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The Association of Serum Lactate Dehydrogenase Levels with In-Hospital Mortality due to Pulmonary Embolism

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ABSTRACT

Background: A significant correlation exists between elevated lactate dehydrogenase (LDH) levels and thrombotic events, yet the prognostic value of this biomarker in patients with pulmonary embolism (PE) remains elusive. Finding new biomarkers can help us achieve better risk stratification and treatment strategies to reduce the mortality of PE patients.

Objectives: We aimed to determine the possible association between serum LDH and the in-hospital mortality of PE patients.

Methods: In this cross-sectional study, 217 patients with PE (diagnosed by computed tomography angiography) and a serum LDH level documented within the first 24 hours of admission were included. Our exclusion criteria were hepatic and renal diseases, pregnancy, hemolytic disorders, left ventricular infarction, recent stroke, positive history of active cancer, acute and chronic infections, and reticuloendothelial-related diseases.

Results: The mean age of patients was 63.04 ± 16.81 years; 23 patients (10.6%) died during hospitalization. Multivariate analysis showed that LDH and white blood cells (WBC) were independent predictors of in-hospital mortality; however, this association was insignificant. Univariate analysis showed that higher levels of LDH, WBC, and red cell distribution width (RDW) had a significant association with in-hospital mortality ($P < 0.05$). The receiver operating characteristics curve showed that an LDH cut-off value of 515 U/l had a sensitivity of 91.3% and specificity of 45.9% in predicting in-hospital mortality (95% CI = 0.636 – 0.761, P = 0.0003).

Conclusion: LDH can be an excellent prognostic marker for predicting in-hospital death in patients with pulmonary embolism.

1. Background

A pulmonary embolism (PE) can be life-threatening, making an accurate and immediate diagnosis critical (1). Together with deep vein thrombosis (DVT), it is referred to as venous thromboembolism (VTE). Validated Wells (2) and revised Geneva rules (3), which categorize patients according to the pre-test probability of PE, are frequently used as clinical tools to help diagnose PE. In a non-high-risk patient, a D-dimer level below 500 µg/L can confidently rule out PE in about 20% to 30% of patients without needing additional imaging (4).

Identifying high-risk patients is essential because of the limited number of intensive care unit (ICU) beds in many health centers and the high cost of ICU admissions. Although scoring systems such as the pulmonary embolism severity index (PESI) define high-risk PE patients, we still require further investigations to identify biomarkers associated with greater mortality.

Lactate dehydrogenase (LDH) is an enzyme found in almost all body cells. It has five subtypes with different tissue distributions, released into the bloodstream with cell and/or tissue injuries (5).

Previous studies reported a significant association between

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serum LDH levels and pump thrombosis in patients with left ventricular assist devices (6, 7). The LDH-1 isoenzyme demonstrated a strong link with pump thrombosis (8). A significant correlation between elevated LDH levels and other thrombotic events has also been established. In a study about predictors of splanchnic vein thrombosis, LDH < 500 U/L was associated with thrombosis (9). Another study observed an association between elevated LDH levels and thrombosis risk in paroxysmal nocturnal hemoglobinuria patients (10, 11).

Because LDH is associated with tissue damage and is involved in the anaerobic metabolism of glucose during decreased oxygen supply, its increased levels could theoretically predict adverse outcomes in patients with severe PE (12). Elevated serum LDH is also an independent risk factor for VTE in patients undergoing chemotherapy with testicular germ cell tumors (11). Higher serum LDH levels have been reported in PE patients (13). Based on another study, no association was found between LDH level and bleeding or thrombosis. However, higher LDH level on ICU admission was significantly associated with increased 7-day and 30-day mortality (14). The importance of LDH as a marker of severity in PE has been stated in some studies (15), while others have reported no significant association between PE and LDH levels (16).

2. Objectives

In the current study, we aimed to determine the possible association between serum LDH levels and the in-hospital mortality of PE patients.

3. Patients and Methods

This cross-sectional study included 217 patients with acute PE admitted to two tertiary hospitals between 2018 and 2020. Our inclusion criteria included hospitalized patients over 18 years of age, confirmed PE diagnosis with computed tomography (CT) angiography, and available serum LDH level in the first 24 hours upon admission. Our exclusion criteria were hepatic and renal diseases, pregnancy, hemolytic disorders, left ventricular infarction, recent stroke, positive history of active cancer, acute and chronic infections, and reticuloendothelial-related diseases. Segmental and subsegmental PE were treated with an anticoagulant, while massive PE (defined as PE with systolic blood pressure less than 90 and/or the existence of thrombus in the left or right or main pulmonary artery) was treated with thrombolytic therapy (17). Two expert radiologists reported the CT pulmonary angiogram (CTPA) films (Siemens 32-slice CT scan device) independently and in a blinded fashion. The diagnosis of PE was made accordingly.

The institutional ethics committee approved the study protocol. All patients filled out informed consent forms, and our study preserved patient anonymity. Any death due to PE during the hospital course was defined as in-hospital mortality. Patients were excluded from the study when the death occurred due to non-PE causes (e.g., myocardial infarction, intracranial or gastrointestinal bleeding). One patient had intracranial bleeding after fibrinolytic therapy and was excluded.

We measured the simplified Pulmonary Embolism Severity Index (sPESI) value for all patients. Factors including age over 80 years, positive history of cancer, heart rate below 110 beats/minute, chronic cardiopulmonary disease, systolic blood pressure (SBP) less than 100 mmHg, and oxyhemoglobin saturation less than 90% are assessed in this scoring system, and each variable has one point. The patient is categorized as high risk even with one point (18).

Information about the demographic characteristics of the patients, past medical history, presenting vital signs, laboratory variables, and oxygen saturation was collected from their medical records. Hypertension was defined as SBP ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg.(19) Diabetes mellitus was defined as fasting plasma glucose levels of ≥ 126 mg/dL and HbA1c ≥ 6.5% (20). A simplified pulmonary embolism severity index was calculated (18).

In echocardiography findings, right ventricular dysfunction was defined as right ventricular dilatation and a tricuspid annular plane systolic excursion (TAPSE) less than 16 mm (21). Two expert cardiologists checked every electrocardiogram for the ventricular strain pattern (inverted T wave in V1-V3).

3.1. Statistical Analysis

We used the t-test for quantitative values and the chi-squared test for qualitative variables. Multiple linear regression and ROC (receiver operating characteristics) curve were used to find the cut-off value for LDH level in predicting mortality. Univariate and multivariate analyses were employed to analyze risk factors for mortality, all using SPSS V.22 (IBM Corp., Armonk, NY, USA).

4. **Results**

In this cross-sectional study, we included 217 patients with a definite diagnosis of PE. The mean age of patients was 63.04 ± 16.81 years; 98 patients (45.2%) were female. During hospital admission, 23 patients (10.6%) died. Past medical history showed that 40 patients (18.4%) had diabetes mellitus, 78 (35.9%) had hypertension, and 31 (14.3%) had a history of smoking. Table 1 compares the demographic, laboratory, and physical exam findings in patients with PE according to their in-hospital mortality status. Table 2 shows the association between LDH and other variables.

Univariate analysis showed that among the laboratory data findings, higher levels of LDH, white blood cells (WBC), and red cell distribution width (RDW) were significantly associated with in-hospital mortality (P values < 0.05) (Table 2). Only LDH and WBC were independent predictors of in-hospital mortality; however, this association was not significant statistically (Table 2). The ROC curve showed that an LDH cut-off value of 515 U/l had a sensitivity of 91.3% and specificity of 45.9% in predicting in-hospital mortality (95% confidence interval = 0.636 – 0.761, P = 0.0003) (Figure 1). Table 3 shows the association between LDH and other variables.

5. Discussion

This cross-sectional study showed that serum LDH was associated with a higher risk of in-hospital death, but this association was not significant in multivariate analysis. By

Table 1. The Association of Demographic, Laboratory, and Physical Exam Findings with in-Hospital Mortality.

Variable	In-Hospital Mortality		P-value
	Yes 23 (10.6)	No 194 (89.4)	
Age	64.04 ± 18.18	62.93 ± 16.69	0.763
Gender (female)	13 (56.5%)	85 (43.8%)	0.247
Hypertension	9 (39.1%)	69 (35.6%)	0.895
Diabetes mellitus	6 (26.1%)	34 (17.5%)	0.391
Laboratory variables			
Lactate dehydrogenase (LDH)	873.65 ± 514.15	609.15 ± 343.57	0.024
White blood cells ($\times 10^3$)	13.69 ± 44.46	10.51 ± 15.07	0.003
Hemoglobin	23.74 ± 2.77	12.96 ± 2.15	0.647
Mean corpuscular volume	80.48 ± 5.43	81.29 ± 5.43	0.496
Platelets ($\times 10^3$)	213.22 ± 86.50	206.07 ± 72.91	0.664
Red cell distribution width (RDW)	16.40 ± 2.32	15.07 ± 2.58	0.019
Total cholesterol	160.13 ± 37.19	167.16 ± 42.45	0.449
Triglyceride	141.74 ± 67.86	142.43 ± 97.78	0.974
Physical exam and electrocardiogram findings			
Heart rate	104.83 ± 17.01	96.35 ± 19.54	0.048
Systolic blood pressure	101.22 ± 18.77	121.53 ± 21.14	< 0.001
Diastolic blood pressure	63.91 ± 12.77	74.72 ± 12.06	< 0.001
Oxygen saturation	81.30 ± 7.92	87.62 ± 9.15	0.001
T inversion in V1-V3	8 (34.8%)	71 (36.6%)	0.846
Echocardiography findings			
Tricuspid regurgitation gradient	39.65 ± 16.13	34.73 ± 20.32	0.264
Right ventricular enlargement	19 (82.6%)	122 (62.9%)	0.067
Right ventricular dysfunction	19 (82.6%)	114 (58.8%)	0.040
Computed tomography angiography and sPESI score			
Massive emboli	2 (8.7%)	4 (2.1%)	< 0.001
sPESI score ≥1	23 (100.0%)	124 (63.9%)	< 0.0001

Abbreviations: sPESI: Simplified Pulmonary Embolism Severity Index

Table 2. Univariate and Multivariate Analysis of Risk Factors of In-Hospital Mortality

Variable	Univariate Analysis			Multivariate Analysis		
	Unadjusted OR	95% CI	P-value	Unadjusted OR	95% CI	P-value
Oxygen saturation	0.932	0.893 – 0.974	0.002	0.996	0.930 – 1.067	0.907
Heart rate	1.022	1.000 – 1.045	0.051			
Systolic blood pressure	0.949	0.924 – 0.974	< 0.001	0.968	0.929 – 1.009	0.126
Diastolic blood pressure	0.934	0.900 – 0.968	< 0.001	0.991	0.930 – 1.057	0.794
WBC	1.00	1.00 – 1.00	< 0.001	1.000	1.000 – 1.000	0.052
Creatinine	2.077	1.047 – 4.119	0.036	1.091	0.389 – 3.064	0.868
RDW	1.189	1.026 – 1.378	0.022	1.141	0.925 – 1.408	0.217
LDH	1.001	1.000 – 1.002	0.005	1.001	1.000 – 1.003	0.082
RV strain	1.082	0.437 – 2.679	0.864			
RV dysfunction	0.300	0.098 – 0.915	0.034	2.327	0.668 – 8.103	0.185
Massive emboli	0.168	0.055 – 0.511	0.002	0.165	0.042 – 0.651	0.010
sPESI	3.047	1.912 – 4.857	< 0.001	2.304	1.245 – 4.266	0.008

Abbreviations: OR, Odds Ratio; CI, Confidence Interval; WBC, White Blood Cell; RDW, Red Cell Distribution Width; LDH, Lactate Dehydrogenase; RV, Right Ventricle; sPESI, Simplified Pulmonary Embolism Severity Index

studying new biomarkers affecting the outcome of patients and attaining a better understanding of the pathophysiology of the disease, earlier and more effective treatment with lesser cost could be achieved. Increased LDH has been linked to a higher risk of acute respiratory distress syndrome (22), ICU complications (23), and death (22, 24). Pulmonary thromboembolism is one of the most dangerous cardiovascular system complications (25). Evaluating and predicting the course and outcome of the disease has been an area of interest for researchers. A few studies investigate the association between LDH levels in PE patients and in-hospital mortality.

In line with our study, Leite et al., in a retrospective study of 165 patients with acute PE with the primary endpoint of in-hospital and all-cause mortality assessment, showed LDH had a significant association with in-hospital and late all-cause mortality; an LDH cut-off value of 310 U/l could predict an adverse outcome with a sensitivity of 54.5% and specificity of 71.3% (26). Our study, with a larger sample size, showed that an LDH cut-off value of 515 U/l had a sensitivity of 91.3% and specificity of 45.9% in predicting in-hospital mortality. Serum LDH levels are higher in massive PE than in sub-massive and non-massive PE (27, 28). Increased LDH levels are associated

Table 3. Correlation between Different Variables and Lactate Dehydrogenase Level

Source	Variable	Type III Sum of Squares	Standardized Coefficients Beta	P-value
LDH	Right ventricular strain	42.406	0.092	0.353
	Oxygen saturation	13241.039	-0.131	0.441
	White blood cells	2568640821.813	0.145	0.276
	RDW	1083.184	0.068	0.978
	Heart rate	72241.562	**-0.009**	**0.044**
	Systolic blood pressure	87679.514	-0.102	0.237
	Diastolic blood pressure	29181.577	0.123	0.228
	RV dysfunction	45.151	-0.059	0.082
	Massive emboli	46.194	0.027	0.267
	sPESI	210.916	0.032	0.367

Abbreviations: RDW, Red Cell Distribution Width; LDH, Lactate Dehydrogenase; RV, Right Ventricle; sPESI, Simplified Pulmonary Embolism Severity Index

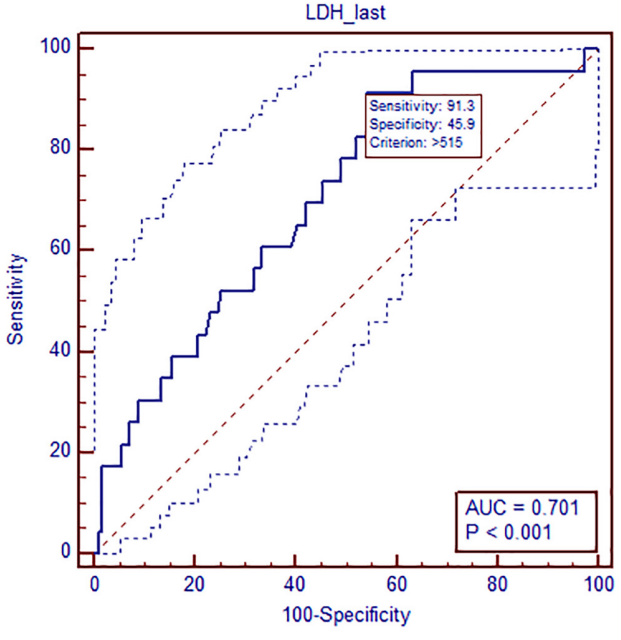

Figure 1. The ROC (Receiver Operating Characteristic) Curve Shows the Best Cut-Off Point for Lactate Dehydrogenase (LDH) to Predict Hospital Death.

with higher pulmonary artery pressure and right ventricular dysfunction (27).

Lactate dehydrogenase is abundantly made in the human body. The LDH-1 and LDH-3 isozymes are present in cardiomyocytes and pneumocytes, respectively (29, 30). Karlsson et al. showed that LDH was significantly correlated with hypoxic-ischemic encephalopathy in newborn infants (31). LDH is an essential enzyme in the anaerobic metabolism of glucose during hypoxia, catalyzing the conversion of pyruvate to lactate (12). A recent study showed that patients with COVID-19 and high LDH levels are more susceptible to developing acute respiratory distress syndrome (32). Increased cardiac and lung hypoxic tissue damage makes LDH a suitable biomarker for predicting the outcome of patients with PE. Ben et al. suggested that using LDH-3 and D-dimer together could improve the diagnosis of PE (33). Our study showed that massive embolism and higher sPESI were better predictors of in-hospital mortality, but higher LDH and WBC also could help differentiate patients.

5.1. Limitations

We did not have an autopsy for all deaths, and pure PE-related death may have been misdiagnosed in a few cases.

5.2. Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of Urmia University of Medical Sciences and was performed under the principles of the Declaration of Helsinki and the International Conference on Harmonization notes for guidance on Good Clinical Practice (ICH/CPMP/135/95). All patients provided written informed consent prior to any study-related procedure. The ethics approval code for this study is IR.UMSU.REC.1399.143.

5.3. Informed Consent

All patients were provided written and oral explanations of the study course and goals. Then, they gave written informed consent.

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Authors' Contribution

SG and RH designed the study; TM, KM, MM, SG, AS, and HK collected data, interpreted data, and drafted the manuscript; RH and AS revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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