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Lactate Dehydrogenase as a Prognostic Biomarker in Severe Sepsis in Intensive Care Unit

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ABSTRACT

Sepsis ranks as one of the principal death-causing conditions in present-day society. The medical community identifies lactate dehydrogenase (LDH) as a potential tool to assess sepsis severity. **Objectives:** To assess how LDH blood concentrations relate to severe sepsis progression. **Methods:** A retrospective examination took place within the intensive care unit (ICU) at Shahida Islam Medical Complex. Data of patients of both genders, aged between 18-75 years, and who were admitted to the intensive care unit with sepsis. Biochemical data, including necessary laboratory investigations, infection areas, and comorbidities, were documented. The study subjects were analyzed concerning LDH ≤230 U/L (n=41) and LDH >230 U/L (n=55). Univariate Cox regression analysis for 21-day mortality was also carried out. **Results:** The records of 96 patients as per inclusion and exclusion criteria were considered for this study. There were 61 (63.5%) patients who were male. The overall mean age was 54.2 ± 12.6 years. LDH ≥230 U/L was found to have a significant association with findings that included significantly higher CRP (p=0.0001) and LDH levels (p=0.0001) in patients with LDH ≥230 U/L compared to LDH <230 U/L. A significant association high SOFA score (p=0.002), and APACHE-II score (p=0.001) was found with LDH≥230 U/L. Strong associations of the biochemical levels, which included LDH levels (HR=1.006, p=0.010), lactate levels (HR=1.498, p=0.002), and creatinine levels (HR=1.483, p=0.005) were seen with mortality. **Conclusions:** It was concluded that elevated LDH levels were associated with increased disease severity and adverse clinical outcomes, including higher mortality rates, in severe sepsis patients.

INTRODUCTION

The human body develops sepsis when it responds poorly to infections [1]. The medical condition displays complex inflammatory mechanisms coupled with immune-organism dysfunction that produces declining organ functions [2]. Sepsis remains the world's top contributor to mortality and among the United States population sepsis causes death in 57 male per 100,000 persons alongside 45.1 female per 100,000 persons [3]. The worldwide medical impression of the disease is concerning since medical records indicate 50 million annual cases. Sepsis became responsible for 11 million fatalities in 2020 thus representing 19.7% of total global fatalities [4]. Sepsis prevalence remains poorly documented in Pakistan though its high rates of infectious diseases indicate a large impact which is made worse by the scarcity of both diagnostic tools and advanced critical care resources. Sepsis prevalence shows differences based on three key elements: socio-economic status as well as healthcare system structure and underlying health conditions incidence [5]. Research evidence indicates that bacterial infections lead to sepsis rates between 14.7% in Pakistan [6]. The intensive care unit (ICU) admission prevalence rate of sepsis patients reached 35% according to research conducted at a Karachi tertiary care hospital [7]. The physiological response of sepsis originates from unregulated immunity and metabolic disruptions that

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modify blood glucose metabolism and create elevated serum lactate. Lactate dehydrogenase (LDH) functions as an enzyme to transform both lactate and pyruvate into one another thereby being essential for metabolic reprogramming. Tissue hypoxia frequently emerges during septic shock to increase LDH enzymatic activity that leads to enhanced lactate production and subsequent damage throughout affected organs [8, 9]. The levels of LDH in blood establish connections to severe sepsis and unsatisfactory results in patients. The tools used most commonly for sepsis risk assessment such as Sequential Organ Failure Assessment (SOFA) score and Systemic Inflammatory Response Syndrome (SIRS) criteria assess clinical variables as their primary elements. These tools may not fully account for metabolic abnormalities. Recent evidence suggests that integrating biomarkers like LDH into prognostic models could enhance the accuracy of sepsis severity assessments [10, 11]. This research targets the present understanding deficit about LDH prognostic value for severe sepsis patients across Pakistan. Researchers have emphasized the particular biomarker in this study because it demonstrates both metabolic dysfunction characteristics and shows direct relationships to ICU patient disease severity and treatment results. This research subject was chosen because Pakistan requires region-relevant information and economical biomarkers to improve sepsis treatment management. Sepsis patients benefit from LDH as a reliable diagnostic marker since this tool enables a simple assessment of patient outcomes even when limited diagnostic options exist. This research investigation increases worldwide understanding of sepsis biomarkers while at the same time, addressing essential research gaps leading to better outcomes in low and middle-income countries(LMICs).

This study aims to investigate the relationship between sepsis seriousness and LDH measurements for evidence-based routine clinical practice that would enhance resource-limited patient risk assessment and healthcare management.

METHODS

This retrospective study was carried out at the ICU of Shahida Islam Medical Complex, Lodhran, Pakistan, from October 2023 to April 2024. Approval from the ethical committee of the institution was obtained (Letter number: SIMC/H.R./7337/23). Non-probability, consecutive sampling techniques were used for sample selection. Data were extracted for 119 patients from electronic medical records, the record of 22 patients didn't fit the inclusion criteria. The data analyzed patients of both genders, aged between 18 and 75 years, and who were admitted to the ICU with sepsis. All included patients were diagnosed with sepsis during their ICU stay with complete medical records available for data extraction. Patients with incomplete medical records who died within 24 hours of ICU admission, pregnant, immunocompromised (including but not limited to human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS), malignancy, receiving immunosuppressive therapy) and patients with chronic liver disease were excluded from the study. The SOFA score and APACHE II score were calculated for all patients. Acute physiology and chronic health evaluation (APACHE) II scores (0-71 inclusive) determined sepsis severity risk because they used 12 physiological variables from first ICU admission day measurements (temperature, MAP, heart rate, respiratory rate, PaO2 with A-a gradient if FiO2 ≥0.5 or PaO2 if FiO2 <0.5, pH, sodium, potassium, creatinine, hematocrit, white blood cell count, Glasgow coma score (GCS)) along with age and chronic healthcare conditions. Daily SOFA scores (range 0-24, higher scores indicating higher mortality risk) assessed dysfunction across six systems including respiration (PaO2/FiO2: >400=0, ≤400=1, ≤300 with ventilation=2, ≤200 with ventilation=3, ≤100 with ventilation=4), coagulation (platelets: ≥150=0, <150=1, <100=2, <50=3, <20=4), liver (bilirubin: <1.2=0, 1.2-1.9=1, 2.0-5.9=2, 6.0-11.9=3, >12.0=4), cardiovascular (Mean arterial pressure (MAP)/vasopressors: MAP ≥70=0, MAP <70=1, Dopamine ≤5 or dobutamine=2, Dopamine >5 or epinephrine/norepinephrine ≤0.1=3, Dopamine >15 or epinephrine/norepinephrine >0.1=4), CNS (GCS: 15=0, 13-14=1, 10-12=2, 6-9=3, <6=4), and renal (creatinine/urine: <1.2=0, 1.2-1.9=1, 2.0-3.4=2, 3.5-4.9 or <500 mL/24h=3, >5.0 or <200 mL/24h=4). The study subjects were analyzed concerning LDH ≤230 U/L (n=41) and LDH >230 U/L (n=55) [12]. Survivors and non-survivors were compared concerning their characteristics for this study. Organ dysfunction and the treatment regimens that were employed in the treatment within the ICU were assessed. All the required information was recorded on a specifically predesigned proforma.Data analysis was done using IBM-SPSS Statistics, version 26.0. The quantitative variables like gender, infection area, and history of comorbidities were expressed in the form of frequency and percentage. For the qualitative data, such as age, SOFA score, APACHE II score, and biochemical assessments, means and standard deviations were computed. Comparisons of the groups were made using an independent t-test and a chi-square test with p-values less than 0.05, signifying the importance of the differences observed. To further evaluate LDH about its predictive validity for 21-day mortality, Cox regression was applied.

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RESULTS

The records of 96 patients as per inclusion and exclusion criteria were considered for this study. There were 61 (63.5%) patients who were male. The overall mean age was 54.2 ± 12.6 years. There were 55 (57.3%) patients who had LDH levels ≥ 230 U/L. Male and female contributions for patients with LDH levels < 230 U/L were 26 (63.4%) and 15 (36.6%), respectively. The mean age of the patients with LDH <230 U/L was recorded as 54.1±13.1 years, and for those who had LDH ≥230 U/L, it was 54.4 ± 11.9 years. LDH ≥230 U/L was found to have a significant association with findings that included significantly higher CRP (p=0.0001) and LDH levels (p=0.0001) in patients with LDH ≥230 U/L compared to LDH <230 U/L. A significant association high SOFA score (p=0.002), and APACHE-II score (p=0.001) was found with LDH ≥230 U/L. Infection areas or comorbidities were not found to have any significant association with LDH levels (p>0.05). Most of the abnormal biochemical data revealed a statistically significant association with raised LDH levels (p<0.05) and the details are shown in Table 1.

Table 1: Characteristics of Patient Based on LDH Levels (n=96)

Parameters		LDH Levels		Total (n=96)	p-value
		LDH <230 U/L (n=41)	LDH ≥ 230 U/L (n=55)		
Gender	Male	26 (63.4%)	35 (63.6%)	96	0.982*
	Female	15 (36.6%)	20 (36 .4%)		
Age in Years (mean ± SD)		54.1 ± 13.1	54.4 ±11.9		0.532♦
SOFA Score (mean ± SD)		10.04 ± 1.52	11.25 ± 2.07		0.002♦
APACHE II score (mean±SD)		18.90 ± 5.14	23.01 ± 5.99		0.001♦
Biochemical Data (mean ± SD)	WBC (x10^3/mm^3)	14.86 ± 6.28	16.6 ± 6.98		0.211♦
	CRP (mg/L)	42.01 ± 18.99	56.99 ± 23.01		0.001♦
	D-dimer (mg/L)	1.31 ± 0.81	1.51 ± 1.14		0.341♦
	Serum albumin (g/dL)	29.99 ± 4.60	30.01 ± 5.01		0.984♦
	Serum creatinine (mg/dL)	4.19 ± 1.08	4.79 ± 1.30		0.018♦
	Pa-O_2/Fi-O_2 (mmHg)	339.72 ± 74.02	304.03 ± 76.99		0.025♦
	B-type natriuretic peptide (pg/ml)	424.09 ± 432.14	410.09 ± 351.98		0.025♦
	Serum lactate (mmol/L)	2.41 ± 1.29	3.19 ± 1.79		0.020
	Interleukin-1b (pg/mL)	91.81 ± 18.01	105.01 ± 20.97		0.002♦
Infection Area	Lung	17 (41.5%)	20 (36.5%)		0.612*
	Abdomen	13 (31.7%)	19 (34.5%)		0.770*
	Urinary Tract	2 (4.9%)	6 (10.9%)		0.290*
	Circulation	7 (17.1%)	8 (14.5%)		0.736*
	Cranial Cavity	2 (4.9%)	2 (3.6%)		0.763*
Comorbidities	Hypertension	7 (9.8%)	9 (13.9%)		0.926*
	Arrhythmia	4 (5.6%)	4 (6.2%)		0.663*
	Diabetes	8 (11.2%)	9 (13.9%)		0.689*
	Cerebral Infarction	13 (18.3%)	17 (26.3%)		0.933*
	COPD	6 (8.4%)	5 (7.7%)		0.399*

*Chi-Square Test, ♦Independent t-test

The analysis showed survival in 65 patients (67.7%) with 31 patients (32.3%) experiencing mortality during the study period. ANOVA tests confirmed the APACHE II score (p<0.001), SOFA score (p<0.001), LDH and CRP levels (p<0.001), Pa-O2/Fi-O2 measurements (p<0.001) as well as serum creatinine and interleukin-1 b (p<0.001) values between survivors and non-survivors, as in Table 2.

Table 2: Characteristics of Patient Based on LDH Levels (n=96)

Characteristics	Survived (n=65)	Not-Survived (n=31)	p-value
Age (Years)	61.9 ± 13.0	62.9 ± 13.1	0.699*
SOFA Score	9.78 ± 1.49	12.59 ± 1.31	<0.001*
APACHE II Score	18.97 ± 5.77	26.02 ± 3.59	<0.001*
WBC (x10^3/mm^3)	15.42 ± 6.66	16.91 ± 7.01	0.316*
C-Reactive Protein (mg/L)	51.89 ± 24.24	45.78 ± 21.94	<0.001*
D-Dimer (mg/L)	1.29 ± 1.09	1.41 ± 1.07	0.613*
Pa-O_2/Fi-O_2 (mmHg)	341.21 ± 80.80	290.14 ± 66.34	<0.001*
Serum Albumin (g/dL)	29.81 ± 4.89	30.01 ± 5.02	0.853*
Serum Lactate (mmol/L)	2.04 ± 0.81	4.31 ± 1.51	<0.001*
LDH (U/L)	199.95 ± 107.08	330.41 ± 114.53	<0.001*
Serum Creatinine (mg/dL)	4.02 ± 1.24	5.29 ± 1.03	<0.001*
Interleukin-1b (pg/mL)	93.21 ± 18.01	112.95 ± 21.00	<0.001*
B-type Natriuretic Peptide (pg/ml)	419.09 ± 418.05	394.78 ± 339.51	0.772*

*Independent t-test

Strong associations of the biochemical levels, which included LDH levels (HR=1.006, p=0.010), lactate levels (HR=1.498, p=0.002), and creatinine levels (HR=1.483,

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p=0.005) were seen with mortality. The univariate Cox regression analysis for 21-day mortality concerning age and biochemical evaluations is expressed in Table 3.

Table 3: Univariate Analysis for 21-day Mortality (n=31)

Parameters	Hazard Ratio	Confidence Interval	p-value
Age	1.001	0.980-1.019	0.878
LDH	1.006	1.000-1.005	0.010
White Blood Cells	1.000	0.950-1.040	0.941
C-Reactive Protein	0.016	0.969-1.002	0.002
Interleukin-1b	1.003	0.990-1.020	0.761
Serum Lactate	1.498	1.290-1.800	0.002
Serum Albumin	1.030	0.959-1.200	0.439
Serum Creatinine	1.483	1.130-1.920	0.005
Pa-02/Fi-02	1.001	0.986-1.001	0.083
B-Type Natriuretic Peptide	0.989	0.996-1.002	0.399
D-Dimer Score	1.001	0.969-1.002	0.980

An increased incidence of ARDS (p=0.041), AKI (p=0.040), and septic shock (p=0.013) in patients with LDH ≥230 U/L compared to LDH <230 U/L was observed. A large proportion of patients with LDH ≥230 U/L received ventilation (p=0.050), CRRT (p=0.039), and vasopressors (p=0.007) in contrast to those with LDH <230 U/L. The prevalence of organ dysfunctions, which included acute respiratory distress syndrome (ARDS), Acute kidney injury (AKI), acute heart failure (AHF), acute lung injury (ALI), coagulopathy, and septic shock, along with the treatments offered like ventilation, Continuous renal replacement therapy (CRRT), and vasopressors, about LDH, is demonstrated in Table 4.

Table 4: Prevalence of Organ Dysfunction and Treatment of LDH (n=96)

Parameters		LDH <230 U/L (n=41)	LDH <230 U/L (n=55)	p-value
Organ Dysfunction	ARDS	6 (5.9%)	16 (29.1%)	0.041
	AKI	11 (26.8%)	25 (45.5%)	0.040
	AHF	2 (4.8%)	4 (7.3%)	1.021
	ALI	2 (4.8%)	3 (5.5%)	1.010
	Coagulopathy	8 (19.5%)	7 (12.7%)	0.998
	Septic Shock	13 (31.7%)	30 (54.5%)	0.013
ICU Treatment	Ventilation	4 (9.8%)	13 (23.6%)	0.050
	CRRT	11 (29.3%)	21 (38.2%)	0.039
	Vasopressor	11 (29.3%)	30 (54.5%)	0.007

LDH has a hazard ratio of 1.006 and 95% Confidence Interval=1.000-1.005, Serum Lactate (1.498, 1.297-1.800) and Serum Creatinine (1.483, 1.166-1.902). Multivariate Cox Regression for 21 Day Mortality are shown in Table 5.

Table 5: Multivariate Cox Regression for 21 Day Mortality

Parameters	Hazard Ratio	95% Confidence Interval	p-value
LDH	1.006	1.000-1.005	0.009
CRP	0.016	0.969-1.002	0.002
Serum Lactate	1.498	1.297-1.800	0.001
Serum Creatinine	1.483	1.166-1.902	0.003

DISCUSSION

The study demonstrates that patients who have an LDH level ≥230 U/L show higher values for both APACHE II and SOFA scores than those with lower LDH levels. The blood tests CRP, creatinine and lactate showed clear differences in patients who had higher LDH levels. Medical research by Zhang *et al.*, showed that higher levels of LDH in septic patients increased their chances of dying. In their study OR=1.83, 95% CI (1.68-1.98), p<0.001. The research data matches our results because LDH levels showed a strong connection to death with a p<0.001 value [13, 14]. Research indicates more mortal patients had higher lactate levels and this matches findings from Shetty *et al.*, and Algebaly *et al.*, earlier study. Research shows septic patients who have more advanced blood lactate levels face a greater risk of dying. A blood test showing lactate levels above 4 mmol/L proves a greater chance of dying. They found higher lactate levels led to higher mortality rates and our data back these results [15, 16]. A study by Algebaly confirmed that higher levels of LDH match worse sepsis cases which validates our present study findings [16]. The research links more severe sepsis disease with higher blood creatinine values in patients. The study connects with research published by Jaurila *et al.*, which showed creatinine levels above baseline increase the risk of poor outcomes in septic patients [17]. The results of a study done by Flannery *et al.*, also report similar findings [18]. Higher chances of death and severe health problems are directly associated with higher LDH measures and worsen patient results. The results show LDH serves as a useful sepsis monitoring tool and past research from Deng *et al.*, Jeon *et al.*, and Mohammad *et al.*, confirms these findings [19-21]. In addition to sepsis, LDH shows important changes in severe pneumonia and strokes [22, 23]. The diagnostic significance of LDH in septic assessments drives its important role in choosing the best care approaches for these patients.

CONCLUSIONS

It was concluded that the LDH levels that increase above average levels appeared linked to serious sepsis symptoms and raised the chances of dying. The current research demonstrates that LDH measurements offer helpful medical insights to help doctors evaluate septic patients and tailor their treatment options.

Authors Contribution

Conceptualization: AB
Methodology: AB, MRH
Formal analysis: SB, AZ
Writing review and editing: NN, SK

All authors have read and agreed to the published version of the manuscript

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Conflicts of Interest

All the authors declare no conflict of interest.

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