Serum lactate dehydrogenase level may predict acute respiratory distress syndrome of patients with fever infected by SARS-CoV-2

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As of March 9, 2020, more than 100,000 cases of coronavirus disease-2019 (COVID-19) were reported in more than 100 countries with thousands deaths globally. It is now known that Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is a new type of coronavirus causing COVID-19 infection (1). The most common clinical feature of SARS-CoV-2 infection is fever (2). Moreover, acute respiratory distress syndrome (ARDS) is the most frequent cause of admission to intensive care unit in COVID-19 patients (1). Lactate dehydrogenase (LDH), a key enzyme in the glycolytic pathway and a cytoplasmic enzyme found in most organs, has been linked to inflammation response and cell damage. Currently, the role of serum LDH levels in ARDS patients infected by SARS-CoV-2 is unclear.

Between January 30 and Feb 22, 2020, 77 fever patients diagnosed with SARS-CoV-2 infection were admitted to the hospital of Changsha Public Health Center. In all patients, fever was defined assessed as follows: reported a fever history during the time from the onset symptom to admission, fever was defined as a rise in body temperature and presence of axillary temperature ≥37.0 ℃. Exclusion criteria included onset symptoms without fever, and patients with cancer. Clinical information of COVID-19 patients such as age, gender, days from onset of symptoms, medical history, physical examination, clinical presentation, laboratory tests, and imaging studies during admission were collected. Laboratory findings including erythrocyte sedimentation rate, C-reactive protein, procalcitonin,

liver and renal function, blood chemistry, coagulation test, complete blood count, LDH and creatine kinase were collected. ARDS was diagnosed as a decrease in the PaO_2/FiO_2 index below 300 mmHg according to the Berlin definition.

Data were statistical analyzed with Student's *t*-test, Mann-Whitney U-test, Fisher exact test and Chi-square analysis. Variables that were significant on univariate analysis were included in multivariate logistic regression analysis. Receiver-operator characteristic (ROC) analysis for ARDS was applied to determine the cut-off point and area under the curve (AUC). Survival curves without ARDS were established using Kaplan-Meier method and the log-rank test.

The 77 fever patients were categorized as non-ARDS group (n=63, 81.81%) and ARDS group (n=14, 18.19%). The baseline characteristics are shown in *Table 1*. Univariate and multivariable regression analyses identified that serum LDH level was a predictor of ARDS in SARS-CoV-2-infected patients with fever (*Table 2*, OR: 1.02; 95% CI, 1.00–1.04). The AUC of ROC curve showing the ability of LDH levels to predict development of ARDS was 0.809, and the best threshold of ≥273 U/L on admission revealed a sensitivity of 57.1% and a specificity of 93.7% (*Figure 1*). Survival curves for development of ARDS are showed in *Figure 2*. Analysis of the curves indicate that patients with LDH ≥273 U/L are more likely to develop ARDS (P<0.001, log-rank test).

LDH is an important enzyme in anaerobic metabolism

Page 2 of 5

Zhou et al. LDH may predict ARDS in COVID-19

Table 1 Characteristics of SARS-CoV-2-infected patients with fever

Characteristics	Total (n=77)	Non-ARDS (n=63)	ARDS (n=14)	P value
Age, years, mean (SD)	47.99±15.75	46.37±15.65	55.29±14.57	0.055
Gender, n (%)				0.073
Female	33 (42.86%)	30 (47.62%)	3 (21.43%)	
Male	44 (57.14%)	33 (52.38%)	11 (78.57%)	
Hubei exposure	52 (67.53%)	42 (66.67%)	10 (71.43%)	0.731
Systolic pressure, mmHg, mean (SD)	124.47±11.87	124.95±11.88	122.29±12.03	0.451
Diastolic pressure, mmHg, mean (SD)	78.30±8.96	78.70±9.17	76.50±8.03	0.410
Heart rate, beats per min, mean (SD)	91.01±13.87	88.73±13.44	101.29±11.16	0.002
Respiratory rate, IQR	20 [20, 21]	20 [20, 20]	21.5 [20, 23]	<0.001
Days from illness onset to first hospital admission (days), IQR	5 [3, 7]	5 [3, 7.5]	4.5 [3, 6.75]	0.779
Signs and symptoms, n (%)				
Fatigue	32 (41.56%)	27 (42.86%)	5 (35.71%)	0.624
Cough	48 (62.34%)	38 (60.32%)	10 (71.43%)	0.438
Anorexia	2 (2.60%)	2 (3.17%)	0 (0.00%)	0.499
Myalgia	8 (10.39%)	6 (9.52%)	2 (14.29%)	0.597
Dyspnea	11 (14.29%)	5 (7.94%)	6 (42.86%)	<0.001
Expectoration	20 (25.97%)	18 (28.57%)	2 (14.29%)	0.270
Sore throat	5 (6.49%)	5 (7.94%)	0 (0.00%)	0.276
Dizziness	3 (3.90%)	3 (4.76%)	0 (0.00%)	0.405
Headache	7 (9.09%)	5 (7.94%)	2 (14.29%)	0.455
Any comorbidity, n (%)				
Hypertension	14 (18.18%)	9 (14.29%)	5 (35.71%)	0.060
Cardiovascular disease	3 (3.90%)	2 (3.17%)	1 (7.14%)	0.488
Diabetes	4 (5.19%)	3 (4.76%)	1 (7.14%)	0.717
Laboratory tests				
White blood cell count, $\times10^9$/L, mean (SD)	4.52±1.52	4.62±1.41	4.07±1.91	0.076
Neutrophil count, $\times10^9$/L, mean (SD)	3.05±1.30	3.04±1.20	3.14±1.72	0.787
Lymphocyte count, $\times10^9$/L, mean (SD)	1.52±3.63	1.69±4.00	0.75±0.34	0.001
Hemoglobin, g/L, mean (SD)	130.16±21.49	128.98±22.67	135.43±14.62	0.313
Platelet count, $\times10^9$/L, mean (SD)	173.06±113.71	177.16±123.21	154.64±52.43	0.506
C-reactive protein, mg/L, mean (SD)	19.8 (8.6, 39)	16.2 (7.6, 38.1)	33 (21.9, 74.8)	0.011
Procalcitonin, ng/mL, IQR	0.05 (0.05, 0.05)	0.05 (0.05, 0.05)	0.05 (0.05, 0.05)	0.465
Erythrocyte sedimentation rate, mm/h, IQR	48 [27, 72]	46 [25, 77]	51.5 [45.5, 66]	0.837
Alanine aminotransferase, U/L, mean (SD)	24.90±12.84	24.44±13.01	26.98±12.29	0.507
Aspartate aminotransferase, U/L, mean (SD)	30.09±14.03	27.87±11.63	40.08±19.32	0.003

Table 1 (*continued*)

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Characteristics	Total (n=77)	Non-ARDS (n=63)	ARDS (n=14)	P value
Albumin, g/L, IQR	37 [34.7, 39.1]	38 [35, 40]	34 [31.9, 35.6]	0.002
Total bilirubin, mmol/L, mean (SD)	12.64±5.21	12.61±5.29	12.79±5.07	0.909
Direct bilirubin, mmol/L, mean (SD)	4.64±2.39	4.52±2.30	5.19±2.78	0.343
Lactate dehydrogenase, U/L, mean (SD)	204.30±75.70	187.88±61.97	278.20±89.41	<0.001
Creatinine, µmol/L, mean (SD)	56.17±24.66	56.78±26.57	53.42±13.36	0.648
Blood urea nitrogen, mmol/L, mean (SD)	4.43±1.87	4.26±1.89	5.18±1.60	0.097
Uric acid, µmol/L, mean (SD)	258.68±99.46	261.41±104.09	246.41±77.22	0.613
Prothrombin time, s, mean (SD)	11.95±0.98	11.83±1.00	12.50±0.67	0.020
Activated partial thromboplastin time, s, mean (SD)	32.94±3.57	33.06±3.66	32.39±3.20	0.526
D-dimer, ug/mL, IQR	0.2 (0.1-0.4)	0.2(0.1, 0.4)	0.4 (0.1, 0.5)	0.065
Chest radiography, n (%)				
Unilateral pneumonia	6 (7.79%)	6 (9.52%)	0 (0.00%)	0.229
Bilateral pneumonia	64 (83.12%)	50 (79.37%)	14 (100.00%)	0.062

SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; ARDS, acute respiratory distress syndrome; IQR, interquartile range; SD, standard deviation.

Table 2 Univariate and Multivariate analyses for the association between SARS-CoV-2-infected patients with ARDS and without ARDS

Characteristics	Univariate analysis			Multivariate analysis		
	OR	95% CI	P value	OR	95% CI	P value
Lactate dehydrogenase, U/L	1.01	(1.01, 1.02)	0.001	1.02	(1.00, 1.04)	0.020
Aspartate aminotransferase, U/L	1.05	(1.01, 1.10)	0.008	1.00	(0.93, 1.07)	0.964
Albumin, g/L	0.81	(0.69, 0.95)	0.009	1.00	(0.70, 1.35)	0.862
Prothrombin time, s	2.07	(1.09, 3.93)	0.026	1.42	(0.46, 4.35)	0.617
Lymphocyte count, ×10^9/L	0.05	(0.01, 0.40)	0.005	0.19	(0.01, 3.38)	0.261
C-reactive protein, mg/L	1.03	(1.00, 1.05)	0.016	0.99	(0.94, 1.03)	0.487
Heart rate, beats per min	1.08	(1.02, 1.14)	0.004	1.10	(1.00, 1.21)	0.059
Respiratory rate, breaths per min	1.76	(1.16, 2.67)	0.008	2.00	(0.97, 4.13)	0.062
Dyspnea	8.70	(2.15, 35.22)	0.002	2.15	(0.11, 42.83)	0.617

SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; OR, odds ratio; CI, confidence interval.

in almost all living organisms (3). Several studies suggested that serum LDH was elevated in severe COVID-19 patients (4,5). Consistently, we show that patients infected by SARS-CoV-2 with high levels of LDH on admission are more likely to develop ARDS. Inflammation and cell damage play an important role in the pathological processes of pulmonary tissues (6). Higher LDH levels have been found in COVID-19 patients than in patients with SARS-CoV-2 negative confirmed pneumonia (7). Yuan *et al.* found that COVID-19 mRNA clearance ratio was highly associated with LDH levels (8). Research has shown that SARS-CoV-2 as a positive-sense RNA virus may activate inflammasomes, leading to cellular pyroptosis and aggressive symptoms (9). This may partly explain the association of LDH with

Page 4 of 5

Zhou et al. LDH may predict ARDS in COVID-19
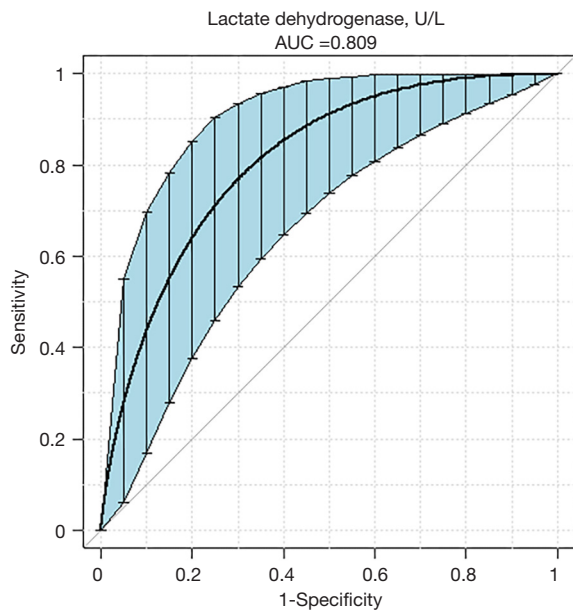
Figure 1 Receiver operating characteristic curves. The AUC value of LDH in predicting ARDS. Blue shading shows the bootstrap estimated 95% CI with AUC. LDH, lactate dehydrogenase; ARDS, acute respiratory distress syndrome.
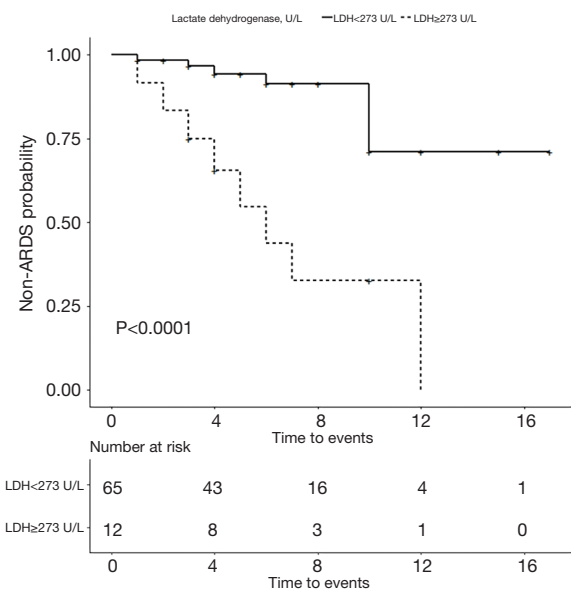

Figure 2 Kaplan-Meier curve showing development of ARDS in SARS-CoV-2-infected patients with fever stratified by LDH levels < and ≥273 U/L on admission. LDH, lactate dehydrogenase; ARDS, acute respiratory distress syndrome.

ARDS in COVID-19 patients. However, we found that the best threshold for predicting ARDS was 273 U/L. LDH level was independently associated with ARDS, and could strongly predict the incidence of ARDS. To our knowledge, this is the first study reporting the association of LDH with ARDS in COVID-19 patients with fever on admission. Our findings will help physicians to evaluate the condition of the illness at an earlier stage.

However, we note the following limitations to our study. First, this is a single-center retrospective study. Secondly, the serum level of LDH was only tested on admission. Thus, it should be tested at different times for better evaluation of its predicting value. Third, since all patients were from Changsha, our results may not apply to other regions since the clinical features of COVID-19 may vary in other regions.

Acknowledgments

Footnote

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