellular injury, LDH is secreted, resulting in an elevation of its baseline concentration in the extracellular environment, circulation, and other body fluids. As a result, LDH has been suggested for use as a broad indicator of cell/tissue damage or to assist in the identification of injured cell or tissue types [17]. Extensive research has been conducted on the predictive importance of serum LDH in numerous solid tumours and haematological malignancies. However, its precise impact on the survival and response rate of acute myeloid leukaemia patients is unknown. The development and progression of AML are attributed to pathogenic genomic aberrations, which confer an advantage to clones in proliferating and possessing self-renewing characteristics. The genomics of AML play a critical role in determining the clinical response, risk categorization, and staging of conventional therapeutics [18].Therefore, a comprehensive understanding of the clinical significance and prognostic value of various biomarkers, including LDH levels, is essential to contribute toward the development of an improved prognostic model for AML.

The present study aimed to determine the clinical relevance of serum LDH levels in individuals diagnosed with AML, in order to establish a more effective model for predicting patient outcomes and guiding treatment decisions. In support of our research, a study was conducted on 265 patients including 50 acute lymphoblastic leukemia (ALL) and 30 AML. The LDH levels of patients were significantly elevated in contrast to control group samples. It was also determined that patients exhibiting elevated levels of LDH had a heightened susceptibility to early relapse of their ailment. These results support the notion that serum LDH serves as a significant biomarker in both the diagnosis and prognosis of haematological malignancies [19].

An earlier research investigation carried out in Egypt sought to assess the prognostic significance of LDH in individuals diagnosed with acute lymphoblastic leukaemia (ALL) and AML. 33 AML patients, 17 ALL patients, and 20 healthy controls participated in the study. LDH levels were significantly elevated in patients diagnosed with acute leukaemia relative to the control group, according to the findings of the study. Furthermore, ALL patients had significantly elevated LDH levels compared to AML patients ($p < 0.001$). Further analysis using the Kaplan-Meier method demonstrated that patients with LDH activity levels greater than 350 IU/L had significantly shorter OS and DFS in both studied acute leukemia groups [20].

The research conducted by **DiNardo and co-authors** [21] on 1652 untreated AML and MDS found that elevated LDH levels are correlated with inferior survival outcomes. Through the use of multivariate analysis, the study identified a set of factors that were predictive of poor prognosis in cases of proliferative diseases. The results showed that elevated LDH levels, along with other factors such as leucocytosis (WBC $\geq 25 \times 10^9$ /L), advanced age, poor risk cytogenetics, and therapy-related disease were associated with poor survival outcomes. The hazard ratio for elevated LDH was calculated to be 1.24, with a statistically significant p-value of 0.0015.

Our study aligns with the research conducted by **Ma *et al.*** [22] revealed that LDH levels exceeding 500 IU/L were recognised as a poor prognostic factor for OS in univariable analysis. However, the multivariable Cox regression analysis did not support this finding. Recent research by **Memeh *et al.*** [23] showed that the prognostic value of age, gender, conventional karyotyping (CK)

findings, LDH concentration, WBC count, and bone marrow blast percentage at diagnosis on OS was determined in a cohort of 98 patients. The results showed that patients with LDH levels greater than 450 IU/L, WBC counts exceeding 50 X 10^9/L, BM blast% greater than 50%, and AML-M0 had a significantly shorter OS compared to other groups.

CONCLUSION

The evaluation of serum lactate dehydrogenase (LDH) levels serves as a valuable and easily accessible prognostic factor for patients diagnosed with AML. High serum LDH levels, in conjunction with other factors, may potentially indicate a negative prognosis for survival outcomes. Further research recruiting a large population of patients is warranted to validate the effectiveness of conventional clinical and laboratory features as reliable predictors of disease outcomes and to assess their significance at the time of diagnosis.

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