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Serum lactate dehydrogenase as a prognostic marker for 90-day mortality in connective tissue disease patients receiving glucocorticoids and hospitalized with pneumonia: a cohort study

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Elevated serum lactate dehydrogenase (LDH) levels have been associated with poor prognosis in various diseases. This study investigates the relationship between serum LDH levels and 90-day mortality in patients with connective tissue disease (CTD) receiving glucocorticoids and hospitalized with pneumonia. A total of 298 CTD patients were included in this study. The cohort was divided into three groups based on serum LDH levels (Group 1: < 246 U/L, 0% mortality; Group 2: 246–407 U/L, 26% mortality; Group 3: ≥ 407 U/L, 48% mortality). Clinical and laboratory data were analyzed to evaluate the association between LDH levels and 90-day mortality using Kaplan-Meier survival curves, Cox regression models, and subgroup analyses. Elevated LDH levels were significantly associated with increased mortality. The Kaplan-Meier survival analysis demonstrated that patients in Group 3 (highest LDH levels) had the highest 90-day mortality rate, while those in Group 1 (lowest LDH levels) had the lowest ($p < 0.0001$). Multivariate Cox regression analysis revealed that every 100 U/L increase in LDH was associated with a higher risk of mortality (HR 1.07, 95% CI 1.01–1.13, $p = 0.02$). Patients in Group 3 showed a significantly increased risk of mortality (HR 2.29, 95% CI 1.06–4.96, $p = 0.036$). The subgroup analyses demonstrated stable results across different clinical subgroups. Elevated serum LDH levels, particularly in Group 3, are independently associated with increased 90-day mortality in CTD patients receiving glucocorticoids and hospitalized with pneumonia. LDH may serve as an important prognostic marker for these patients.

Keywords Serum lactate dehydrogenase, 90-day mortality, Connective tissue disease, Prognosis, Mortality

Lactate dehydrogenase (LDH) is a crucial enzyme involved in cellular metabolism and energy production, playing a key role in the conversion of lactate to pyruvate[1]. Elevated serum LDH levels are often associated with tissue damage and are considered a nonspecific biomarker for various conditions, including infections, malignancies, and inflammatory diseases[2–4]. In patients with connective tissue disease (CTD), LDH has been linked to disease activity and organ involvement, but its role as a prognostic marker in CTD patients receiving glucocorticoid therapy and hospitalized for pneumonia remains unclear.

Pneumonia is a common and serious complication in patients with CTD, particularly those undergoing immunosuppressive treatment with glucocorticoids[5,6]. Glucocorticoids, while effective in controlling autoimmune inflammation, are known to impair immune function, increasing the susceptibility to infections, including pneumonia[7,8]. The high morbidity and mortality rates associated with pneumonia in this patient population necessitate the identification of reliable biomarkers to predict outcomes and guide treatment strategies[9].

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Previous studies have demonstrated the prognostic value of LDH in various infectious and inflammatory conditions[10], but its specific association with mortality in CTD patients remains underexplored. This cohort study aims to investigate the relationship between serum LDH levels and 90-day mortality in CTD patients receiving glucocorticoids who are hospitalized with pneumonia. Understanding the predictive value of LDH could provide critical insights into patient prognosis and help guide clinical decision-making in this vulnerable group.

This study aimed to assess the association between serum LDH levels and 90-day mortality in CTD patients receiving glucocorticoids who were hospitalized with pneumonia. We hypothesize that higher serum LDH levels are associated with an increased risk of mortality in CTD patients hospitalized with pneumonia, and that LDH could serve as a useful biomarker for monitoring disease severity and predicting outcomes in this cohort.

Methods

Study population

This study extends a prior retrospective cohort analysis[11] conducted across six academic hospitals in China from January 1, 2013, to December 31, 2017. The initial cohort included 1397 patients with various immunocompromised conditions, including connective tissue diseases, nephrotic syndrome, idiopathic interstitial pneumonia, bronchial asthma, and chronic obstructive pulmonary disease (COPD).

Exclusion criteria

[1] CTD patients not receiving glucocorticoids;[2] Patients without available pathogen testing;[3] Patients without CTD;[4] Patients without Lactate dehydrogenase.

Inclusion criteria

[1] Patients receiving glucocorticoids or intravenous treatments for pneumonia;[2] Patients with available sputum or bronchoalveolar lavage fluid (BALF) data for etiological testing;[3] Patients with available serum Lactate dehydrogenase levels;[4] Patients with CTD.

Data source

The data for this study were obtained from the 'DATADRYAD' database, based on the dataset provided by Li et al. (2020). The dataset included variables such as patient demographics, laboratory parameters (WBC, hemoglobin, ALB, ALT, creatinine, glucose, PCT, and D-dimer), clinical features (respiratory failure, mechanical ventilation, ICU admission, PSI scores), and treatment factors (use of high-dose glucocorticoids and immunosuppressants)[12]. The primary outcome measured was 90-day mortality[13].

Statistical analysis

All analyses were conducted using R statistical software (http://www.R-project.org) and Free Statistics software version 2.0. Continuous variables were reported as mean ± standard deviation or median with interquartile range, while categorical variables were presented as counts and percentages. Depending on the data type, chi-square tests, One-Way ANOVA, or the Kruskal-Wallis H test were used for statistical comparisons.

Survival between groups was compared using Kaplan-Meier curves and the log-rank test. A P-value of less than 0.05 was deemed statistically significant.

Results

Baseline characteristics of study participants by serum lactate dehydrogenase levels

A total of 298 patients were included (Fig. 1), categorized into three groups based on serum LDH levels (Group 1: < 246 U/L, 0% mortality; Group 2: 246–407 U/L, 26% mortality; Group 3: ≥ 407 U/L, 48% mortality). There were no significant differences in age, gender, coronary heart disease (CHD), diabetes mellitus (DM), smoking, alcoholism, or shock among the groups (all $p > 0.05$). Significant differences were observed in clinical parameters. Group 3 had the lowest oxygenation index (199.1 ± 126.9), lowest Albumin (31.0 ± 5.6), highest white blood cell count (WBC, 10.0 ± 5.3), and highest blood glucose (GLU, 8.0 ± 4.2) compared to Groups 1 and 2 ($p < 0.001$ for all). The pneumonia severity index (PSI) was also highest in Group 3 (82.8 ± 33.0, $p = 0.012$). The 90-day mortality rate was significantly higher in Group 3 (48%) compared to Group 2 (26%) and Group 1 (10.2%) ($p < 0.001$). Elevated lactate dehydrogenase (LDH) levels were associated with higher mortality, particularly in Group 3 (Table 1). These results suggest that Lower oxygenation index and Higher WBC, GLU, PSI, and LDH levels are associated with increased mortality in patients with connective tissue disease receiving glucocorticoids and hospitalized with pneumonia.

Association between serum lactate dehydrogenase levels and 90-mortality rate in connective tissue disease

The Kaplan-Meier curve revealed that CTD patients in LDH Tertile 3 had the highest 90-day mortality, while those in LDH Tertile 1 had the lowest ($p < 0.0001$, Fig. 2).

Univariate predictors of 90-day mortality in CTD-associated pneumonia patients showed significant associations for older age (peak HR = 3.07 for 50-59y), high-dose glucocorticoids (HR 2.49), leukocytosis (HR 1.08/10^9/L), hyperglycemia (HR 1.07/mmol/L), higher PSI scores (HR 1.02/point), and elevated LDH (HR = 1.0008/U/L), while better oxygenation (HR 0.99) and higher albumin (HR 0.92/g/L) were protective. Other variables including comorbidities and inflammatory markers were non-significant (all $p > 0.05$) (Table S1).

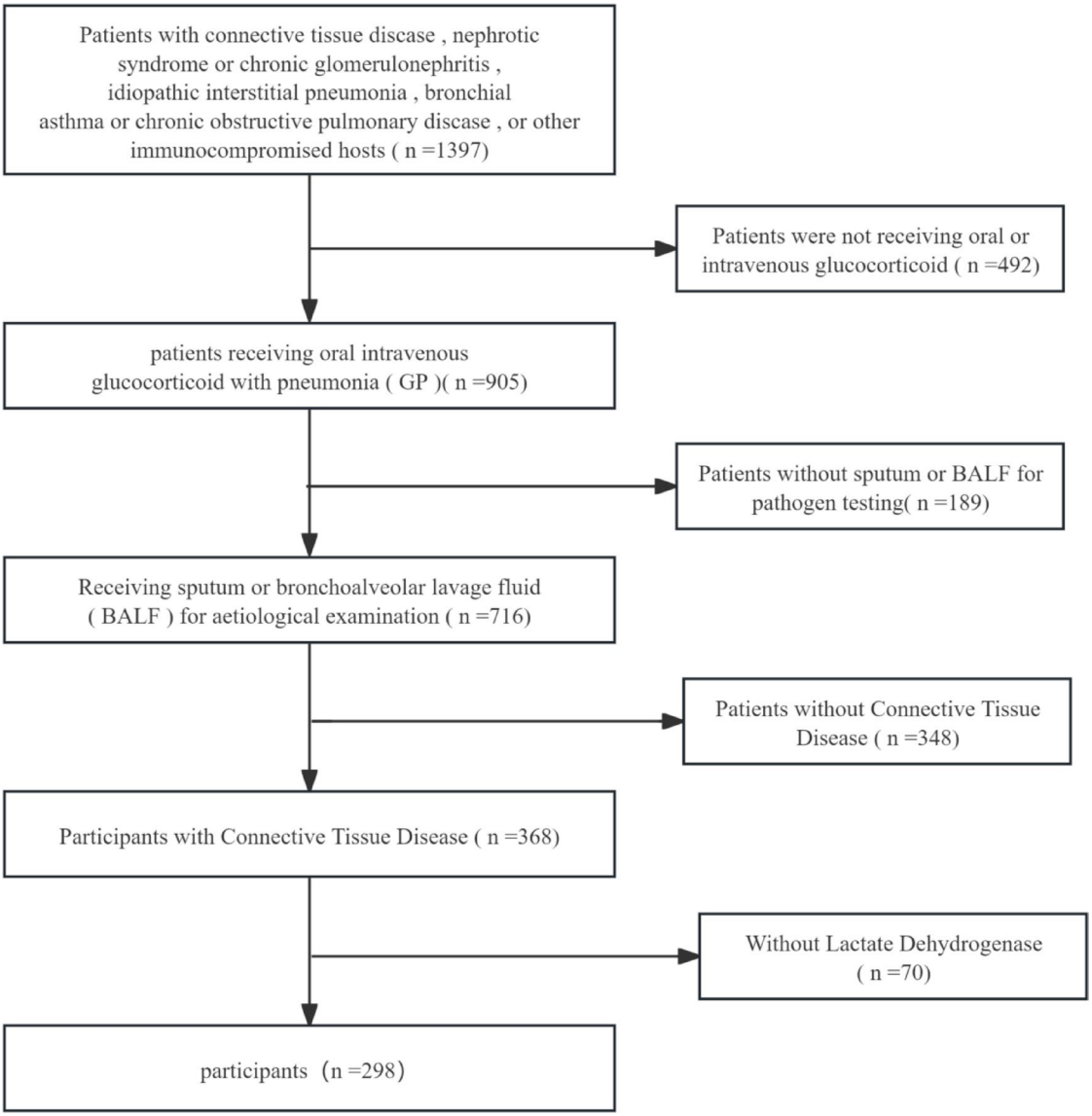

Fig. 1. Study flow diagram in the our study.

Multivariate Cox regression analysis (Table 2) revealed that lactate dehydrogenase (LDH) remained a significant predictor of 90-day mortality after adjusting for potential confounders. For per 100U/L increase in LDH was associated with a higher risk of mortality (HR 3.46, 95% CI 1.6–7.46, $p = 0.02$).

LDH levels in Group 3 (HR 3.46, 95% CI 1.6–7.46, $p = 0.02$) were significantly associated with higher mortality. Trend testing confirmed a significant association between increasing LDH levels and mortality ($p < 0.001$). These findings highlight that elevated LDH levels, particularly LDH levels in Group 3, are independently associated with higher mortality in patients with connective tissue disease receiving glucocorticoids and hospitalized with pneumonia.

A non-linear regression analysis revealed a significant overall association between LDH and mortality ($p = 0.723$). This suggests a potential inverse relationship between LDH levels and risk, with higher LDH values associated with lower hazard ratios (Fig. S1).

Subgroup analyses

Subgroup and interaction analyses were conducted to assess whether the relationship between serum LDH levels and 90-day mortality in CTD patients varied by age, sex, Highdoseglucocorticoid and DM (Fig. 3). No significant interactions were found across these subgroups.

Discussion

This study investigates the association between serum lactate dehydrogenase (LDH) levels and 90-day mortality in patients with connective tissue disease (CTD) who were receiving glucocorticoids and hospitalized with pneumonia. Our results suggest that higher LDH levels are associated with increased 90-day mortality in this

Variables	Total	Lactate dehydrogenase (U/L)			*P*-value
		<246	246–407	≥407	
Participants	298	98	100	100	
Age (years), n (%)					0.184
<40	42 (14.1)	12 (12.2)	12 (12)	18 (18)	
40–49	45 (15.1)	15 (15.3)	14 (14)	16 (16)	
50–59	55 (18.5)	17 (17.3)	19 (19)	19 (19)	
60–69	84 (28.2)	21 (21.4)	33 (33)	30 (30)	
70–79	44 (14.8)	21 (21.4)	10 (10)	13 (13)	
≥80	28 (9.4)	12 (12.2)	12 (12)	4 (4)	
Gender, n (%)					0.485
Male	120 (40.3)	35 (35.7)	44 (44)	41 (41)	
Female	178 (59.7)	63 (64.3)	56 (56)	59 (59)	
CHD, n (%)					0.826
No	263 (88.3)	88 (89.8)	88 (88)	87 (87)	
Yes	35 (11.7)	10 (10.2)	12 (12)	13 (13)	
Diabetes mellitus, n (%)					0.361
No	223 (74.8)	77 (78.6)	70 (70)	76 (76)	
Yes	75 (25.2)	21 (21.4)	30 (30)	24 (24)	
Alcoholism, n (%)					0.958
No	276 (92.6)	91 (92.9)	92 (92)	93 (93)	
Yes	22 (7.4)	7 (7.1)	8 (8)	7 (7)	
Highdoseglucocorticoid, n (%)					<0.001
No	177 (59.4)	77 (78.6)	66 (66)	34 (34)	
Yes	121 (40.6)	21 (21.4)	34 (34)	66 (66)	
Oxygenationindex, mean ± SD	271.7 ± 133.9	333.2 ± 112.1	284.0 ± 127.2	199.1 ± 126.9	<0.001
White cell(×109/L), mean ± SD	8.7 ± 4.8	6.9 ± 3.2	9.1 ± 5.1	10.0 ± 5.3	<0.001
Glucose(mmol/L), mean ± SD	7.2 ± 4.2	5.9 ± 3.1	7.8 ± 4.7	8.0 ± 4.2	<0.001
NA(mmol/L), mean ± SD	137.2 ± 7.8	137.6 ± 5.1	136.9 ± 4.8	137.1 ± 11.7	0.824
Procalcitonin (ng/ml), Mean ± SD	2.5 ± 12.5	3.3 ± 20.3	1.5 ± 3.9	2.8 ± 7.0	0.599
PSI, mean ± SD	76.8 ± 31.3	69.8 ± 29.1	77.7 ± 30.6	82.8 ± 33.0	0.012
Albumin(g/L), mean ± SD	32.8 ± 5.5	35.1 ± 5.2	32.2 ± 4.9	31.0 ± 5.6	<0.001
CRP(mg/L), median (IQR)	3.1 (1.1, 11.3)	2.5 (0.9, 10.9)	2.5 (1.2, 11.9)	3.7 (1.1, 11.2)	0.695
d90, n (%)					<0.001
Alive	214 (71.8)	88 (89.8)	74 (74)	52 (52)	
Death	84 (28.2)	10 (10.2)	26 (26)	48 (48)	

Table 1. Baseline characteristics of participants according to the serum lactate dehydrogenase levels. *CHD* coronary heart disease, *NA* sodium, *PSI* pneomonia severity index, *CRP* C-reactive protein.

Variable	Model I		Model II		Model III		Model IV	
	HR (95%CI)	Pvalue	HR (95% CI)	Pvalue	HR (95% CI)	Pvalue	HR (95% CI)	Pvalue
LDH(per 100U/L increase)	1.08 (1.04 ~ 1.11)	<0.001	1.12 (1.07 ~ 1.17)	<0.001	1.06 (1.01 ~ 1.12)	0.025	1.08 (1.02 ~ 1.14)	0.005
LDH tertile								
T1	Ref		Ref		Ref		Ref	
T2	2.77 (1.33 ~ 5.74)	0.006	2.86 (1.37 ~ 5.96)	0.005	1.65 (0.76 ~ 3.56)	0.205	1.71 (0.78 ~ 3.72)	0.178
T3	6.21 (3.14 ~ 12.27)	<0.001	7.51 (3.74 ~ 15.06)	<0.001	2.22 (1.04 ~ 4.74)	0.04	3.46 (1.6 ~ 7.46)	0.002
Trend.test	2.42 (1.79 ~ 3.27)	<0.001	2.71 (1.98 ~ 3.71)	<0.001	1.45 (1.03 ~ 2.05)	0.035	1.9 (1.33 ~ 2.73)	<0.001

Table 2. Relationship between LDH and 90-day mortality. *LDH* lactate dehydrogenase, *HR* hazard ratio, *CI* confidence index, *CHD* coronary heart disease, *NA* sodium, *PSI* pneomonia severity index, *CRP* C-reactive protein. Model I: No adjust. Model II: Adjust for Age, Gender, Alcoholism, CHD, Diabetes mellitus. Model III: Adjust for Age, Gender, CHD, Diabetes mellitus, Alcoholism, Oxygenationindex, White cell, Glucose, sodium, Procalcitonin, C-reactive protein, Albumin. Model IV: Adjust for Age, Gender, CHD, Diabetes mellitus, Alcoholism, Oxygenationindex, White cell, Glucose, sodium, Procalcitonin, C-reactive protein, Albumin, PSI, Highdoseglucocorticoid.

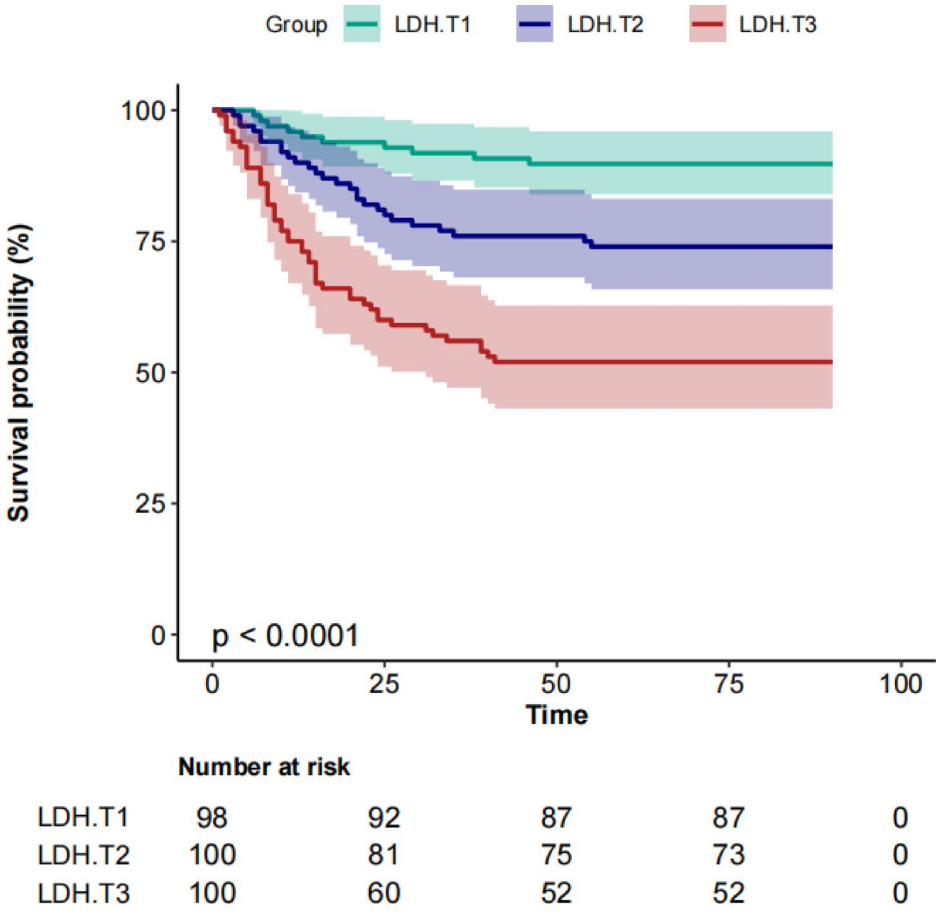

Fig. 2. Kaplan-Meier survival curves for 90-day mortality of connective tissue disease patients.

cohort. This finding underscores the potential utility of LDH as a prognostic biomarker in critically ill CTD patients and may help guide clinical decision-making in this high-risk population.

Lactate dehydrogenase is a key enzyme involved in cellular metabolism, and its elevated levels are often indicative of tissue damage, hypoxia, or inflammation[14–16]. Previous studies have suggested that LDH is associated with poor prognosis in various diseases, including cancer[17], cardiovascular diseases[18], and autoimmune disorders[19]. In CTD, where patients are often immunocompromised due to both the disease and its treatment with glucocorticoids, elevated LDH levels may reflect severe organ dysfunction or uncontrolled inflammation[20,21]. Our findings extend this knowledge, showing that elevated LDH levels are significantly correlated with higher mortality in CTD patients hospitalized with pneumonia.

Although our study did not directly incorporate the Charlson Comorbidity Index (CCIS), we adjusted for major comorbidities (e.g., DM, CHD) and systemic severity markers (e.g., PSI, oxygenation index) in our multivariate models. Future studies should explicitly evaluate CCIS or other composite indices to further validate the independent prognostic role of LDH in this population. Additionally, while lung-specific biomarkers (e.g., KL-6, SP-D) show promise in AE-IP, their role in CTD-associated pneumonia remains less defined. LDH, as a marker of systemic cellular injury, may capture broader disease severity in this population, including extrapulmonary complications. Direct comparisons between LDH and lung-specific biomarkers in future studies could clarify their respective prognostic roles, particularly in cases where pneumonia coexists with CTD-driven multiorgan dysfunction.

In our cohort, patients with LDH levels ≥ 407 U/L had a substantially higher risk of mortality, with a hazard ratio (HR) of 3.46. This highlights the importance of monitoring LDH levels in CTD patients, as higher values may indicate the need for more aggressive interventions. While LDH levels ≥ 246 U/L did not reach statistical significance in our multivariate analysis, the trend suggests a dose-dependent relationship between LDH levels and mortality, which warrants further investigation in larger cohorts or longitudinal studies.

In addition to LDH, several other factors were found to be significant predictors of mortality, including age, oxygenation index, white blood cell count (WBC), blood glucose levels, and the pneumonia severity index (PSI)[22,23]. Older age, lower oxygenation index, and higher WBC and glucose levels were all associated with an increased risk of mortality, which aligns with findings from previous studies in critically ill patients[24]. The PSI, a well-established tool for predicting mortality in pneumonia patients, was also significantly associated with 90-day mortality in our cohort[25]. These results further validate the importance of comprehensive clinical evaluation, including assessment of laboratory parameters, in predicting outcomes in this vulnerable population.

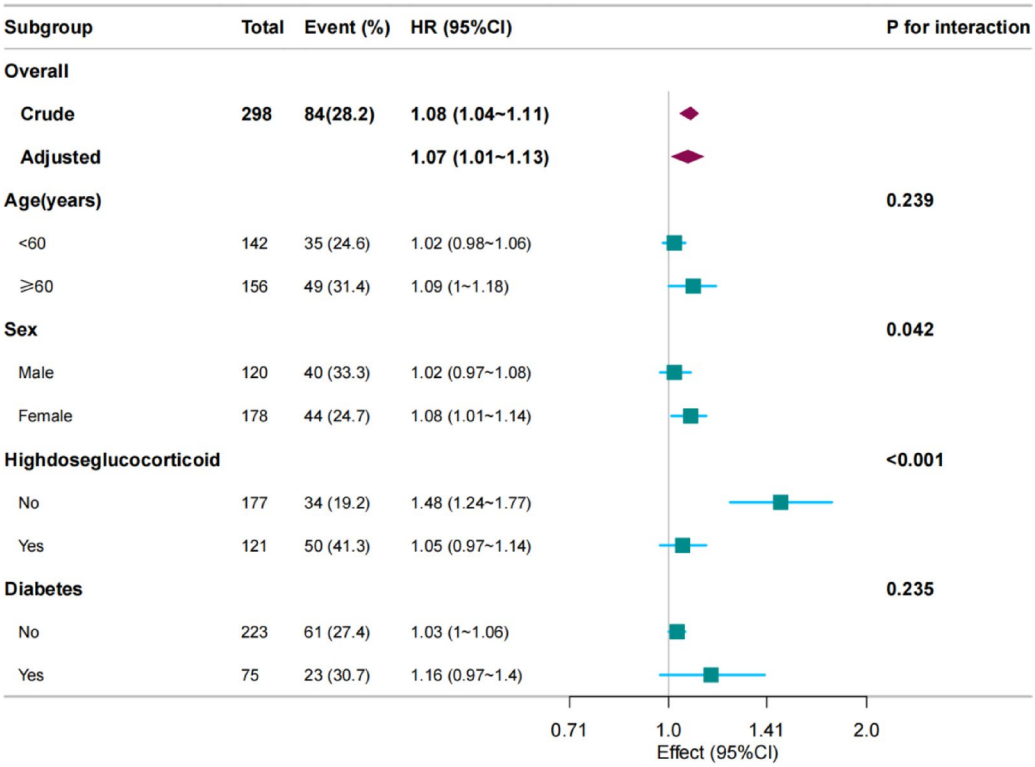

Fig. 3. Subgroup analyses of the association between serum lactate dehydrogenase and 90-day mortality.

Subgroup analyses were conducted to determine whether the association between LDH and mortality differed by age, sex, smoking, alcoholism, CHD, and DM. No significant interactions were observed, suggesting that the relationship between LDH and mortality is consistent across these subgroups. This finding is reassuring, as it implies that LDH can be a broadly applicable biomarker for predicting mortality in this patient population, regardless of these common demographic and clinical factors.

While our study provides important insights into the role of LDH in predicting mortality in CTD patients, several limitations should be acknowledged. First, this is a single-center, retrospective cohort study, which may limit the generalizability of our findings. Larger, multicenter studies are needed to confirm these results and explore the underlying mechanisms linking LDH to mortality. While our sample size was adequate to detect clinically relevant effects, wider CIs in subgroup analyses suggest future studies with larger cohorts could refine precision. Additionally, the exact cutoff values for LDH that predict mortality in CTD patients need to be further validated. Our analysis did not account for the potential effects of different treatment regimens (e.g., type and duration of glucocorticoid therapy), which could influence both LDH levels and patient outcomes. Future studies should investigate these factors in greater detail. Third, detailed information on glucocorticoid regimens (e.g., exact dosages, duration, and tapering protocols) and specific immunosuppressive therapies (e.g., cyclophosphamide, rituximab) was not available in the dataset. Although we adjusted for high-dose glucocorticoid use to account for treatment variability, the lack of granular treatment data may introduce residual confounding.

To address these limitations, we strongly advocate for multicenter prospective studies that rigorously capture:[1] glucocorticoid dosing and duration[2], concomitant immunosuppressive therapies, and[3] serial LDH measurements. Such studies could clarify whether LDH's prognostic value is modified by treatment intensity or specific medications.

Conclusion

In conclusion, elevated serum LDH levels are independently associated with increased 90-day mortality in CTD patients receiving glucocorticoids and hospitalized with pneumonia. Our findings suggest that LDH may serve as a valuable prognostic marker in this high-risk population, helping to identify patients who are at increased risk of poor outcomes. Further research is needed to confirm these results and explore the potential clinical applications of LDH in managing CTD patients with pneumonia.

Data availability

Data will be made available upon reasonable request (Yuansheng Lin).

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Author contributions

Conceptualization: YSL. Methodology: XKC. Investigation: LLL. Visualization: YMT. Writing—original draft: YSL. Writing—review & editing: XKC.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

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