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U-Shaped Relationship Between Serum Lactate Dehydrogenase with All-Cause Mortality in Patients with Chronic Obstructive Pulmonary Disease

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Purpose: In the anaerobic metabolic pathway, lactate dehydrogenase (LDH) plays an important role in hypoxia, inflammation, and cell damage, making it a potential biomarker for the progression of chronic obstructive pulmonary disease (COPD). We aimed to examine the relationship between LDH levels and all-cause mortality in participants with COPD.

Patients and Methods: Data of participants in the US National Health and Nutrition Examination Surveys (NHANES) 2007–2012 aged ≥20 years who underwent spirometry tests were examined, and follow-up mortality data were obtained. According to serum LDH levels, participants with COPD were divided into five groups (59–111, 112–123, 124–135, 136–150, and 151–344 U/L). To evaluate whether LDH levels were independently associated with COPD mortality, we used multivariate Cox regression analysis and smooth curve fitting.

Results: We included 1320 subjects, 64 with stage III or IV COPD and 541 with stage II COPD. Over a median follow-up of 9.7 years (IQR: 7.8, 11.2), 252 of the 1320 subjects died. The mean LDH level was 132.5 U/L (standard deviation [SD], 27.0). A U-shaped relationship was observed between LDH levels and all-cause mortality. Below and above the inflection point, which was approximately 110 U/L, we found different slopes for the correlation between LDH and all-cause mortality of patients with COPD. Below the threshold, per 1-standard deviation (1SD) increase in LDH resulted in a 68% reduced risk of all-cause mortality (hazard ratio [HR] 0.32, 95% confidence interval [CI] 0.13–0.81, P=0.016); conversely, above the threshold, per 1SD increase in LDH accelerated the risk of all-cause mortality (HR 1.23, 95% CI: 1.08–1.41, P= 0.002).

Conclusion: Using the nationally representative NHANES data, we found a U-shaped association between LDH level and all-cause mortality in participants with COPD. An optimal LDH level of approximately 110 U/L was associated with the lowest risk of all-cause mortality.

Keywords: lactate dehydrogenase, pulmonary disease, chronic obstructive, nutrition surveys, nonlinear, threshold

Introduction

Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable disease characterized by persistent respiratory symptoms and progressive airflow obstruction.[1] In 2018, COPD was the fourth most common cause of death in the United States.[2] COPD was diagnosed in nearly 15.7 million Americans (6.4%).[3] In more than half of COPD cases, adults were unaware of their condition.[4] Age-adjusted mortality rates for COPD in the United States decreased among men between 1999 and 2014 but remained stable among women during the same period.[5] The

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prediction of mortality is important since it allows the identification of patients whose outcomes can be improved by implementing specific therapeutic measures.

As a marker of tissue injury, necrosis, and hypoxia, lactate dehydrogenase (LDH) has an essential value in the diagnosis, treatment, and prognosis of cancer.[6] Furthermore, patients with COPD have increased LDH levels. These levels indicate underlying lung damage and inflammation and show the usefulness of LDH and its isoenzymes as indicators of lung damage or inflammation.[7] However, the relationship between LDH and all-cause mortality in patients with COPD has scarcely been studied. The primary aim of this study was to assess the association between LDH levels and all-cause mortality.

Materials and Methods

Data Source and Study Design

The National Health and Nutrition Examination Survey (NHANES) is a major program of the National Center for Health Statistics (NCHS), an agency of the Centers for Disease Control and Prevention (CDC). This national survey is being conducted to assess the health of the entire United States (US) population. To generate population-level estimates, data is collected annually on a two-year cycle using a multistage probabilistic sampling design. Based on a design variable, we approximated the number of civilians (not institutionalized) using the data from the NHANES from 2007 to 2012. Demographic data, spirometry test results, disease information, and laboratory and questionnaire data related to disease definitions were also extracted and combined. We enrolled patients aged ≥ 20 years who completed spirometry and had their serum LDH levels measured (Figure 1). Data from this study are freely available on the NHANES homepage (http://www.cdc.gov/nchs/nhanes.htm) which has been approved by the NCHS Institutional

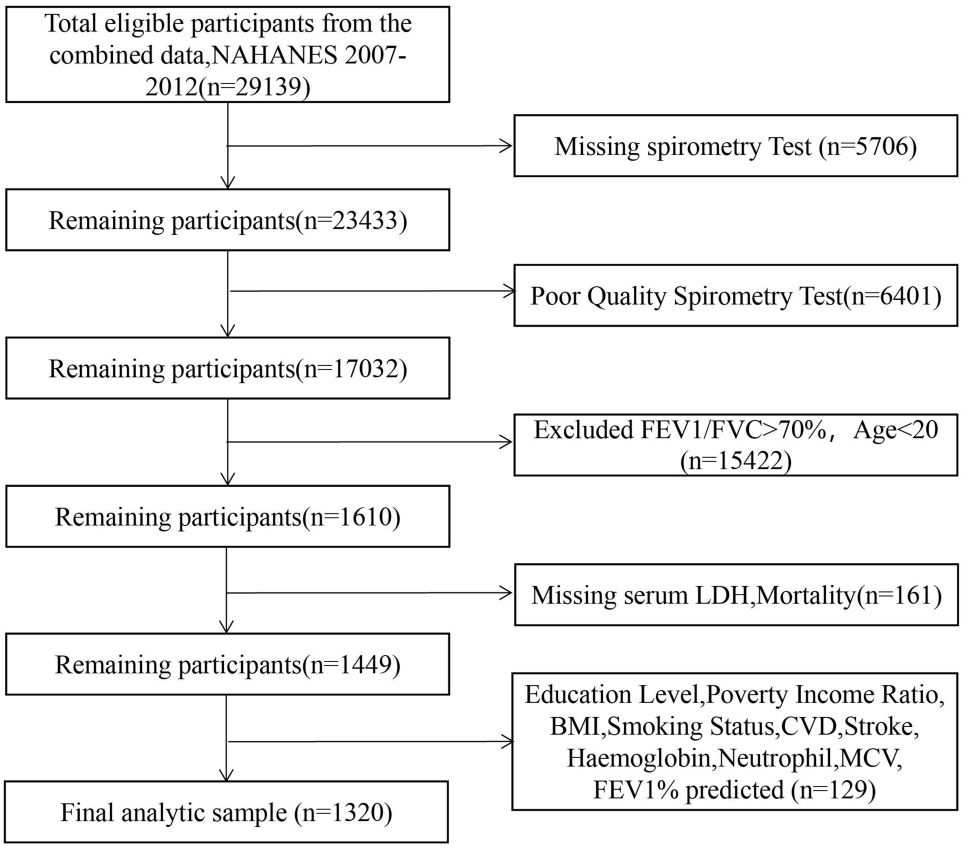

Figure 1 Study flowchart.

Abbreviations: NHANES, National Survey of the National Center for Health Statistics; FVC, forced vital capacity; FEV1, forced expiratory volume in the first 1 second; LDH, serum lactate dehydrogenase; BMI, body mass index; CVD, cardiovascular diseases; MCV, mean corpuscular volume; FEV1% predicted, forced expiratory volume in 1 second percent of predicted.

Review Board of the CDC. All participants provided informed written consent at the time of enrollment to the NHANES study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of The Second Affiliated Hospital of Gannan Medical University (number EFRJ20220819003).

LDH Levels

NHANES 2007–2012 used the enzyme rate method to measure serum LDH levels in all adult participants at baseline. We determined the LDH quintiles of study groups with COPD and chose 59–111 U/L, 112–123 U/L, 124–135 U/L, 136–150 U/L, and 151–344 U/L as the cut-off values for grouping. Patients were then divided into five groups (T1, T2, T3, T4, and T5).

Spirometry Test and COPD

During the NHANES 2007–2012, a spirometry test was performed on subjects who met specific inclusion criteria. To obtain reliable data, we only used forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) quality grade A and B data (A= meets American Thoracic Society [ATS] data collection standards: three acceptable curves present and two reproducible curves; two observed values within 100 mL, B= meets ATS data collection standards: three acceptable curves present and two reproducible curves; two observed values within 150 mL) In most subjects, spirometry tests were not performed post-bronchodilator use. Therefore, COPD was defined using pre-bronchodilator values of FEV1/FVC < 0.7; this is different from the Global Initiative definition for COPD.[8] The predicted FEV1 was derived from Hankinson's formula for age, sex, race, and height.[9] Classification was based on modified COPD classification criteria: stage III–IV (FEV1/FVC < 0.70, FEV1% [FEV1% of predicted] < 50% prediction, stage II (FEV1/FVC < 0.70, 50%≤ FEV1% < 80% prediction), and stage I (FEV1/FVC < 0.70, FEV1% ≥ 80% prediction).[8]

Definitions

We analyzed age, sex, race/ethnicity, body mass index (BMI), smoking status, modified GOLD stage (as described above), diabetes, cardiovascular disease (CVD), hypertension, stroke, and education level. Age was classified at baseline and used in table classifications (<65 and ≥65) and as a continuous variable in the regression analysis. Race/ethnicity was defined as Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black, or other (including multiracial). Using responses to a series of questions, the subjects were classified as current smokers, former smokers, or never smokers. To qualify as current or former smokers, a person must have smoked more than 100 cigarettes in their lifetime. Hypertension was defined as a systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, self-reported hypertension later diagnosed by a physician, or elevated BP requiring antihypertensive medication. Recorded systolic and diastolic blood pressures were the average of one to three blood pressure measurements. Diabetes was defined as fasting blood sugar level >126 g/L or a diagnosis of diabetes by a physician. A person was considered to have CVD if a doctor diagnosed heart disease, coronary artery disease, congestive heart failure, or stroke. A person was considered to have had a stroke if they reported being diagnosed with a stroke by a physician or other health professional. A person was considered to have cancer if they reported being diagnosed with cancer or malignancy by a physician. Education level was divided into three levels: <9 years, 9–13 years, and ≥13 years. For income-to-poverty ratios ($income/threshold), the ratio of family income to the poverty threshold was based on the number of people in the family or unrelated individuals. Family income was divided by poverty guidelines depending on the size of the family, appropriate year, and state in which it was calculated. Physical activity (PA) levels were evaluated. A detailed PA questionnaire, based on the Global Physical Activity Questionnaire, was used to assess leisure-time, occupation-related, and transportation-related PA. Questions about the frequency (per week), duration (minutes), and intensity (vigorous vs moderate) of a typical week were assessed for each type of PA. With details provided elsewhere.[10]

Mortality

We obtained mortality status and follow-up information for all subjects using the National Mortality Index as of December 31, 2019.

Statistical Analysis

Analysis of descriptive statistics was performed for all patients. Categorical variables are expressed as numbers and percentages. For normally distributed data, continuous variables are expressed as mean and standard deviation (SD) or median and interquartile range. For categorical, normally distributed, and non-normally distributed continuous variables, we used the chi-square test, one-way analysis of variance, and Kruskal–Wallis test, respectively. Multivariable Cox regression and smooth curve-fitting methods were used to examine the independent association between LDH levels and all-cause mortality. Three multivariable models were constructed. Model I was adjusted based on the age (continuous, years), sex (male or female), race (Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black, or other including multiracial), educational level (< 9 years, 9–13 years or ≥13 years), and Poverty Income Ratio (continuous). In model II, the results were further adjusted based on the BMI (continuous), smoking status (never, former, and current), and medical history (diabetes, hypertension, CVD, stroke, and cancer). In model III, the results were adjusted based on the alanine aminotransferase (ALT) (continuous), albumin (ALB) (continuous), neutrophil (continuous), hemoglobin (continuous), mean corpuscular volume (MCV) (continuous), and FEV1% predicted (continuous). Furthermore, a two-piecewise linear regression model with a smoothing curve was used to examine the nonlinear relationship between LDH levels and all-cause mortality. One-line linear regression was compared with two-piecewise linear regression using likelihood ratio tests. To determine the threshold value, we chose the point with the highest likelihood among all possible values.

Sensitivity analyses were conducted to further evaluate the robustness of the results. The analyses were stratified by age (<65 or ≥ 65 years), sex (male or female), race/ethnicity (non-Hispanic white or other), smoking status (never, ever, or current), BMI (<25, 25–30, ≥30), hypertension (yes or no), diabetes (yes or no), CVD (yes or no), GOLD stage (I or II-IV), former or current smoker with age ≥40 years (yes or no). The P values for the production terms between serum LDH levels and the stratified factors were used to estimate the significance of interactions.

We also conducted a series of sensitivity analyses. (1) To test the robustness of the results, we redefined the inclusion criteria for COPD patients. We used data from the NHANES from 2007 to 2012. The patients were diagnosed with COPD based on the presence of the following criteria: (I) available post-bronchodilator spirometry results with an FEV1/FVC <70%; (II) previous diagnosis of emphysema by a physician; (III) use of selective phosphodiesterase-4 inhibitors, mast cell stabilizers, leukotriene modifiers, or inhaled corticosteroids and age above 40 years with a history of smoking or chronic bronchitis. COPD is diagnosed as long as one of the criteria is met. We repeated the main analyses according to quintiles of serum LDH levels. (2) Further studies were conducted to explore the association between physical activity and serum LDH levels in patients with COPD. To assess the influence of PA on LDH in COPD patients, the patients were divided based on their LDH levels (LDH<110U/L and LDH>110U/L). Multivariate linear regression analyses was also performed. Then, the results were adjusted based on age, sex, race, education, BMI, predicted FEV1%, smoking status, diabetes, hypertension, and CVD.

R 4.1.3 (http://www.R-project.org, The R Foundation) and Free Statistics version 1.6 were used for all analyses. Differences were considered statistically significant with two-sided $p \leq 0.05$.

Results

Study Participants and Baseline Characteristics

Baseline characteristics of the subjects by quintiles or categories of LDH (59–111 U/L, 112–123 U/L, 124–135 U/L, 136–150 U/L and 151–344 U/L) are shown in Table 1. Of the 1320 patients with COPD, those who fulfilled the inclusion criteria were identified (Figure 1). The mean LDH was 132.5 U/L (SD, 27.0). Participants with higher quintiles of serum LDH levels tended to be older, non-Hispanic black, have lower levels of education and a higher prevalence of obesity, never smokers, more likely to have CVD and hypertension, have lower levels of FVC, FEV1, white blood cells (WBC), neutrophils, and hemoglobin, and higher levels of alanine aminotransferase (ALT). Group T3 (124–135 U/L) had a lower rate of mortality than the other groups.

Table 1 Baseline Characteristics of the Study Participants

Variables	Serum LDH Levels						
	Total (n = 1320)	59–111 (U/L) T1 (n = 253)	112–123 (U/L) T2 (n = 267)	124–135 (U/L) T3 (n = 278)	136–150 (U/L) T4 (n = 266)	151–344 (U/L) T5 (n = 256)	*P*-value
Age, years, n (%)							< 0.001
<65	814 (61.7)	184 (72.7)	172 (64.4)	180 (64.7)	148 (55.6)	130 (50.8)	
≥65	506 (38.3)	69 (27.3)	95 (35.6)	98 (35.3)	118 (44.4)	126 (49.2)	
Mean ± SD	57.9 ± 14.2	52.9 ± 15.3	56.4 ± 14.7	58.6 ± 12.7	60.0 ± 13.4	61.4 ± 13.4	< 0.001
Sex, n (%)							0.133
Male	823 (62.3)	153 (60.5)	182 (68.2)	172 (61.9)	169 (63.5)	147 (57.4)	
Female	497 (37.7)	100 (39.5)	85 (31.8)	106 (38.1)	97 (36.5)	109 (42.6)	
Race-ethnicity, n (%)							0.027
Mexican American	90 (6.8)	16 (6.3)	23 (8.6)	22 (7.9)	12 (4.5)	17 (6.6)	
Other Hispanic	90 (6.8)	13 (5.1)	25 (9.4)	17 (6.1)	22 (8.3)	13 (5.1)	
Non-Hispanic White	836 (63.3)	169 (66.8)	172 (64.4)	185 (66.5)	166 (62.4)	144 (56.2)	
Non-Hispanic Black	240 (18.2)	43 (17)	35 (13.1)	42 (15.1)	55 (20.7)	65 (25.4)	
Other Race-Including Multi Racial	64 (4.8)	12 (4.7)	12 (4.5)	12 (4.3)	11 (4.1)	17 (6.6)	
Education Level, n (%)							0.007
Low (<9 years)	128 (9.7)	13 (5.1)	22 (8.2)	35 (12.6)	28 (10.5)	30 (11.7)	
Medium (9–13 years)	576 (43.6)	125 (49.4)	97 (36.3)	122 (43.9)	115 (43.2)	117 (45.7)	
High (≥13 years)	616 (46.7)	115 (45.5)	148 (55.4)	121 (43.5)	123 (46.2)	109 (42.6)	
Poverty Income Ratio,(%) Mean ± SD	2.6 ± 1.6	2.5 ± 1.6	2.7 ± 1.7	2.6 ± 1.6	2.6 ± 1.6	2.6 ± 1.6	0.661
BMI, kg/m2, n (%)							0.044
Under weight (<18.5)	25 (1.9)	9 (3.6)	1 (0.4)	6 (2.2)	6 (2.3)	3 (1.2)	
Normal weight (18.5–24.9)	447 (33.9)	98 (38.7)	82 (30.7)	101 (36.3)	89 (33.5)	77 (30.1)	
Over wight (25–29.9)	463 (35.1)	85 (33.6)	108 (40.4)	96 (34.5)	89 (33.5)	85 (33.2)	
Obese (>30)	385 (29.2)	61 (24.1)	76 (28.5)	75 (27)	82 (30.8)	91 (35.5)	
Mean ± SD	27.8 ± 6.1	27.1 ± 6.3	28.0 ± 5.6	27.5 ± 5.7	28.0 ± 6.2	28.6 ± 6.4	0.066
Smoking Status, n (%)							0.004
Never Smoker	389 (29.5)	66 (26.1)	80 (30)	81 (29.1)	76 (28.6)	86 (33.6)	
Former Smoker	463 (35.1)	73 (28.9)	88 (33)	95 (34.2)	108 (40.6)	99 (38.7)	
Current Smoker	468 (35.5)	114 (45.1)	99 (37.1)	102 (36.7)	82 (30.8)	71 (27.7)	
Comorbidity							
CVD, n (%)	212 (16.1)	30 (11.9)	38 (14.2)	33 (11.9)	56 (21.1)	55 (21.5)	0.001
Hypertension, n (%)	689 (52.2)	107 (42.3)	134 (50.2)	126 (45.3)	156 (58.6)	166 (64.8)	< 0.001
Diabetes, n (%)	280 (21.2)	51 (20.2)	59 (22.1)	45 (16.2)	63 (23.7)	62 (24.2)	0.144
Stroke, n (%)	62 (4.7)	15 (5.9)	12 (4.5)	7 (2.5)	15 (5.6)	13 (5.1)	0.350
Cancer, n (%)	202 (15.3)	37 (14.6)	40 (15)	47 (16.9)	38 (14.3)	40 (15.6)	0.925

(*Continued*)

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Table 1 (Continued).

Variables	Serum LDH Levels						
	Total (n = 1320)	**59–111 (U/L) T1 (n = 253)**	**112–123 (U/L) T2 (n = 267)**	**124–135 (U/L) T3 (n = 278)**	**136–150 (U/L) T4 (n = 266)**	**151–344 (U/L) T5 (n = 256)**	***P*-value**
Follow-up in years Median (IQR)	9.7 (7.8, 11.2)	9.6 (7.8, 10.9)	9.7 (7.8, 11.0)	10.0 (8.4, 11.3)	9.6 (7.9, 11.2)	9.6 (7.6, 11.1)	0.205
Mortality, n (%)	252 (19.1)	40 (15.8)	50 (18.7)	41 (14.7)	62 (23.3)	59 (23)	0.028
Pulmonary function test							
FVC, (mL) Median (IQR)	3650.0 (2886.0, 4612.0)	3910.0 (3074.0, 4751.0)	3877.0 (3094.0, 4891.0)	3605.0 (3059.0, 4587.0)	3528.0 (2768.0, 4423.0)	3074.0 (2535.0, 4201.0)	< 0.001
FEV1, (mL) Median (IQR)	2282.0 (1846.0, 2992.0)	2428.0 (1900.0, 3044.0)	2321.0 (1902.0, 3076.0)	2330.0 (1874.0, 3066.0)	2210.0 (1848.0, 2938.0)	2116.0 (1628.0, 2658.0)	0.023
FEV1/FVC,(%) Mean ± SD	0.64 ± 0.07	0.63 ± 0.08	0.64 ± 0.06	0.64 ± 0.06	0.63 ± 0.07	0.64 ± 0.06	0.621
FEV1% predicted,(%) Mean ± SD	0.81 ± 0.18	0.79 ± 0.18	0.83 ± 0.17	0.83 ± 0.18	0.81 ± 0.17	0.81 ± 0.19	0.077
GOLD stage, n (%)							0.512
GOLD stage (I)	715 (54.2)	130 (51.4)	149 (55.8)	153 (55)	145 (54.5)	138 (53.9)	
GOLD stage (II)	541 (41.0)	105 (41.5)	112 (41.9)	112 (40.3)	107 (40.2)	105 (41)	
GOLD stage (III–IV)	64 (4.8)	18 (7.1)	6 (2.2)	13 (4.7)	14 (5.3)	13 (5.1)	
Laboratory							
WBC,($\times 10^9$/L) Mean ± SD	7.25 ± 2.05	7.48 ± 1.93	7.19 ± 1.92	7.54 ± 2.18	7.17 ± 2.19	6.84 ± 1.96	< 0.001
Neutrophil,($\times 10^9$/L) Mean ± SD	4.38 ± 1.64	4.50 ± 1.56	4.32 ± 1.56	4.59 ± 1.74	4.37 ± 1.76	4.08 ± 1.51	0.004
Hemoglobin,(g/dL) Mean ± SD	14.42 ± 1.48	14.37 ± 1.48	14.62 ± 1.46	14.56 ± 1.46	14.41 ± 1.46	14.15 ± 1.52	0.003
MCV, (fL) Mean ± SD	90.77 ± 5.57	90.84 ± 5.67	90.68 ± 5.69	90.59 ± 5.25	91.27 ± 5.30	90.46 ± 5.94	0.5
ALT,(U/L) Median (IQR)	20.0 (16.0, 27.0)	18.0 (15.0, 23.0)	19.0 (15.0, 25.0)	21.0 (17.0, 28.0)	21.0 (17.0, 27.0)	23.0 (18.8, 31.0)	< 0.001
ALB,(g/L) Mean ± SD	42.4 ± 3.1	42.3 ± 3.4	42.6 ± 3.1	42.7 ± 2.9	42.3 ± 2.8	42.0 ± 3.1	0.106
LDH, (U/L) Mean±SD	132.5 ± 27.0	100.9 ± 9.2	118.0 ± 3.5	129.1 ± 3.4	142.3 ± 4.1	172.2 ± 27.2	< 0.001

Abbreviations: FVC, forced vital capacity; FEV1, forced expiratory volume in the first 1 second; LDH, serum lactate dehydrogenase; BMI, body mass index; CVD, cardiovascular disease; FEV1% predicted, FEV in 1 second percent of predicted ratio of FEV1 to FVC; MCV, mean corpuscular volume; ALT, alanine aminotransferase; ALB, albumin.

Univariate Analysis of Risk Factors Associated with All-Cause Mortality in Patients with COPD

Table 2 shows the HR and 95% CI for the risk of all-cause mortality among patients with COPD. Age, male sex, low education level, low prevalence of poverty income ratio, smoking, low level of FVC, FEV1, FEV1% predicted, higher GOLD stage, albumin (ALB), WBC, neutrophil, hemoglobin, and mean corpuscular volume (MCV) were significantly associated with all-cause mortality ($p<0.05$) (Table 2).

Table 2 Univariate Analysis of Risk Factor Associated with All-Cause Mortality in Patients with COPD

Variables	HR (95% CI)	*P*-value
Age, n (%)		
<65	Ref.	
≥65	3.61 (2.78, 4.69)	< 0.001
Age (years)	1.07 (1.05, 1.08)	< 0.001
Sex, n (%)		
Male	Ref.	
Female	0.77 (0.59, 1)	0.046
Race-ethnicity, n (%)		
Mexican American	Ref.	
Other Hispanic	1.51 (0.68, 3.37)	0.311
Non-Hispanic White	1.93 (1.02, 3.65)	0.043
Non-Hispanic Black	1.88 (0.95, 3.72)	0.071
Other Race-Including Multi-Racial	1.13 (0.43, 2.96)	0.809
Education Level, n (%)		
Low (≤9 years)	Ref.	
Medium (9–13 years)	1.02 (0.68, 1.53)	0.92
High (≥13 years)	0.65 (0.42, 0.99)	0.045
Poverty Income Ratio, (%)	0.76 (0.7, 0.83)	< 0.001
BMI, kg/m^2, n (%)		
Under weight (<18.5)	0.78 (0.36, 1.69)	0.533
Normal weight (18.5–24.9)	Ref.	
Over wight (25–29.9)	0.77 (0.36, 1.67)	0.509
Obese (>30)	0.78 (0.36, 1.69)	0.533
BMI (kg/m^2)	0.9956 (0.9747, 1.0169)	0.681
Smoking Status, n (%)		
Never Smoker	Ref.	
Former Smoker	1.81 (1.3, 2.53)	< 0.001
Current Smoker	1.63 (1.16, 2.29)	0.005
Comorbidity		
CVD (YES vs NO), n (%)	2.62 (2.01, 3.43)	< 0.001
Hypertension (YES vs NO), n (%)	2.08 (1.59, 2.7)	< 0.001
Diabetes (YES vs NO), n (%)	2.15 (1.66, 2.79)	< 0.001
Stroke (YES vs NO), n (%)	2.26 (1.47, 3.48)	< 0.001
Cancer (YES vs NO), n (%)	1.44 (1.06, 1.95)	0.02
Pulmonary function test		
FVC, (mL)	0.9996 (0.9995, 0.9997)	< 0.001
FEV1, (mL)	0.9992 (0.9991, 0.9994)	< 0.001
FEV1/FVC, (%)	0.004 (0.001, 0.014)	< 0.001
FEV1% predicted,(%)	0.08 (0.04, 0.16)	< 0.001
GOLD stage, n (%)		
GOLD stage (I)	Ref.	
GOLD stage (II)	1.77 (1.35, 2.31)	< 0.001
GOLD stage (III or IV)	5.05 (3.4, 7.51)	< 0.001
Laboratory		
WBC,($\times 10^9$/L)	1.10 (1.04, 1.17)	0.002
Neutrophil,($\times 10^9$/L)	1.16 (1.08, 1.25)	< 0.001

(*Continued*)

Table 2 (Continued).

Variables	HR (95% CI)	*P*-value
Hemoglobin,(g/dL)	0.9 (0.82, 0.97)	0.01
MCV,(fL)	1.06 (1.03, 1.09)	< 0.001
ALT,(U/L)	0.9993 (0.9922, 1.0064)	0.839
ALB,(g/L)	0.9 (0.87, 0.94)	< 0.001
LDH,(U/L)	1.0069 (1.0028, 1.011)	0.001

Abbreviations: FVC, forced vital capacity; FEV1, forced expiratory volume in the first 1 second; LDH, serum lactate dehydrogenase; BMI, body mass index; CVD, cardiovascular disease; FEV1% predicted, forced expiratory volume in 1 second percent of predicted; MCV, mean corpuscular volume; ALT, alanine aminotransferase; ALB, albumin.

Multivariate Cox Proportional Hazards Regression Analysis of LDH Levels on All-Cause Mortality in Patients with COPD

All-cause mortality was 19.1% overall. Table 1 shows the all-cause mortality for different LDH levels. The all-cause mortality in groups T1–T5 was 15.8%, 18.7%, 14.7%, 23.3%, and 23.0%, respectively. Table 2 and Table 3 show the results of the univariate and multivariate Cox regression models, respectively. A multivariate Cox regression analysis using categorized LDH revealed a non-linear relationship between LDH and all-cause mortality in model III (the fully adjusted model). Group T3 (LDH 124–135 U/L) had the lowest all-cause mortality. Compared with group T3 (LDH 124–135 U/L), the HR of T1 (LDH 59–111 U/L), T2 (LDH 112–123 U/L), T4 (LDH 136–150 U/L), and T5 (LDH 151–344 U/L) were 1.22 (95% CI: 0.78–1.92), 1.60 (95% CI: 1.05–2.44), 1.52 (95% CI: 1.01–2.27), and 1.64 (95% CI: 1.08–2.47) after adjusting for all covariates in model III.

Nonlinear Relationship Between LDH and All-Cause Mortality of COPD

Using a multivariate Cox regression model and smooth curve fitting, we observed a nonlinear relationship between LDH level and all-cause mortality (Figure 2). A piecewise multivariate Cox regression model was fitted to the data, and two different slopes were obtained. We used a two-piecewise model to fit the link between LDH level and mortality in our study, where the P-value for the non-linear test was 0.005 (Table 4). On the left side of the inflection point, the HR was

Table 3 Multivariate Cox Regression for LDH on All-Cause Mortality of COPD

Variable	Total n	Non-Adjusted Model HR (95% CI)	*p* value	Model I HR (95% CI)	*p* value	Model II HR (95% CI)	*p* value	Model III HR (95% CI)	*p* value
Continuous variable									
LDH (per SD)	1320	1.2 (1.08~1.34)	0.001	1.15 (1.02~1.3)	0.023	1.16 (1.03~1.3)	0.016	1.17 (1.03~1.32)	0.013
Binary variable									
T1 LDH 59–111 (U/L)	253	1.14 (0.74~1.76)	0.558	1.46 (0.94~2.26)	0.094	1.32 (0.84~2.05)	0.225	1.22 (0.78~1.92)	0.386
T2 LDH 112–123 (U/L)	267	1.34 (0.88~2.02)	0.168	1.61 (1.06~2.44)	0.026	1.48 (0.98~2.26)	0.065	1.60 (1.05~2.44)	0.030
T3 LDH 124–135 (U/L)	278	Ref.		Ref.		Ref.		Ref.	
T4 LDH 136–150 (U/L)	266	1.66 (1.12~2.47)	0.011	1.65 (1.11~2.45)	0.013	1.54 (1.03~2.29)	0.035	1.52 (1.01~2.27)	0.043
T5 LDH 151–344 (U/L)	256	1.68 (1.13~2.51)	0.01	1.66 (1.11~2.48)	0.013	1.60 (1.06~2.40)	0.024	1.64 (1.08~2.47)	0.020
P for trend			0.022		0.420		0.316		0.247

Notes: Model I: adjusted for age + sex + race + education + poverty income ratio; Model II: adjusted for Model I+ BMI + smoking status + diabetes + hypertension + CVD + stroke + cancer; Model III: adjusted for Model II+ ALT+ ALB + neutrophil + hemoglobin + MCV + FEV1% predicted. FVC, FEV1, and FEV1/FVC were not included in the final model due to collinearity with the FEV1% predicted; WBC was not included in the final model due to collinearity with neutrophils.

Abbreviations: FVC, forced vital capacity; FEV1, forced expiratory volume in the first 1 second; LDH, serum lactate dehydrogenase; BMI, body mass index; CVD, cardiovascular disease; FEV1% predicted, forced expiratory volume in 1 second percent of predicted; MCV, mean corpuscular volume; ALT, alanine aminotransferase; ALB, albumin.

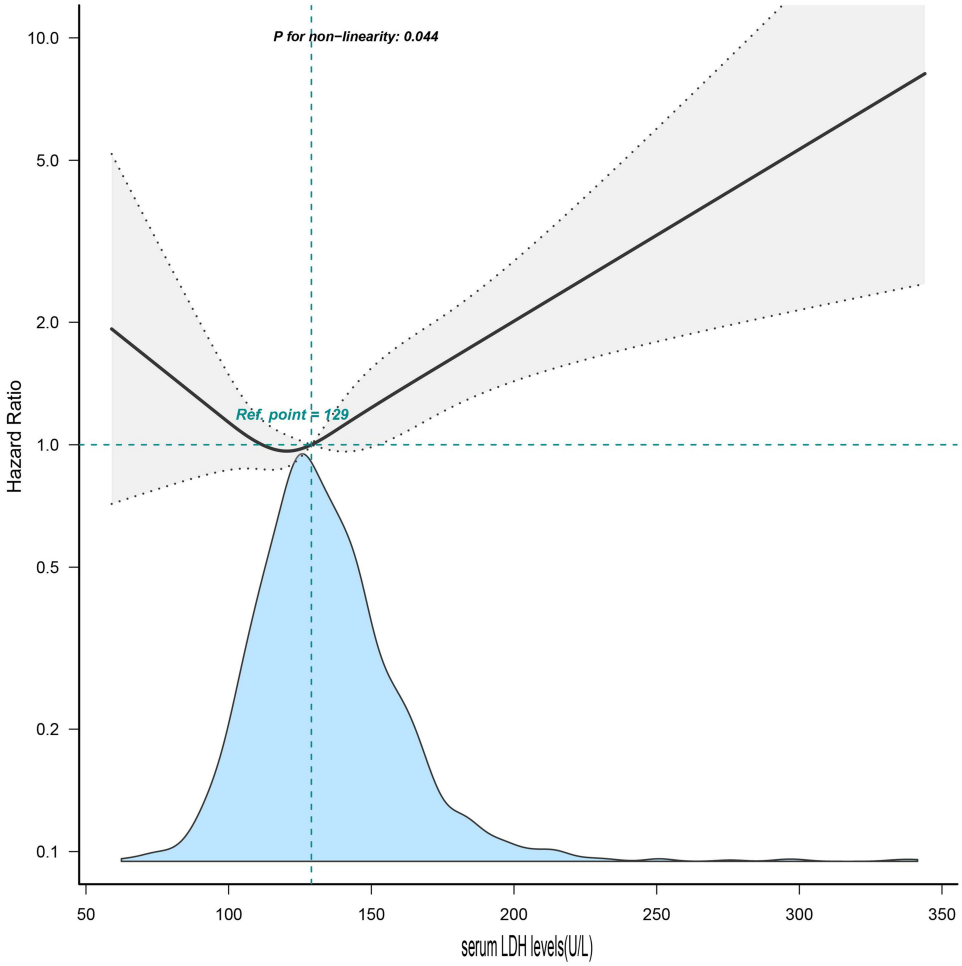

Figure 2 Association between serum LDH levels and all-cause mortality after adjusted for Model III. Adjusted for age + sex + race + education + poverty income ratio + BMI + smoking status + diabetes + hypertension + CVD + stroke + cancer + ALT + ALB + neutrophil + hemoglobin + MCV + FEV1% predicted.
Note: The black and dotted lines represent the estimated values and their corresponding 95% confidence intervals, respectively.
Abbreviations: BMI, body mass index; CVD, cardiovascular disease; MCV, mean corpuscular volume; FEV1% predicted, forced expiratory volume in 1 second percent of predicted; ALT, alanine aminotransferase; ALB, albumin.

0.32 (95% CI: 0.13–0.81). On the right side of the inflection point, the HR was 1.23 (95% CI: 1.08–1.41). As the LDH changed by 1SD, the risk of all-cause mortality began to decrease by 68% until an LDH level of approximately 110 U/L. Following that point, an all-cause mortality increase of 23% for per 1SD change in LDH was observed.

Table 4 The Non-Linear Relationship Between Serum LDH and All-Cause Mortality

Two-Piecewise Linear Regression Model	HR	95% CI	P-value
LDH<110 (U/L)(per sd)	0.32	0.13~0.81	0.016
LDH≥110 (U/L)(per sd)	1.23	1.08~1.41	0.002
Non-linear test			0.005
Likelihood Ratio test			0.004

Notes: Adjusted for age + sex + race + education + poverty income ratio + BMI + smoking status + diabetes + hypertension + CVD + stroke + cancer + ALT + ALB + neutrophil + hemoglobin + MCV + FEV1% predicted.
Abbreviations: FVC, forced vital capacity; FEV1, forced expiratory volume in the first 1 second; LDH, serum lactate dehydrogenase; BMI, body mass index; CVD, cardiovascular disease; FEV1% predicted, forced expiratory volume in 1 second percent of predicted; MCV, mean corpuscular volume; ALT, alanine aminotransferase; ALB, albumin.

Stratified and Sensitivity Analyses

No significant changes were observed after stratification by stage, and no significant interactions were found (Table S1). When we redefine COPD by new diagnostic criteria, 969 patients were included. The basic characteristics of the study population are summarized in Table S2. Similarly, A U-shaped association was observed between LDH and all-cause mortality among patients with COPD (Table S3 and Figure S1).

In the participants with a serum LDH below 110U/L, the PA positively correlated with LDH (β=29.21, 95% CI:2.74–55.68, P=0.032), However, among patients with a serum LDH greater than110U/L, no significant association was found between the PA and LDH (β= −1.54, 95% CI: −7.02–3.94, P=0.581) (Tables S4 and S5).

Discussion

We examined the optimal LDH level in patients with COPD in a nationally representative dataset of a US population. In this cohort, LDH was associated with all-cause mortality in a U-shaped pattern. Below and above the inflection point of 110 U/L, the correlation between LDH and all-cause mortality for patients with COPD differed significantly. Below the threshold value, a lower serum LDH level was associated with an increased all-cause mortality rate. Above the threshold value, a higher serum LDH level was associated with an increased all-cause mortality rate.

LDH is an important cytoplasmic enzyme in the anaerobic metabolic pathway that is present in virtually all major organ systems. Despite having no further metabolic function outside the cell, LDH is important because it serves as an indicator of a disorder in cell integrity caused by a pathological condition. LDH is released into the peripheral blood after cell death from conditions such as: ischemia, overheating or hypothermia, hunger, dehydration, injury, and exposure.[11] Because of this mechanism, high levels of LDH are often used as a poor prognostic marker in many diseases.[12–14] However, The study revealed that serum LDH levels below 110 U/L were associated with increased all-cause mortality rates. This differs from that reported in previous literature. A possible explanation is that in patients with LDH < 110 U/L, increasing physical activity may lead to the elevation of LDH, and physical activity has been shown to be negatively associated with all-cause mortality in patients with COPD. In healthy participants with normal LDH levels, higher average LDH levels were found to be significantly associated with more years, days/week, and minutes/week of leisure time activity.[15,16] Moreover, the positive correlation between physical activity and LDH has been confirmed in marathon athletes.[17] A study of patients with stable COPD revealed that physical activity was inversely associated with all-cause mortality in COPD.[18] In this study, our results confirmed this hypothesis, which stated that in patients with an LDH < 110 U/L, increasing physical activity increased the LDH levels. This mechanism may explain why LDH levels less than 110 U/L were inversely associated with all-cause mortality in COPD in our study. Moreover, LDH was only measured once, and it may be subject to errors in measurement. The association between a serum LDH below 110 U/L and all-cause mortality remains unclear. Further research is needed to address this issue. However, with LDH levels above 110 U/L, the positive association between physical activity and LDH found in the normal population may not be fully applicable in the COPD population. This may explain the positive association of LDH with all-cause mortality in patients with COPD found in our study. Previously, elevated LDH has been reported in the COPD population; however, prior to our study, its direct association with mortality had not been explored. Our results showed that LDH levels greater than 110 U/L were positively associated with all-cause mortality in patients with COPD. Increased LDH levels in the COPD population may influence all-cause mortality through numerous mechanisms. First, COPD is a systemic inflammatory disease, and multiple inflammatory-related markers, such as neutrophils, fibrinogen, C-reactive protein, and ALB, have been shown to be significantly associated with mortality in patients with COPD.[19–22] The increase of LDH activity in patients with COPD due to inflammation may be due to disruption (necrosis) of airway and/or alveolar epithelial cells, alveolar macrophages, or other lung cell types; increased flux of plasma-derived LDH through the air/blood barrier to exacerbate permeability in lung injury (eg edema and bleeding); and increased plasma LDH concentration increases the plasma-alveolar concentration gradient, which leads to an increase in the rate at which LDH passes through the air/blood barrier of the normal lung.[7] Hypoxia leads to an increase in red blood cell (RBC) volume, RBC distribution width (RDW), and changes in the pulmonary gas exchange microenvironment in patients with COPD.[22] MCV has been shown to correlate positively with COPD mortality,[23] and changes in MCV and RDW reflect the disruption of the erythrocyte membrane. The resulting release of large amounts of LDH from the RBC into the peripheral blood leads to an increase in serum LDH. Finally,

LDH has five different isozymes (LDH1, LDH2, LDH3, LDH4, and LDH5), and LDH3 dominates in the lung. Increased plasma LDH3 activity has been suggested to reflect acute lung injury-induced cell injury and cell death because plasma LDH3 levels are elevated during pulmonary embolism.[7] Castelli et al[24] also demonstrated a positive association between elevated LDH and all-cause death in a cohort of patients with pulmonary embolism. However, a cross-sectional study revealed that the increase in LDH in patients with acute exacerbation of COPD (AECOPD) was mainly due to the increase in LDH1 and LDH2, whereas the proportion of LDH3 and LDH4 decreased.[25] The underlying cause is that AECOPD mimics the increased aerobic metabolism caused by exercise fatigue, unlike uncomplicated respiratory infections. This leads to an increase in the LDH isozyme level of the main aerobic function. Although the effect of the proportion of LDH isozymes in patients with COPD remains controversial, the common denominator is an increase in serum LDH levels. In summary, all-cause mortality in patients with COPD is affected by an increase in LDH through the above possible mechanisms. Our study further confirmed that LDH levels above 110 U/L were positively correlated with all-cause death in COPD.

Previous studies reported many factors influencing all-cause mortality in patients with COPD; age, sex, smoking status, comorbidity, obstructive status, FEV1% predicted, ALB, neutrophil, hemoglobin, and RBC volume were found to be independently associated with all-cause mortality in patients with COPD. However, after adjusting for these variables, we still found a curvilinear relationship between LDH and all-cause mortality in COPD.

Limitations

LDH levels were measured at a single point in time; therefore, a temporal association between LDH levels and any of the markers of disease could not be determined. Because most subjects lacked post-bronchodilator spirometry data, COPD was defined as a pre-bronchodilator FEV1/FVC < 0.7, which is different from the global COPD Management Initiative definition. Consequently, some participants with asthma may have been considered as having COPD in this analysis. Additionally, not all participants were physically able to undergo pulmonary function testing, which may have biased the sample toward healthier individuals. We did not have access to other indicators of disease activity in COPD, such as exacerbation measures or radiographic data. Finally, we did not analyze LDH isozyme levels and could not validate the association of LDH with all-cause mortality in COPD using changes in the LDH isozyme. We look forward to clarifying this in our next study.

Conclusion

In conclusion, both low and high levels of serum LDH were significantly associated with an increased risk of all-cause mortality in the US general population with COPD. This suggests focusing more on these high-risk populations in future studies.

Abbreviations

LDH, lactate dehydrogenase; COPD, chronic obstructive pulmonary disease; SD, standard deviation; HR, hazard ratio; CI, confidence interval; NHANES, National Health and Nutrition Examination Survey; NCHS, National Center for Health Statistics; CDC, Centers for Disease Control; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; ATS, American Thoracic Society; FEV1% predicted, FEV in 1 second percent of predicted ratio of FEV1 to FVC; BMI, body mass index; CVD, cardiovascular disease; WBC, white blood cells; ALT, alanine aminotransferase; ALB, albumin; RBC, red blood cells; RDW; RBC distribution width; AECOPD, acute exacerbation of COPD.

Data Sharing Statement

The data are available at the NHANES website (http://www.cdc.gov/nchs/nhanes.htm).

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Disclosure

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