The Association between Serum Lactate Dehydrogenase Level and In-hospital Death due to Pulmonary Embolism

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Abstract

Background: Few studies are evaluating the prognostic value of lactate dehydrogenase (LDH) in patients with pulmonary embolism (PE). We analyzed the possible power of serum LDH levels to predict in-hospital mortality.

Methods: In this cross-sectional study 217 patients with confirmed PE diagnosis with CT angiography and available serum LDH level at first 24-hours upon admission were included.

Results: The mean age of patients was 63.04±16.81 years old, 23 patients (10.6%) died during hospitalization. Multivariate analysis showed that only LDH, WBC were independent predictors of in-hospital mortality, however, this association was not significant.

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

Introduction

Pulmonary embolism (PE), together with deep vein thrombosis (DVT) termed as venous thromboembolism (VTE), can be a life-threatening condition. So, accurate and immediate diagnosis is critical. [1] 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 diagnosis of PE. In a non-high risk patient based on one of these criteria, D-dimer level below 500 μg/L can rule out the PE diagnosis with high confidence in about 20–30% of patients without the need for additional imaging. [4]

On the other hand, because of limited number of intensive care unit (ICU) beds in many health centers and because of high cost of ICU admissions, finding high risk patients and risk stratification of patients are very important. Although there are some scoring systems such as pulmonary embolism severity index (PESI) to define high risk PE patients, still we need more investigations to find biomarkers which have association with higher mortality to extend our knowledge about pathophysiology of disease.

LDH is an enzyme found in almost all cells of body. It has five different subtypes with different distribution in tissues and releases in the bloodstream with cell and/or tissue injuries. [5].

According to previous studies, significant association has been reported between serum LDH level and pump thrombosis in patients who have left ventricular assist device (LVAD). [6, 7] LDH-1 isoenzyme especially showed high relation to pump thrombosis.[8] Significant correlation between elevated LDH level and some other thrombotic events has been demonstrated. In a study about predictors of splanchnic vein thrombosis, LDH < 500U/L was found to be associated with thrombosis.[9] In another study, an association was seen between elevated LDH level –as a marker of hemolysis- and thrombosis risk in paroxysmal nocturnal hemoglobinuria patients. [10, 11] Because LDH has association with tissue

damage and is involved in anaerobic metabolism of glucose in decreased oxygen supply, theoretically its increased levels could predict adverse outcome in patients with severe pulmonary thromboembolism. [12]

Elevated serum LDH also was identified as an independent risk factor for venous thromboembolism in patients with testicular germ cell tumor undergoing chemotherapy. [11]

Higher serum LDH level has been reported in PE patients.[13] Based on another study, no association was found between LDH level and bleeding or thrombosis, but higher LDH level on ICU admission was shown to be significantly associated with increased 7-day and 30-day mortality. [14]

Importance of LDH as a marker of severity in PE has been stated in some studies [15], while others has been reported no significant association between PE and LDH level. [16] Finding new biomarkers can help us to achieve better risk stratification and treatment strategies in order to reduce mortality of PE patients.

In current study, we aimed to find out the possible association of serum LDH level and in hospital mortality of PE patients.

Methods

In this cross-sectional study 217 patients admitted between 2018 till 2020 in two tertiary hospitals with acute PE were included. Our inclusion criteria included as hospitalized patients aged over 18 years, confirmed PE diagnosis with CT angiography and available serum LDH level at 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 were excluded. Segmental and sub-segmental PE was treated with anticoagulant while massive PE defined as PE with systolic blood pressure less than 90 or/and existence of thrombus in left or right or main pulmonary artery took thrombolytic therapy. [17] Pulmonary computed tomography (CT) angiogram films were reported by two expert radiologists.

Diagnosis of PE was made by CTPA (Siemens 32-slice computed tomography scanners). Two expert radiologists were investigated CTPA images as blinded fashion.

This study was approved by ethics committee of our University. All patients had signed informed consent form and patient anonymity was preserved in our study.

Any death during hospital course due to PE was defined as in-hospital mortality. When death occurred due to non-PE causes (e.g. myocardial infarction, intracranial or gastrointestinal bleeding), patients were excluded from study. Overlay one patient had intracranial bleeding after fibrinolytic therapy and was excluded.

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

Information about demographic characteristics of the patients, past medical history as well as presenting vital sings, laboratory variables and oxygen saturation, were collected from their medical records.

Hypertension was defined as SBP ≥ 140 mmHg or DBP ≥ 90 mmHg.[19] Diabetes mellitus was defined as fasting plasma glucose levels of ≥ 126 mg/dl and HbA1c ≥ 6.5%. [20]

Simplified pulmonary embolism severity index was calculated according to previous studies. [18]

Right ventricular dysfunction was defined as the presence of right ventricular dilatation and a TAPSE less than 16 mm in echocardiography findings. [21] Every ECG was reported by two expert cardiologists to find out right ventricular strain pattern (inverted T wave in V1-V3).

Statistical analysis

IBM SPSS V.22 software was used for statistical analysis (IBM Corp., Armonk, NY, USA). We used t-test for quantitative values and chi-squire test for qualitative variables. Multiple linear regression and ROC (receiver operating characteristics) curve were used to find cutoff value for LDH level and mortality. Univariate and multivariate analyses were employed to analyze risk factors for mortality

Results

In this cross-sectional study, we included 217 patients with definite diagnosis of pulmonary embolism. 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 patients (35.9%) had hypertension, 31 patients (14.3%) had history of smoking. Pulmonary embolism was confirmed in all cases by computed tomography (CT) angiography. Table 1 shows demographic, laboratory and physical exam findings in patients with pulmonary embolism according to their in-hospital mortality. Table 2 shows association between LDH and other variables.

Table 1
the association between demographic, laboratory and physical exam findings and hospital death.

Variable	Hospital death		p-value
	Yes	NO	
	23(10.6)	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 ECG 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
O2 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
CT angiography and sPESI score			

Variable	Hospital death		p-value
	Yes	NO	
	23(10.6)	194(89.4)	
Massive Emboli	2(8.7%)	4(2.1%)	< 0.001
Simplified PESI score ≥ 1	23(100.0%)	124(63.9%)	< 0.0001

Table 2
univariate and multivariate analysis of risk factors of in-hospital mortality

Variable	Univariate			multivariate		
	Unadjusted OR	95% CI	P-value	Unadjusted OR	95% CI	P-value
O_2 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
Cr	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

WBC; white blood cell, Cr; creatinine, PESI; pulmonary embolism severity index RV; right ventricle, WBC; white blood cell, RDW; red cell distribution width, PESI; pulmonary embolism severity index

Univariate analysis showed that among laboratory data findings, higher levels of LDH, white blood cells (WBC), red distribution width (RDW) had significant association with in-hospital mortality. (P values < 0.05). (Table 2) only LDH, WBC were independent predictors of in-hospital mortality, however this association was not significant statistically (Table 2). 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) (Fig. 1).

Table 3 shows the association between LDH and other variables.

Table 3
Correlation between different variables and LDH.

Source	variables	Type III Sum of Squares	df	Mean Square	F	Sig.
LDH	Right ventricular strain	42.406	179	.237	1.119	.353
	O2 saturation	13241.039	179	73.972	1.054	.441
	White blood cell	2568640821.813	179	14349948.725	1.185	.276
	RDW	1083.184	179	6.051	.620	.978
	Heart rate	72241.562	179	403.584	1.608	.044
	Systolic blood pressure	87679.514	179	489.830	1.224	.237
	Diastolic blood pressure	29181.577	179	163.026	1.234	.228
	RV dysfunction	45.151	179	.252	1.474	.082
	Massive Emboli	46.194	179	.258	1.194	.267
	Simplified PESI	210.916	179	1.178	1.108	.367

LDH; lactate dehydrogenase, RDW; red cell distribution width, RV; right ventricle, PESI; pulmonary embolism severity index

Discussion

In this cross-sectional study, we evaluated the level of lactate dehydrogenase in 217 patients with a definite diagnosis of pulmonary embolism. Our study showed that serum LDH was associated with higher risk of in-hospital death, but this association was not significant in multivariate analysis. By studying new biomarkers affecting outcome of patients and better understanding of pathophysiology of disease, early and more effective treatment with lesser cost could be achieved.

Increased LDH has been linked to higher risk of ARDS [22], in ICU complications [23], and death. [22, 24]

Pulmonary thromboembolism is one of the most dangerous complications involving cardiovascular system. [25] The importance of evaluating and predicting the course and outcome of the disease has been an era of interest for researchers. There are a few studies investigating the association between LDH level in PE patients and in-hospital mortality.

In line with our study, Leite et al in a retrospective study included 165 patients with acute PE. The main end point of this study were in-hospital and all-cause mortality. They showed that LDH had significant association with in-hospital and late all-cause mortality and LDH cut-off value of 310 U/l with a sensitivity of 54.5% and specificity of 71.3% could predict adverse outcome. [26] Our study by a larger sample size, showed that a 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 level has been reported to be higher in massive PTE compared to sub-massive and non-massive PTE. [27, 28] The increased LDH level was associated with higher pulmonary artery pressure, right ventricular dysfunction. [27]

Lactate dehydrogenase is abundantly made in the human body.It has 5 types of isozymes, LDH-1 and LDH-3 isozymes are presented in cardiomyocytes and pneumocytes respectively. [29, 30] Karlsson et al showed that LDH had significant correlation with hypoxic ischemic encephalopathy in newborn infants. [31] By catalyzing pyruvate to lactate, LDH is an important enzyme in anaerobic metabolism of glucose during hypoxia. [12]

A recent study showed that patients with COVID-19 and high LDH levels are more susceptible to develop acute respiratory distress syndrome. [32] Increasing in cardiac, lung and hypoxic tissue damage makes LDH a suitable biomarker for predicting outcome of patients with pulmonary embolism. Ben et al suggested that using LDH-3 and D-dimer together could improve the diagnosis of PE. [33] Our study showed that presence of massive embolism and higher sPESI were better predictors of in-hospital death, but higher LDH and WBC also could help in better differentiation of patients. Further studies by revealing pathophysiology of underlying causes of LDH related morbidity and mortality could improve patients' management and outcome.

Limitations of study

We didn't have autopsy for all deaths and pure PE related death could be misdiagnosed in few cases. Although we used our exclusion criteria to decrease the effect of confounding factors, still other factors such as undiagnosed cancers and some medications could affect our results adversely.

Abbreviations

LDH: lactate dehydrogenase

PE: pulmonary embolism

VTE: venous thromboembolism

CTPA: Computed tomography pulmonary angiography

LVAD: left ventricular assist device

ICU: Intensive care unite

Declarations

Ethics approval and consent to participate

This study was approved by ethics committee of Urmia University of Medical Sciences and were performed in accordance with 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 approved ethical code for this study is IR.UMSU.REC.1399.143.

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author, A.S , upon reasonable request.

Competing interests

The authors declare that they have no conflict of interest.

Funding

The authors declare no funding for this study.

Authors' contributions

The study was designed by S.G. and R.H., data collection and manuscript written by T.M., K.M., M.M., S.G., H.K., and A.S. interpreted the data, and R.H. and A.S. revised the manuscript for important intellectual content. All authors read and approved the final manuscript

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Figures

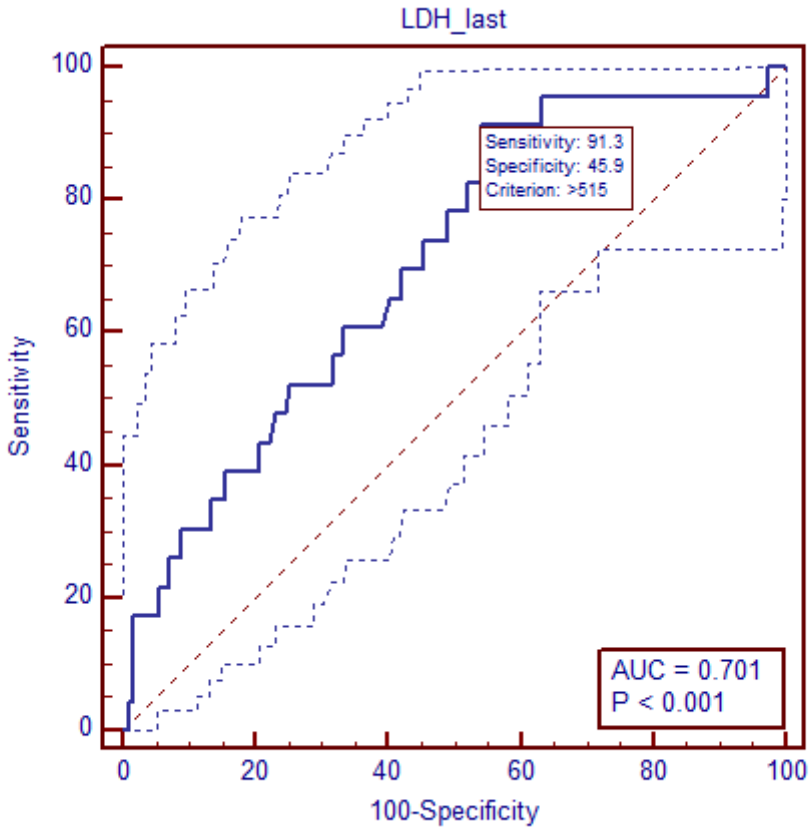

Figure 1

A ROC curve (receiver operating characteristic curve) shows the best cut off point for LDH to predict hospital death.