

Combination of serum lactate dehydrogenase and sex is predictive of severe disease in patients with COVID-19

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Abstract

Elevated serum lactate dehydrogenase (LDH) was commonly reported in COVID-19 patients. However, the relationship between LDH and the incidence of severe cases has not been characterized in those patients.

We retrospectively analyzed the characteristics of patients from a designated isolation medical center for COVID-19 patients diagnosed from February 6 to March 1. Variables accessed within 48 hours on admission were compared between patients with and without the severe disease. Logistic model analyses were performed to examine the prognostic value of LDH for predicting severe disease.

52 (28.6%) patients later developed severe disease. Comparing to non-severe cases, severe cases had a higher level of serum LDH (321.85 ± 186.24 vs 647.35 ± 424.26 , $P < .001$), neutrophils (5.42 ± 3.26 vs 9.19 ± 6.33 , $P < .001$), and C-reactive protein (38.63 ± 43.14 vs 83.20 ± 51.01 , $P < .001$). The patients with severe disease tended to be male (44.6% vs 80.8%, $P < .001$), lower level of serum albumin (31.41 ± 6.20 vs 27.18 ± 5.74 , $P < .001$), and SpO₂ (96.30 ± 2.75 vs 92.37 ± 8.29 , $P < .001$). In the multivariate analysis model, LDH and sex remained independent risk factors for severe disease. The serum LDH predicted severe cases with an area under the curve (AUC) of 0.7999. A combination of serum LDH and sex predicted severe cases with an AUC of 0.849. A combination of serum LDH accessed on admission and sex had a better predictive performance than the serum LDH ($P = .0238$).

Serum LDH on admission combined with sex is independently associated with severe disease in COVID-19.

Abbreviations: ALB = serum albumin, ALT = alanine aminotransferase, ARDS = acute respiratory distress syndrome, AST = aspartate aminotransferase, BMI = body mass index, BUN = blood urea nitrogen, CHD = chronic heart disease, CK-MB = creatine kinase muscle-brain, COVID-19 = coronavirus disease 2019, CRP = C-reactive protein, HR = hazard ratios, hs-TNI = high-sensitivity troponin I, LDH = lactate dehydrogenase, NPV = negative predictive value, PPV = positive predictive value, ROC = receiver operating characteristic, SARS = severe acute respiratory syndrome, SD = standard derivation, WBC = white blood cell.

Keywords: COVID-19, predict, serum lactate dehydrogenase, severe

1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic continues to take a heavy toll on families, communities, and nations the

world over.^[1] Globally, as of 2:00 am CEST, Apr 7, 2020, 1,247,242 confirmed cases of COVID-19, including 69,213 deaths, had been reported to WHO.^[2] COVID-19 patients were reported that most of them with mild or moderate state, 13.8% with a serious state, 4.7% with a critically ill state by the Chinese Centers for Disease Control, on February 24, 2020.^[3] Published research from Wuhan Jingyintan by January 26, 2020, reported that 658 patients were included in their study. Fifty two (7.9%) patients developed critically ill state and 57.7% of critical patients died.^[4] Consequently, early detection of seriously and critically ill patients is particularly important for reducing mortality in patients with COVID-19.

New coronavirus pneumonia prevention and control program (7th ed, in Chinese) was published on Mar 4, 2020.^[5] The guideline showed the definition of seriously and critically ill patients and the characteristics of clinical indicators that may be used to predict the early stage of infection, as follows:

1. lymphocyte levels that increase progressively;
2. inflammatory factor (interleukin 6, C-reactive protein) levels that increase progressively;
3. serum lactic acid levels that increase progressively;
4. lung lesions that progress rapidly in the short term.

However, recently most published studies had shown that serum lactate dehydrogenase (LDH) increased significantly in serious and critical patients with COVID-19.^[6–9] LDH, which is widely expressed in tissues, is a cytoplasmic enzyme. Elevated

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Jin Hu and Jun Zhou contributed equally.

The authors report no conflicts of interest.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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LDH was witnessed in some disease processes such as tissue injury, necrosis, hypoxia, malignant tumors.^[10–12] The role of LDH in the involvement of viruses (the human immunodeficiency virus,^[13] influenza A virus,^[14] and white spot syndrome virus^[15]) had been reported. In order to further evaluate those parameters and find a laboratory finding obtained with a convenient and efficient method, we conducted a retrospective study to verify whether serum LDH on admission within 48 hours is a powerful predictor for seriously and critically ill cases in COVID-19.

2. Methods

2.1. Patients

We retrospectively analyzed 252 consecutive patients from the Wuhan Union Hospital, which was converted to a designated hospital for COVID-19 patients. All the patients were confirmed COVID-19 and diagnosed from February 6 to March 1. Patients were excluded when their outcome records, lactate dehydrogenase within 48 hours on admission, or body mass index (BMI) were not available. (Fig. 1) The levels of the LDH were determined by routine laboratory diagnostics (reference range 109 to 245 U/L, Roche Diagnostics, Basel, Switzerland). Severe cases consisted of admission to intensive care unit, or invasive ventilation, or death.^[16]

2.2. Demographic and clinical features

The demographic variables were recorded, including age, sex, BMI. Symptoms and signs on admission included fever, dry cough, dyspnea, chest tightness/chest pain, fatigue, headache, and diarrhea. The comorbidities included hypertension, chronic heart disease (CHD), and diabetes. Laboratory data on admission within

48 hours were recorded, including white blood cell (WBC, $\times 10^9/L$), neutrophils ($\times 10^9/L$), lymphocytes ($\times 10^9/L$), C-reactive protein (CRP, mg/dL), LDH (U/L), hemoglobin (g/L), serum albumin (ALB, g/L), aspartate aminotransferase (AST, U/L), alanine aminotransferase (ALT, U/L), high-sensitivity troponin I (hs-TNI, ng/ml), creatine kinase muscle-brain (CK-MB, U/L), blood urea nitrogen (BUN, mmol/L), and serum creatinine (umol/L). The clinical outcome for the series was the severe disease.

2.3. Statistical analysis

All statistical analyses were performed utilizing SPSS statistical software (version 22.0; IBM Corporation, Armonk, NY, USA). Receiver operating characteristic (ROC) curves were plotted and compared by Stata (version 14). Continuous data were shown as means and standard derivation (SD). Categorical variables were reported as frequency. The differences of characteristics between patients with or without severe disease were compared by Mann–Whitney *U* test and Student *t* test. Multiple group comparisons were performed using the Chi-Squared test or Fishers exact test for categorical variables and the Kruskal–Wallis test for continuous data. All variables with statistically significant difference in the univariate analysis model and with clinical value were included for further multivariate logistic regression analysis. Hazard ratios (HR) and 95% confidence intervals (95% CI) were recorded. Then, variables shown to have statistical significance ($P < .05$) by multivariate analysis entered logistic regression model to obtain prediction probability. ROC was plotted for the range of LDH and prediction probability values. The difference between ROC was analyzed by the Chi-Squared test. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were presented.

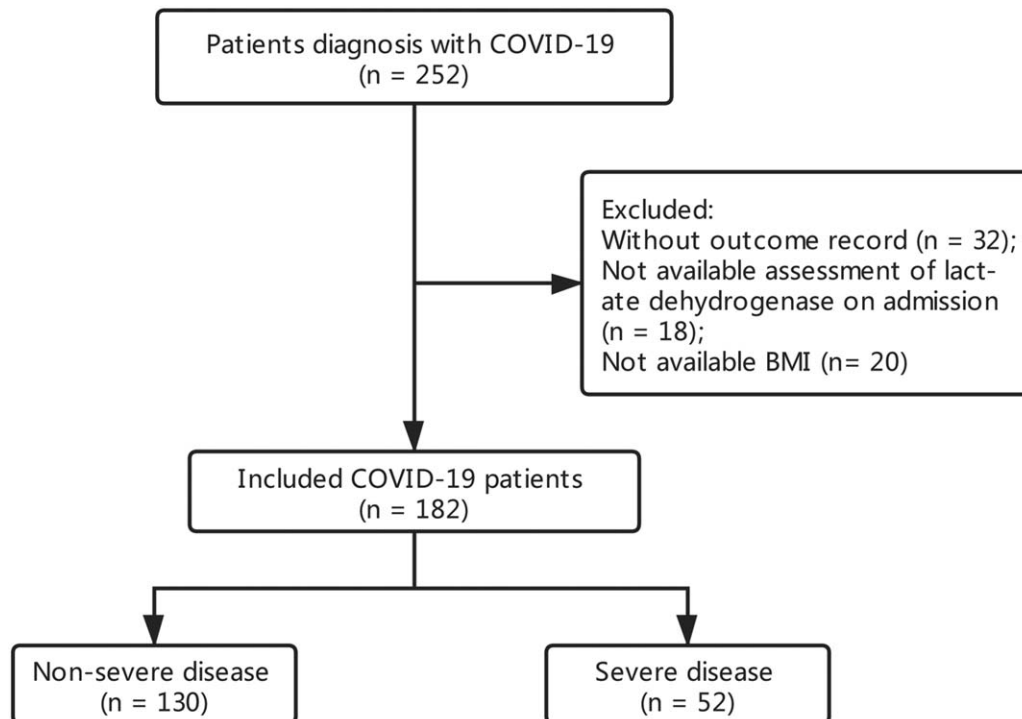


Figure 1. Flow diagram illustrating the selection of patients. BMI = body mass index, COVID-19 = coronavirus disease 2019.

2.4. Ethical approval and consent to participate

Informed consent for individual patient was not obtained since all data were retrieved retrospectively from the laboratory test information system without additional blood samples or laboratory analysis. The study was approved by Union hospital Tongji Medical College, Huazhong University of Science and Technology Ethics Committee.

3. Results

3.1. Characteristics by patients with different LDH levels

The baseline characteristics of 182 patients with COVID-19 according to LDH levels (elevated or normal) have been shown in Table 1. The mean age or BMI between groups was no difference. The LDH on admission of males seems to be higher than that of females. Additionally, compared with normal LDH levels, elevated group showed statistically significant difference in severe disease (38.3% vs 9.7%, $P < .001$) and in-hospital mortality (25.8% vs

9.7%, $P = .007$). Comorbidities was not related to elevated LDH levels resulted from COVID-19 patients. In this cohort, most patients presented with fever, dry cough, dyspnea, and fatigue. However, there was no difference in most of the symptoms and signs at the time of admission between the 2 groups.

3.2. Comparison between patients with and without severe disease

Demographic and clinical characteristics according to patients with and without severe disease have been shown in Table 2. The significant differences in age (63.06 ± 14.10 vs 63.62 ± 14.41 , $P = .812$) and BMI (23.58 ± 2.78 vs 23.80 ± 3.53 , $P = .649$) were not seen. Additionally, there was no difference in the symptoms and signs observed between 2 groups. No difference in comorbidities was witnessed between the non-severe disease group and the severe disease group. Although the duration of hospital stay had no difference (25.06 ± 8.96 vs 22.72 ± 10.36 , $P = .166$), the severe disease group tended to have a shorter

Table 1
Basic characteristic of COVID-19 patients according to LDH level (normal range < 245 U/L).

Variables	LDH < 245 U/L (n=62)	LDH ≥ 245 U/L (n=120)	P value
Age, years	61.84 \pm 15.74	63.93 \pm 13.28	.345
Body mass index	23.91 \pm 2.82	23.51 \pm 3.10	.393
Sex			.026
Male	27 (43.5)	73 (60.8)	
Female	35 (56.5)	47 (39.2)	
Smoking	4 (6.5)	8 (6.7)	.956
Symptoms and signs			
Fever	50 (80.6)	101 (84.2)	.549
Dry cough	48 (77.4)	76 (63.3)	.053
Dyspnea	19 (30.6)	74 (61.7)	$< .001$
Chest tightness/chest pain	21 (33.9)	46 (38.7)	.527
Respiratory rate ≥ 30 bpm	13 (21.0)	41 (34.2)	.65
SpO ₂	96.82 \pm 2.37	94.33 \pm 6.12	.002
Fatigue	37 (59.7)	67 (55.8)	.619
Headache	7 (11.3)	7 (5.8)	.241
Diarrhea	11 (17.7)	16 (13.3)	.428
Heart rate, beats per min	91.74 \pm 16.79	91.08 \pm 17.34	.806
Mean arterial pressure, mm Hg	95.03 \pm 12.53	98.80 \pm 13.50	.07
Comorbidities			
Hypertension	22 (35.5)	57 (47.5)	.081
Chronic heart disease	6 (9.7)	22 (18.3)	.091
Diabetes	8 (12.9)	23 (19.2)	.197
Laboratory data			
White blood cell, $\times 10^9/L$	6.83 \pm 3.67	10.28 \pm 14.02	.059
Neutrophil count, $\times 10^9/L$	4.85 \pm 3.58	7.32 \pm 4.93	$< .001$
Lymphocyte count, $\times 10^9/L$	1.73 \pm 4.08	2.29 \pm 11.49	.711
Hemoglobin, g/L	117.23 \pm 21.17	114.00 \pm 23.58	.366
Total protein, g/L	62.75 \pm 6.23	62.45 \pm 7.98	.796
Serum albumin, g/L	32.35 \pm 6.68	29.10 \pm 5.91	.001
Aspartate aminotransferase, U/L	29.69 \pm 17.16	184.70 \pm 1442.66	.399
Alanine aminotransferase, U/L	41.76 \pm 32.46	135.76 \pm 836.38	.378
C-reactive protein, mg/dL	26.49 \pm 39.40	64.21 \pm 49.68	$< .001$
High-sensitivity troponin I, ng/ml	58.83 \pm 211.60	335.50 \pm 1240.23	.131
Creatine kinase muscle-brain, U/L	10.88 \pm 9.77	25.93 \pm 64.27	.069
Blood urea nitrogen, mmol/L	6.56 \pm 8.26	9.08 \pm 8.83	.063
Serum creatinine, umol/L	75.05 \pm 55.36	103.31 \pm 183.03	.237
Outcomes			
Severe cases	6 (9.7)	46 (38.3)	$< .001$
In-hospital mortality	6 (9.7)	31 (25.8)	.007

COVID-19 = 2019 novel coronavirus disease, LDH = lactate dehydrogenase.

Table 2
Clinical data of the patients with and without severe disease.

Variables	Non-severe disease (n=130)	Severe disease (n=52)	P value
Age, years	63.06 ± 14.10	63.62 ± 14.41	.812
Body mass index	23.58 ± 2.78	23.80 ± 3.53	.649
Duration in hospital	25.06 ± 8.96	22.72 ± 10.36	.166
Sex			<.001
Male	58 (44.6)	42 (80.8)	
Female	72 (55.4)	10 (19.2)	
Smoking	8 (6.2)	4 (7.7)	.706
Symptoms and signs			
Fever	106 (81.5)	45 (86.5)	.418
Dry cough	93 (71.5)	31 (59.6)	.119
Dyspnea	62 (47.7)	31 (59.6)	.146
Chest tightness/chest pain	49 (38.0)	18 (34.6)	.671
Respiratory rate ≥30 bpm	39 (30.0)	15 (28.8)	.878
SpO ₂	96.30 ± 2.75	92.37 ± 8.29	<.001
Fatigue	75 (57.7)	29 (55.8)	.813
Headache	11 (8.5)	3 (5.8)	.538
Diarrhea	21 (16.2)	6 (11.5)	.429
Heart rate, beats per min	91.14 ± 16.64	91.73 ± 18.40	.834
Mean arterial pressure, mm Hg	97.90 ± 13.23	96.51 ± 13.41	.527
Comorbidities			
Hypertension	56 (43.1)	23 (44.2)	.508
Chronic heart disease	16 (12.3)	12 (23.1)	.059
Diabetes	23 (17.7)	8 (15.4)	.446
Laboratory data			
White blood cell, × 10 ⁹ /L	8.62 ± 13.23	10.33 ± 6.28	.374
Neutrophil count, × 10 ⁹ /L	5.42 ± 3.26	9.19 ± 6.33	<.001
Lymphocyte count, × 10 ⁹ /L	2.66 ± 11.38	0.73 ± 0.51	.233
Hemoglobin, g/L	116.28 ± 22.25	112.15 ± 24.04	.271
Total protein, g/L	63.22 ± 6.93	60.88 ± 8.32	.054
Serum albumin, g/L	31.41 ± 6.20	27.18 ± 5.74	<.001
Aspartate aminotransferase, U/L	34.63 ± 18.76	375.06 ± 2188.74	.077
Alanine aminotransferase, U/L	44.42 ± 33.31	252.04 ± 1267.43	.063
Lactate dehydrogenase, U/L	321.85 ± 186.24	647.35 ± 424.26	<.001
C-reactive protein, mg/dl	38.63 ± 43.14	83.20 ± 51.01	<.001
High-sensitivity troponin I, ng/ml	151.56 ± 1043.28	483.09 ± 1008.34	.076
Creatine kinase muscle-brain, U/L	12.47 ± 16.72	41.65 ± 92.77	.001
Blood urea nitrogen, mmol/L	6.94 ± 8.37	11.41 ± 8.76	.002
Serum creatinine, umol/L	86.19 ± 156.10	112.41 ± 142.61	.296

duration. In laboratory data, the statistically significant differences were observed in neutrophil count (5.42 ± 3.26 vs 9.19 ± 6.33 , $P < .001$), ALB (31.41 ± 6.20 vs 27.18 ± 5.74 , $P < .001$), LDH (321.85 ± 186.24 vs 647.35 ± 424.26 , $P < .001$), CRP (38.63 ± 43.14 vs 83.20 ± 51.01 , $P < .001$), CK-MB (12.47 ± 16.72 vs 41.65 ± 92.77 , $P = .001$), and BUN (6.94 ± 8.37 vs 11.41 ± 8.76 , $P = .002$) between non-severe disease group and severe disease group. Although the severe disease group had a lower value of lymphocyte count, there was no difference (2.66 ± 11.38 vs 0.73 ± 0.51 , $P = .233$) (Supplement 1, <http://links.lww.com/MD/F37> and Supplement 2, <http://links.lww.com/MD/F38>).

3.3. Admission serum LDH combined with sex as an independent prognostic factor

Univariate analysis showed that sex (Female as reference, HR 5.214; 95% CI 2.410, 11.277; $P < .001$), neutrophil count (HR 1.258; 95% CI 1.140, 1.388; $P < .001$), lymphocyte count (HR 0.241; 95% CI 0.113, 0.515; $P < .001$), LDH (HR 1.005; 95% CI 1.003, 1.007; $P < .001$), CRP (HR 1.018; 95% CI 1.011, 1.026; $P < .001$), and ALB (HR 1.012; 95% CI 1.005, 1.020;

$P = .001$) were correlated with the incidence of severe disease. In order to further explore the relationship between serum LDH and the incidence of severe disease, we utilized the multivariate logistic regression model after univariate analysis. In multivariate analysis, only sex (Female as reference, HR 5.389; 95% CI 1.949, 14.905; $P = .001$) and LDH (HR 1.005; 95% CI 1.003, 1.007; $P < .001$) were as independent prognostic factors for severe disease. (Table 3)

3.4. ROC of serum LDH and a combination of serum LDH and sex in predicting severe disease

ROC was plotted for the range of LDH and prediction probability of a combination of serum LDH and sex values. The serum LDH predicted severe cases with an area under the curve (AUC) of 0.7999. The sensitivity, specificity, PPV, and NPV were 67.3%, 87.7%, 68.6% and 87.0%, respectively. A combination of serum LDH and sex predicted severe cases with an AUC of 0.849 ($P = .0238$). The sensitivity, specificity, PPV, and NPV were 94.2%, 60.0%, 48.5%, and 96.3%, respectively. (Fig. 2)

Table 3**Uni- and multi-variate logistic regression analyses of risk factors for severe disease.**

Variables	Univariate analysis Hazard ratio (95%CI)	P value	Multivariate analysis Hazard ratio (95%CI)	P value
Age, years	1.003 (0.980, 1.026)	.811		
Body mass index	1.025 (0.921, 1.142)	.647		
Sex (Female as reference)	5.214 (2.410, 11.277)	<.001	5.389 (1.949, 14.905)	.001
Neutrophil count, $\times 10^9/L$	1.258 (1.140, 1.388)	<.001	1.103 (0.966, 1.260)	.146
Lymphocyte count, $\times 10^9/L$	0.241 (0.113, 0.515)	<.001	0.812 (0.345, 1.909)	.633
Lactate dehydrogenase, U/L	1.005 (1.003, 1.007)	<.001	1.005 (1.003, 1.007)	<.001
C-reactive protein, mg/dl	1.018 (1.011, 1.026)	<.001	1.008 (0.998, 1.018)	.117
Serum albumin, g/L	1.012 (1.005, 1.020)	.001	0.922 (0.850, 1.000)	.050
Total protein, g/L	0.957 (0.915, 1.001)	.056		

4. Discussion

In this study, we proved that serum LDH and male sex were independent prognostic factors for patients with COVID-19. A combination of serum LDH accessed on admission and sex had a better predictive performance than the serum LDH for worse outcome of COVID-19. Additionally, elevated neutrophil count and CRP levels, and reduced lymphocyte count were not associated with severe disease in COVID-19. We also demonstrated that age or BMI was not a risk factor for seriously and critically ill patients with COVID-19.

The utility of the serum LDH in virus was first investigated by Zaman et al^[13] in 1988. They noticed that the level of serum LDH was useful as a marker of *P. jirovecii* pneumonia in patients infected with the human immunodeficiency virus. Ede et al^[17] reported that the severity of nasopharyngeal cellular injury during viral upper respiratory tract infection, as measured by LDH levels in nasopharyngeal secretions, was related to acute otitis media complication. They implied that there was a positive correlation between levels of LDH and all cytokines (interleukin (IL)-1 β , IL-6, and tumor necrosis factor- α). LDH levels in nasopharyngeal secretions were positively associated with acute otitis media risk. Andrejčáková et al.^[18] suggested that LDH levels in the blood serum and tissue extracts could predict the immune status of jejunum mucosa during enterotoxigenic *Escherichia coli* and coronavirus infection in piglets.

The elevated serum LDH was observed in some studies about severe acute respiratory syndrome (SARS). A previous study of SARS data from 2003 found that lymphopenia, elevated LDH,

AST, and creatinine kinase levels were common in serious cases.^[19] Liu et al^[20] suggested that 58% of patients diagnosed with SARS presented elevated LDH on admission. However, another study from Hong Kong that included 156 SARS-positive and 62 SARS-negative patients showed that the positive patients had a lower lymphocyte count and a lower LDH level.^[21] Those results illustrated that the serum LDH may be applied to patients infected with the novel coronavirus.

The laboratory findings, including elevated WBC, neutrophils, CRP, LDH, and total protein, and reduced lymphocyte levels were common in the severe cases of COVID-19. These results were confirmed by the previous reports.^[22,23] The prevention and control program^[5] also suggested that lymphocytes, CRP, and lactic acid levels were correlated with serious and critical illness in COVID-19. In addition, a study from Wu et al,^[7] which included 201 patients with confirmed COVID-19 pneumonia, showed that the serum LDH was one of the risk factors correlated with the development of acute respiratory distress syndrome (ARDS) and progression from ARDS to death. Yuan et al^[24] conducted a retrospective study which aimed to evaluate the relationship between viral clearance and blood biochemical index in patients with COVID-19. They implied that the COVID-19 mRNA clearance ratio was significantly associated with the decline of serum LDH levels. However, in our study, elevated neutrophil count and CRP levels, and reduced lymphocyte count were not associated with severe disease in COVID-19 after the multivariate logistic regression analysis.

Published studies reported that the average age of severe cases was significantly older than in non-severe cases.^[7,25] Another study showed that age below 40 or above 60 years old was not related to severe cases.^[22] In our study, age did not present as an independent risk factor after multivariable analysis. Zhou et al^[26] implied that older age was one of the characteristics that could identify at an early stage those patients who have a poor prognosis. The possible reason was that the difference did not observe in patients with underlying comorbidities. The role of sex in patients with COVID-19 remains controversial. Some studies reported that compared with general status cases, the male gender was common in severe cases.^[8,27] On the other hand, other studies suggested that there was no significant difference in gender.^[22,28,29] In our study, comparing to non-severe cases, the male gender was common in severe cases. In addition, sex was an independent risk factor for severe disease after multivariable analysis. BMI has long been considered to be one of the strongest risk factors for serious and critical illness. As researches^[30–32] shown, for intensive care unit patients receiving endotracheal intubation, higher BMI was correlated with higher mortality and longer length of stay. Liu et al^[33] reported that severe patients

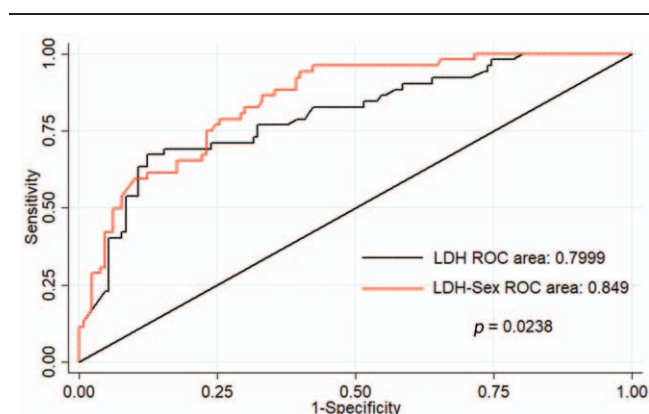


Figure 2. Receiving operator curve of serum LDH and LDH combined with sex in predicting severe disease for COVID-19 patients. LDH= lactate dehydrogenase.

with COVID-19 had higher BMI. The above results led to consider excluding patients without available the values of BMI. However, disease severity was not related to BMI in the univariate analysis model.

5. Strengths

Our study also has several strengths. Firstly, as far as we know, this is the first detailed study of the impact of serum LDH on severe disease in COVID-19 patients. Secondly, all laboratory findings were collected on admission within 48 hours. Thirdly, we found that the predictive performance of a combination of serum LDH and sex was higher than that of serum LDH.

6. Limitation

Our study has certain limitations. First, this study design was that of a retrospective study, such that more detailed therapeutic responses will be needed. Several patients developed disorders of consciousness upon admission, which may have resulted in the involuntary omission of patients information (in particular, a detailed medical history). Missing data can lead to a bias in results. Second, the lack of effective antivirals^[34] and corticosteroid^[26] use may have also contributed to the poor clinical outcomes observed in certain patients. Moreover, the case fatality ratio reported in our study is not representative of the true mortality of COVID-19 patients, due to the large number of critically ill patients found in the Wuhan Union Hospital. Lastly, the interpretation of our findings may also be limited by the sample size. Our research provides a preliminary insight into the identification of variables for the prediction of COVID-19 patient outcomes and serves as a basis for further detailed clinical and pathophysiological studies, which will also be necessary.

7. Conclusions

In conclusion, our present study suggests that a combination of serum LDH on admission and sex is independently correlated with severe status in patients with COVID-19. The combination may serve as a valuable tool for a rapid assessment of severe status in patients.

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