Serum lactate dehydrogenase and its isoenzymes as predictors of clinical outcomes in acute exacerbation of chronic obstructive pulmonary disease: a retrospective analysis of a hospitalized cohort

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Abstract

We aimed to test the relationship between serum lactate dehydrogenase (LDH) and its isoenzymes and treatment outcomes during hospitalization for acute exacerbations of chronic obstructive pulmonary disease (AECOPD). Thirty-eight AECOPD patients were recruited from a tertiary hospital from December 2017 to June 2018. Serum LDH and LDH isoenzymes were measured on venous blood collected at admission. Treatment outcomes included duration of hospital stay, initiation of mechanical or non-invasive ventilation (NIV), initiation of antipseudomonal antibiotics, change in empirical antibiotic treatment, need for intravenous corticosteroids or methylxanthines, and percentage of change in C-reactive protein from admission to the third day. Multivariate linear and binary logistic regression analyses were used to test the study's objectives. We found that, after adjusting for age, gender, comorbidities, COPD severity, level of hypoxemia, and inflammation markers, each 10 U/L increase in serum LDH was associated with prolongation of the hospital stay by 0.25 (0.03, 0.46) days, 42% higher odds [odds ratio (OR) 1.42 (1.00, 2.03)] for need of NIV, and 25% higher odds [OR 1.25 (1.04, 1.49)] for initiation of antipseudomonal treatment. LDH1 and LDH2 were the LDH isoenzymes that mainly drove these relationships. LDH release in the context of AECOPD could originate from lung, muscle, or heart tissue damage due to airway inflammation, respiratory muscle recruitment, and myocardial stress. Myocardial injury and aerobic adaptation in respiratory muscles may explain the predominance of LDH1 and LDH2 isoenzymes in these associations.

Introduction

Lactate dehydrogenase (LDH) is a cytoplasmic enzyme that regulates aerobic and anaerobic metabolisms in five tetrameric forms (isoenzymes). Its release into the bloodstream is caused by aberrant permeability or breakdown of the cell membrane, and its concentration in blood serum is used to detect cell injury or death [1]. In the respiratory system, elevated LDH activity has been linked to chronic cough [2], interstitial lung disease [3], occupational lung disease [4], acute respiratory distress syndrome [5], pulmonary alveolar proteinosis [6], and active pulmonary tuberculosis

[7], indicating its association with severe inflammation and damage of lung tissue. Increased activity of the serum LDH3 isoenzyme has been related to acute immunologic lung injury in animal models [8], but evidence in humans is scarce.

Chronic obstructive pulmonary disease (COPD) is a disorder characterized by chronic inflammation in the pulmonary parenchyma and airways, resulting in structural changes after repeated cycles of injury and repair [9]. Previous studies have reported increased serum LDH activity in COPD patients compared with healthy controls [10,11], leading to the conclusion that the function and biochemical role of LDH and its isoenzymes could be related to COPD alterations, such as chronic inflammation and changes in aerobic and anaerobic metabolism after chronic airway obstruction, ventilation-perfusion abnormalities, and oxidative stress. Another study has found that, in stable COPD patients, serum LDH3 and LDH4 activity are elevated, and serum LDH3 levels positively correlate with the degree of systemic inflammation, measured by high-sensitive C-reactive protein (CRP) [12]. However, no study has evaluated serum LDH activity and serum LDH isoenzymes in COPD patients during an acute exacerbation, a condition that is characterized by an augmentation of these pathophysiological processes, in relation to clinically important outcomes. Analysis of the serum LDH isoenzyme activities could enhance our understanding of the underlying processes that lead to increased morbidity in patients with acute exacerbations of COPD (AECOPD).

Objectives

We aimed to estimate the association between serum LDH levels measured at hospital admission of a patient with AECOPD and treatment outcomes during the hospitalization. Secondarily, we aimed to explore which LDH isoenzymes were responsible for the above-mentioned associations.

Materials and Methods

Study design, setting, and participants

This is a secondary analysis of an exploratory comparative cross-sectional study of hospitalized patients with AECOPD and other lower respiratory tract infections in a tertiary hospital in Greece [13]. Participants were recruited from the 2nd Pulmonary Department of the "Sismanogleion" General Hospital of Attica from December 2017 to June 2018. The research was conducted after approval by the Research Committee of the University of Thessaly (protocol number 2800/2017), and informed consent was obtained from all participants or their healthcare proxy.

In the present analysis, we focused only on patients with AECOPD (n=38). Acute deterioration in at least two of the three cardinal symptoms of COPD (breathlessness, productive cough, and sputum purulence) [14], in the setting of a physician-documented COPD diagnosis, was required for inclusion. Patients who exhibited consolidation on their chest radiograph on admission were excluded.

Variables and data sources

Participants were approached on their first day of hospitalization. After determining eligibility for inclusion and giving signed informed consent, they completed a questionnaire about demographics, comorbidities, use of medication or long-term oxygen, pre-exacerbation dyspnea levels, and exacerbation history in the preceding year.

Serum LDH and LDH isoenzymes (expressed in U/L) were the main predictors in the analyses. Venous blood was drawn on the same day. After centrifugation, blood serum was stored at 2-6°C for a maximum of 48 hours. Macroscopically hemolyzed samples were discarded. For the LDH isoenzyme assay, the isoenzymic kit LD Vis-12 SAS-1 (HELENA Biosciences Europe, Gateshead, UK) was utilized, which is designed for qualitative and quantitative measurements using agar gel electrophoresis.

Age, gender, comorbidities, COPD classification, level of hypoxemia [ratio of partial pressure of oxygen (pO_2) to fraction of inspired oxygen (FiO_2)], and markers of inflammation (serum CRP) were considered confounders in the analysis, while markers of hemolysis (potassium), muscle, and cardiac function [serum creatine phosphokinase (CPK) and troponin I] were tested as effect modifiers. Information regarding demographics and comorbidities was obtained from the questionnaires, while arterial blood gases and laboratory markers were measured at the emergency department. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations, patients were divided into four groups (A-D) based on the assessment of their dyspnea symptoms and their exacerbation risk [9].

The main outcomes were in-hospital mortality, duration of hospital stay, and initiation of non-invasive (NIV) or mechanical (MV) ventilation. Secondary outcomes were initiation of antipseudomonal antibiotics as empirical treatment, need for change in empirical antibiotic treatment (because of clinical deterioration or based on culture results), need for intravenous corticosteroids or methylxanthines, and percentage of change in CRP from admission to the third day of hospitalization. Medical files and discharge notes were retrospectively searched to determine the outcome values.

Statistical methods

In the descriptive statistical analysis, continuous variables are reported as mean ± standard deviation and categorical as count (%). To examine the independent impact of predictors on primary and secondary outcomes, we ran a series of regression analyses, controlling for confounders. Categorical outcomes were tested with binary logistic regression and continuous outcomes with linear regression. Separate analyses were performed for each predictor, and the results for the association between predictors and outcomes are presented as unstandardized regression coefficients and corresponding 95% confidence intervals (CIs) for the linear models or odds ratios (ORs) and 95% CIs for the logistic models. We used three models with progressing adjustments for each analysis: one uncontrolled, one controlled for age, gender, and comorbidities, and one further adjusted for the GOLD group, pO_2/FiO_2, and serum CRP. The GOLD group was entered as a dichotomous variable (group D *versus* groups A, B, and C). Mean serum LDH and serum LDH isoenzymes and percentage of change in CRP were entered as 10-unit intervals to ease interpretation of the results. Effect modification by hemolysis, muscle, or myocardial markers was tested by entering interaction terms between each marker (potassium, CPK, and troponin I) and LDH or LDH isoenzymes as predictors in the fully adjusted regression models.

Multiple imputation was applied to manage missing data using the fully conditional specification method under the missing completely at random assumption [15]. A total of 30 imputed data sets were constructed, and the regression analysis results from each set were aggregated to generate an average estimate. All significance tests were 2-sided, and p values less than 0.05 were considered statistically significant. The statistical software program SPSS® Statistics Version 25 (IBM, Armonk, NY, USA) was used for the analyses.

Results

Descriptive data

There were 29 male (76.3%) and 9 female (23.7%) patients. Their mean age was 70.45±8.86 (range 53-89) years, and their smoking history was at an average of 86.76±41.54 pack/year. Cardiovascular diseases, including hypertension, were the most prevalent comorbidity (67.6%), followed by diabetes mellitus (35.1%). A total of 16 patients (42.1%) were on long-term oxygen therapy. Clinical data regarding pre-exacerbation COPD severity and laboratory results at admission, including LDH isoenzyme values, are presented in Table 1.

Outcome data

None of the patients died during hospitalization. The mean duration of the hospital stay was 10.95±11.04 (range 3-70) days. A total of 10 patients (26.3%) were treated with NIV, while 3 (7.9%) required intubation and MV. A total of 11 patients (28.9%) received antipseudomonal therapy; 27 (71.1%) were treated with corticosteroids, and 8 (21.1%) with methylxanthines. Only 5 patients (13.2%) required alteration of their initial antibiotic therapy. The mean percentage change in CRP from admission to the third day of hospitalization was -58.41±50.62%.

Results of the regression analyses

The results of the regression analyses for the relations between serum LDH and its isoenzymes and primary and secondary outcomes after multiple imputation of missing data are presented in Table 2. Higher serum LDH and higher serum LDH1 and LDH2 isoenzymes at admission were significantly and independently associated with a longer duration of hospital stay, a higher need for NIV, a higher rate of antipseudomonal treatment initiation, and a higher need for additional bronchodilation with methylxanthines. In the fully adjusted model, each 10 U/L increase in serum LDH was associated with prolongation of the hospital stay by 0.25 (0.03, 0.46) days, 42% higher odds [OR 1.42 (1.00, 2.03)] for need of NIV, and 25% higher odds [OR 1.25 (1.04, 1.49)] for initiation of antipseudomonal treatment. Similarly, each 10 U/L increase in serum LDH1 and LDH2 isoenzymes was independently associated with prolongation of the hospital stay by 1.03 (0.30, 1.75) and 0.67 (0.16, 1.19) days, 86% [OR 1.86 (1.09, 3.16)] and 63% [OR 1.63 (1.05, 2.52)] higher odds for initiation of antipseudomonal treatment, and 100% [OR 2.00 (1.07, 3.75)] and 47% [OR 1.47 (1.01, 2.15)] higher odds for additional treatment with methylxanthines, respectively. Moreover, each 10 U/L increase in serum LDH1 isoenzyme predicted 3-times higher odds [OR 2.96 (1.06, 8.29)] for the need for NIV. No evidence for statistically significant effect modification of the above associations by hemolysis, muscle, or myocardial function markers was identified for any of the outcomes (data not shown).

Discussion

We were able to identify significant and independent associations between serum LDH at admission and a variety of subsequent outcomes in the context of hospitalization for AECOPD and to demonstrate which serum LDH isoenzymes contribute the most to these associations. Higher serum LDH levels were related to a longer duration of hospital stay and a higher need for NIV, antipseudomonal antibiotics, and methylxanthine treatment. LDH1

Table 1. Descriptive information on clinical and laboratory data of study participants with missing data frequencies.

Variables	Values	Missing data (%)
COPD classification		8 (21.1)
Mean mMRC dyspnea scale (SD)	2.50 (1.08)	
Mean exacerbations per year (SD)	1.40 (0.93)	
GOLD group (%)		
A	4 (13.3)	
B	7 (23.3)	
C	2 (6.7)	
D	17 (56.7)	
Arterial blood gases		4 (10.5)
Mean pO_2/FiO_2 in mmHg (SD)	216.52 (75.04)	
Mean pCO_2 in mmHg (SD)	51.18 (12.67)	
Mean pH (SD)	7.42 (0.06)	
Mean HCO3 in mmol/L (SD)	32.68 (6.39)	
Biological data		0 (0.0)
Mean serum CRP in mg/L (SD)	39.31 (56.10)	
Mean serum potassium in mmol/L (SD)	4.12 (0.55)	
Mean serum CPK in U/L (SD)	71.03 (55.07)	
Mean serum troponin I in ng/mL (SD)	0.04 (0.05)	
Mean serum LDH in U/L (SD)	239.05 (77.44)	
LDH1 in U/L (SD)	60.94 (21.77)	
LDH2 in U/L (SD)	82.26 (33.10)	
LDH3 in U/L (SD)	40.38 (13.11)	
LDH4 in U/L (SD)	20.51 (10.52)	
LDH5 in U/L (SD)	35.01 (21.21)	

COPD, chronic obstructive pulmonary disease; mMRC, modified Medical Research Council; SD, standard deviation; GOLD, Global Initiative for Chronic Obstructive Lung Disease; pO_2, partial pressure of arterial oxygen; FiO_2, fraction of inspired oxygen; pCO_2, partial pressure of arterial carbon dioxide; CRP, C-reactive protein; CPK, creatine phosphokinase; LDH, lactate dehydrogenase.

and LDH2 were the LDH isoenzymes that mainly drove these relationships, after adjustment for demographic data, comorbidities, pre-exacerbation COPD severity, severity of arterial blood gas abnormalities at admission, and degree of inflammation at admission.

Serum LDH is a marker of cell damage, and its release in the context of an AECOPD could originate from damage in the lung [1], muscle [16,17], or heart tissue [18], because of airway inflammation, airflow limitation with dynamic hyperinflation, increased work of breathing, hypoxemia, and myocardial distress [19]. The need for NIV or MV may particularly relate to alterations in ventilatory mechanics, muscle function, and gas exchange, which in turn could explain the association with the increased LDH levels. COPD patients with or at risk of *Pseudomonas aeruginosa* colonization are more likely to be frequent exacerbators, with multiple hospitalizations, increased antibiotic usage, and chronic steroid therapy, and thus may present with higher LDH levels. Those who required additional systemic bronchodilatory effects beyond inhalers may have developed severe airflow limitations, ventilation-perfusion mismatches, and worsening hyperinflation, all of which could raise LDH levels. Finally, an increased inflammatory response requiring intravenous antibiotic treatment, severe respiratory failure requiring oxygen supplementation or ventilatory support, and myocardial complications are common causes of hospitalization prolongation during an AECOPD.

The novel contribution of this study is the identification of the specific LDH isoenzymes that are associated with treatment outcomes in AECOPD. There are two plausible explanations for their relationship with AECOPD outcomes. Firstly, LDH1 and LDH2 isoenzymes predominate in the heart and blood. During AECOPD, myocardial injury is prevalent and clinically important, especially in patients with underlying ischemic heart disease [18]. Furthermore, COPD patients who have frequent exacerbations have increased arterial stiffness, which has a deleterious impact on right ventricular function [20]. However, we could not identify any difference in the associations between LDH isoenzymes and AECOPD outcomes depending on serum troponin I level, which is a marker of myocardial injury. Secondly, LDH1 and LDH2 are key enzymes in the process of aerobic metabolism, in contrast to LDH4 and LDH5, which are markers of anaerobic metabolism. AECOPD is characterized by inspiratory muscle dysfunction and an increase in expiratory muscle strength to compensate for hyperinflation and air trapping [21]. In COPD, respiratory muscles show signs of trauma, but there are also increases in various aerobic metabolism-related factors, such as the proportion of type I fibers, capillary density, and aerobic

Table 2. Pooled estimates of the associations between serum LDH and LDH isoenzymes and outcomes from 3 models with increasing covariate adjustment after multiple imputation of missing data.

	LDH	LDH1	LDH2	LDH3	LDH4	LDH5
Duration of hospital stay [B (95% CI)]						
Model 1	0.25 (0.05, 0.45)	1.13 (0.46, 1.80)	0.68 (0.23, 1.13)	0.67 (-0.60, 1.94)	0.74 (-0.83, 2.32)	0.11 (-0.69, 0.91)
Model 2	0.26 (0.06, 0.47)	1.05 (0.36, 1.75)	0.68 (0.20, 1.16)	0.60 (-0.76, 1.96)	1.24 (-0.46, 2.93)	0.42 (-0.47, 1.30)
Model 3	0.25 (0.03, 0.46)	1.03 (0.30, 1.75)	0.67 (0.16, 1.19)	0.32 (-1.24, 1.89)	1.03 (-0.83, 2.88)	0.37 (-0.60, 1.34)
Need for non-invasive ventilation [OR (95% CI)]						
Model 1	1.15 (1.03, 1.29)	2.28 (1.22, 4.27)	1.45 (1.06, 2.00)	2.02 (1.08, 3.75)	1.34 (0.69, 2.61)	1.08 (0.77, 1.51)
Model 2	1.28 (1.02, 1.60)	2.51 (1.19, 5.34)	1.51 (1.04, 2.21)	2.25 (0.99, 5.09)	2.40 (0.70, 8.20)	1.58 (0.85, 2.94)
Model 3	1.42 (1.00, 2.03)	2.96 (1.06, 8.29)	1.72 (0.98, 3.02)	2.18 (0.88, 5.39)	2.76 (0.60, 12.65)	2.18 (0.90, 5.25)
Need for mechanical ventilation [OR (95% CI)]						
Model 1	1.11 (0.98, 1.26)	1.54 (0.98, 2.42)	1.21 (0.92, 1.59)	0.97 (0.39, 2.45)	1.49 (0.59, 3.79)	1.37 (0.83, 2.25)
Model 2	1.15 (0.97, 1.37)	1.82 (0.86, 3.87)	1.42 (0.90, 2.23)	1.07 (0.37, 3.13)	2.16 (0.50, 9.31)	1.43 (0.69, 2.97)
Model 3	1.19 (0.95, 1.50)	2.03 (0.84, 4.86)	1.52 (0.89, 2.58)	1.22 (0.38, 3.92)	2.72 (0.45, 16.54)	1.57 (0.63, 3.92)
Antipseudomonal treatment initiation [OR (95% CI]						
Model 1	1.12 (1.01, 1.24)	1.52 (1.01, 2.27)	1.24 (0.98, 1.55)	1.46 (0.85, 2.53)	1.80 (0.89, 3.68)	1.28 (0.91, 1.79)
Model 2	1.16 (1.02, 1.32)	1.59 (1.04, 2.43)	1.31 (0.99, 1.74)	1.68 (0.86, 3.28)	2.69 (1.00, 7.27)	1.69 (1.01, 2.84)
Model 3	1.25 (1.04, 1.49)	1.86 (1.09, 3.16)	1.63 (1.05, 2.52)	2.39 (0.95, 5.98)	9.19 (1.18, 71.56)	1.58 (0.91, 2.73)
Need for change in empiric antibiotic treatment [OR (95% CI)]						
Model 1	0.92 (0.77, 1.10)	0.83 (0.48, 1.44)	0.76 (0.45, 1.30)	0.37 (0.11, 1.23)	0.87 (0.33, 2.32)	1.02 (0.66, 1.59)
Model 2	0.91 (0.74, 1.13)	0.77 (0.39, 1.49)	0.72 (0.38, 1.36)	0.18 (0.03, 1.17)	1.17 (0.36, 3.79)	1.08 (0.64, 1.83)
Model 3	0.94 (0.72, 1.22)	0.79 (0.32, 1.95)	0.77 (0.37, 1.59)	0.02 (0.00, 5,787.47)	1.35 (0.22, 8.35)	1.26 (0.39, 4.10)
Need for intravenous corticosteroids [OR (95% CI)]						
Model 1	0.98 (0.90, 1.08)	1.04 (0.74, 1.46)	1.03 (0.83, 1.30)	0.73 (0.42, 1.25)	0.59 (0.29, 1.18)	0.93 (0.67, 1.30)
Model 2	1.00 (0.90, 1.10)	1.09 (0.76, 1.55)	1.10 (0.85, 1.43)	0.79 (0.43, 1.43)	0.49 (0.20, 1.19)	0.84 (0.53, 1.31)
Model 3	1.01 (0.86, 1.19)	1.13 (0.64, 1.99)	1.15 (0.73, 1.82)	0.86 (0.33, 2.25)	0.31 (0.04, 2.34)	0.96 (0.44, 2.08)
Need for methylxanthines [OR (95% CI)]						
Model 1	1.07 (0.97, 1.17)	1.58 (1.03, 2.42)	1.21 (0.97, 1.51)	1.08 (0.60, 1.96)	0.70 (0.28, 1.73)	0.96 (0.65, 1.40)
Model 2	1.10 (1.04, 1.16)	1.95 (1.07, 3.56)	1.43 (1.01, 2.03)	1.28 (0.65, 2.54)	0.79 (0.32, 1.93)	0.95 (0.64, 1.41)
Model 3	1.10 (0.98, 1.23)	2.00 (1.07, 3.75)	1.47 (1.01, 2.15)	1.24 (0.59, 2.62)	0.68 (0.25, 1.85)	0.89 (0.57, 1.40)
Percentage of change in CRP from admission to day 3 [B (95% CI)]						
Model 1	-0.18 (-3.44, 3.08)	-1.01 (-14.83, 12.81)	-0.38 (-8.17, 7.42)	-2.17 (-28.79, 24.45)	0.12 (-20.88, 21.12)	0.46 (-11.73, 12.65)
Model 2	-0.30 (-4.25, 3.65)	-0.92 (-13.89, 12.04)	-0.55 (-9.19, 8.10)	-2.92 (-34.68, 28.84)	-1.95 (-28.91, 25.01)	-0.22 (-11.45, 11.02)
Model 3	-0.21 (-3.81, 3.39)	-0.69 (-12.99, 11.60)	-0.32 (-8.42, 7.78)	-1.99 (-29.96, 25.98)	-1.18 (-26.19, 23.83)	-0.47 (-12.41, 11.48)

LDH, lactate dehydrogenase; B, unstandardized regression coefficient; CI, confidence interval; OR, odds ratio; CRP, C-reactive protein. Model 1 is unadjusted, model 2 is adjusted for age, gender, comorbid diabetes mellitus, and comorbid cardiovascular disease, and model 3 is additionally adjusted for Global Initiative for Chronic Obstructive Lung Disease group, partial pressure of oxygen/fraction of inspired oxygen and serum C-reactive protein.

enzyme activity [22]. As a result, AECOPD could mimic a state of exercise fatigue that heightens aerobic metabolism, which is promoted by the LDH1 and LDH2 isoenzymes [23]. The above explanation is further supported by the observed shift of the LDH isoenzyme pattern towards the predominance of LDH1 and LDH2 in AECOPD patients compared to patients hospitalized with other lower respiratory tract infections in our comparative study [13].

The finding that some of the outcomes failed to show any association with serum LDH is difficult to explain and could be related to many factors, including the limited sample, their rare occurrence, or the assessment method. Changes in empirical antibiotic treatment could occur following the results of sputum cultures or an acquired superinfection during the hospital stay, regardless of the success of the initial therapy in treating the exacerbation. Similarly, the inclusion of corticosteroids in the treatment regimen is highly based on the subjective criteria of the treating physician since there is no consensus to guide their use in the hospital setting. Finally, neither serum LDH nor LDH5 isoenzyme, which is more sensitive in infections, could predict the reduction in markers of inflammation after treatment initiation. A possible explanation is that a serial measurement of serum LDH, instead of a single value, would be required to identify such correlations.

Generalizability

We sought for the first time to investigate the relationship between serum LDH and its isoenzymes and meaningful AECOPD outcomes. Our study included hospital inpatients with acute respiratory failure, severe COPD, and a high comorbidity burden. Following that, our findings are unlikely to apply to early-stage COPD outpatients with mild infections and no concomitant illnesses.

Limitations

Our research has some limitations. It was a pilot exploratory study performed with convenience sampling from a single site, which could restrict the study's precision and generalizability. Furthermore, because the predictors were only evaluated once, we were unable to capture the shifting influence of LDH isoenzymes on study outcomes over the course of an AECOPD. Finally, some outcomes may have occurred before or simultaneously with the LDH isoenzyme measurement, making it difficult to ascertain their actual predictive value.

Conclusions

Increased levels of serum LDH and serum LDH1 and LDH2 isoenzymes at admission predict a longer hospital stay and are associated with higher odds of initiating NIV, antipseudomonal antibiotics, and intravenous methylxanthines in hospitalized patients with AECOPD. Worse AECOPD outcomes may correlate to the severity of airflow limitation, airway inflammation, and respiratory muscle exhaustion, causing increased LDH release in the circulation, while myocardial stress and the predominance of aerobic metabolism in respiratory muscles could particularly contribute to increases in the LDH1 and LDH2 isoenzymes. The limitations of this pilot study do not allow a clear interpretation to encourage the routine use of serum LDH isoenzymes as biomarkers of AECOPD severity. The usefulness of serum LDH and LDH isoenzyme measurement as risk factors for morbidity outcomes in both stable and acutely exacerbated COPD should be further explored in future research to guide implementation in practice.

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