The Application of Lactate Dehydrogenase in Coronavirus Disease 2019 as the Best Indicator for the Progression and Clinical Status: A Case-Control Study

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Research article

Keywords: COVID-19, SARS-CoV-2, lactase dehydrogenase, indicator

Posted Date: October 14th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-55590/v1

Abstract

Introduction Coronavirus disease 2019 (COVID-19) is now officially a pandemic. Current studies observed extensive abnormal indexes in COVID-19 patients and significant differences between mild and severe patients. However, which index would perform better as the indicator of disease progression merits further investigation.

Methods We enrolled COVID-19 patients who were admitted to Shanghai Public Health Clinical center. We closely monitored the following candidate indictors: white blood cell, lymphocyte, platelet, CD4 T cell, CD8 T cell, alanine aminotransferase, estimated glomerular filtration rate (eGFR), fibrin degradation products (FDP), D-dimer, creatine kinase, myoglobin, troponin T (TnT), N-terminal pro-B-type natriuretic peptide (NT-proBNP), lactase dehydrogenase (LDH), C-reactive protein (CRP), and procalcitonin. The correlation with illness severity were assessed by Spearman analysis and the ability of differentiating the clinical statuses was quantified as the AUC value of the ROC curve.

Results A total of 326 patients were enrolled, including 299 mild-ordinary and 27 severe-critical patients. At admission, D-dimer and CRP were elevated above normal range both in mild-ordinary and severe-critical patients. LDH, NT-proBNP, myoglobin, CD4 T cell, eGFR, FDP and PCT were beyond normal range in the mild-ordinary stages of severe-critical patients, but remained normal in the persistently mild-ordinary patients. Top 5 parameters with highest spearmen coefficient were LDH, procalcitonin, NT-proBNP, myoglobin and D-dimer (Spearman coefficient: 0.488, 0.453, 0.414, 0.412, 0.407). Comparing between mild-ordinary stage and severe/critical stage, LDH showed the highest receiver operating characteristics (ROC) area under the curve (AUC) of 0.951. PCT ranked second, with the ROC AUC of 0.905. Comparing between mild-ordinary and severe stages, only LDH had the ROC AUC of over 0.90 (0.927).

Conclusions This study found LDH to be a superior indicator for COVID-19 status and had the potential to optimize the clinical management strategy.

Introduction

Coronavirus disease 2019 (COVID-19) is now officially a pandemic. Critically ill patients with COVID-19 are marked by the high mortality and catastrophic expenditure, despite the respiratory support and comprehensive treatment that are usually administered to these groups. Therefore, suitable indicators would be of much significance in the early treatment of COVID-19 patients and may play a vital role in the prevention and blockage of the disease course.

Although multiple studies have reported laboratory or clinical markers relating to progression to severe or critical illness, it is still difficult to predict which type of patients may progress or relieve. Current researches generally adopted the laboratory findings on hospital admission as their index variable. However, if some of the patients had already developed severe illness prior to admission, this would

create a bias in which analyzing laboratory findings on admission would reveal only the differences between mild and severe patients, rather than risk factors of disease progression.

What kind of indicators are good predictors? We propose the "CDEF" principle for an ideal indicator, namely correlation, differentiation, early-warning, and feasibility. “Correlation” refers that indicators should clearly parallel with the clinical status. For COVID-19 patients, the indicators are supposed to reflect dynamic fluctuations of the respiratory function. “Differentiation” refers the performances in differentiating between mild and severe illness. “Early-warning” refers that a perfect indicator is expected to show significant abnormalities prior to the clinical status progresses. Oxygen saturation is a satisfactory variable in accordance with the patient's current respiratory status, but it cannot reflect the role of predictive warning. Regarding to the feasibility profile, to make sure an indicator can be wildly used in the clinical routine practice, the abnormalities of indicators in severe cases should be consistent with the established clinical significance, like beyond the normal range.

In order to discover indicators that can reflect early disease progression and issue early warning of possible advances to critically ill status, we followed up 326 cases of laboratory confirmed COVID-19 patients in Shanghai and tried to find the best indicator in line with the “CDEF” rule.

Methods

Study population and definition

This is a retrospective case-control study. From January 20, 2020 and March 15th, 2020, we enrolled all patients with COVID-19 according to World Health Organization (WHO) interim guidance in Shanghai Public Health Clinical Center (SPHCC). The study was approved by the Ethics Committees of Huashan Hospital, Fudan University. All patients who participated in the study gave informed consent.

The severity or clinical condition of COVID-19 patients was classified into mild, ordinary, severe and critical illness according to the Chinese Clinical Guideline for COVID-19 pneumonia diagnosis and treatment (6th edition)[1]. Because the severity of a patient ’s disease can change dynamically, we viewed the severity of COVID-19 as a stage of disease development. We defined the mild, and ordinary illness as mild-ordinary stage, severe illness as the severe stage and critical illness as critical stage. Symptoms, vital signs, laboratory values and chest CT scan or X-ray were monitored daily for patients in the severe or critical stage and every 2–3 days for patients in mild-ordinary stage.

We grouped the patients according to their disease progression and their severity on admission. Patients who continued to be in the mild-ordinary stage during hospitalization were defined as the persistent mild-ordinary group (PM Group), and patients who had experienced the severe or critical stage during the hospitalization were defined as the severe/critical group (S/C Group). Patients in the S/C Group were further divided into a mild-ordinary-at-admission group (MA Group) and a severe-at-admission group (SA Group) according to the clinical stage at admission (Fig. 1).

Data Collection

We obtained epidemiological, demographic, clinical, laboratory and radiology data from patients' medical records. The data were reviewed by a trained team of physicians.

We collected variables with clinical significance based on our clinical experience and previous studies about COVID-19[2–4]. In SPHCC, the following candidate parameters were monitored closely, including white blood cell (WBC), lymphocyte, platelet, CD4 T cell, CD8 T cell, alanine aminotransferase (ALT), estimated glomerular filtration rate (eGFR), fibrin degradation products (FDP), D-dimer, creatine kinase (CK), myoglobin, troponin T (TnT), N-terminal pro-B-type natriuretic peptide (NT-proBNP), lactase dehydrogenase (LDH), C-reactive protein (CRP), and procalcitonin (PCT). We collected the values of these parameters measured at admission, the first day of each clinical stage, the midpoint date of each clinical stage and the day of death.

Data management and statistical analysis

Correlation between the laboratory parameters and disease severity (mild-ordinary, severe, critical, and death) were analyzed using Spearman's correlation. To analyze the performance of candidate parameters for indicators of disease severity, we created receiver operating characteristics (ROC) curves which were summarized by area under the curve (AUC) estimates. ROC curve analysis was also performed to determine the cut-off value, sensitivity and specificity of indicators in differentiating the cases in mild-ordinary stage from those in severe or critical stage.

All statistical analysis was conducted using IBM SPSS software (Version 22.0) and R (Version 3.6.1). Basic characteristics were sorted by median (interquartile range, IQR) or mean (standard deviation, SD) in consecutive variables, count (percentage) in categorical variables. Means for continuous variables were compared using one-way Anova analysis. Categorical variables were compared with the use of Chi-square test. Dynamics of laboratory findings along with disease progression were plotted and Spearman's correlation were used to evaluate the correlation. All tests were two-sided and P value < 0·05 was considered as statistically significance.

Results

Baseline characteristics at admission

A total of 326 COVID-19 patients enrolled. 169 (51.8%) were male. The mean age was 49.7 ± 16.2 years. As of 15th April 2020, 299 patients continued to be in the mild-ordinary stage since admission (PM Group), the other 27 patients experienced severe or critical stage (S/C Group), including 20 patients who as in mild-ordinary stage at admission but deteriorated during hospitalization (MA Group) and 7 patients initially severe at admission (SA Group)(Fig. 1).

There were more men and elders in the S/C Group ($p < 0.05$) (Table 1). 109 (36.5%) in the PM Group and 17 (63.0%) in S/C Group reported comorbidities ($p = 0.002$). Overall symptoms patterns were similar between 3 groups, with fever (80.9%, 264/326) and cough (49.7%, 162/326) being the most common symptoms. Dyspnea was observed in 5 (18.5%) in the S/C Group while 2 (0.67%) in the PM Group ($p < 0.001$). 315 (96.6%) cases had abnormalities consistent with viral pneumonia on chest radiology or lung CT.

Table 1
Baseline characteristics and symptoms on admission of cases with COVID-19

	PM Group (n = 299)	S/C Group (n = 27)		P value
		MA group (n = 20)	SA Group (n = 7)	
Male, N(%)	148(49.5)[a]	15(75.0)[a]	6(85.7)	0.017
Age, mean(SD) y	48.4(15.6)[a,b]	64.5(13.3)[a]	66.3(20.7)[b]	< 0.001
Drinking, N(%)	3(1.0)	0(0.0)	0(0.0)	0.872
Smoking, N(%)	12(4.0)	2(10.0)	0(0.0)	0.376
Comorbidities, N(%)	109(36.5)[a]	10(50.0)	7(100.0)[a]	0.002
Hypertension	64(21.4)	9(45.0)	3(42.9)	0.025
Diabetes	24(8.0)	4(20.0)	1(14.3)	0.168
CHD	14(4.7)[a]	1(5.0)	2(28.6)[a]	0.019
Tumor	7(2.3)	0(0.0)	1(14.3)	0.100
COPD	4(1.3)	0(0.0)	2(28.6)	< 0.001
Immunocompromised	2(0.7)	0(0.0)	1(14.3)	0.001
Cerebrovascular disease	1(0.3)	1(5.0)	0(0.0)	0.034
Others	34(11.4)	4(20.0)	4(57.1)	0.001
Symptoms, N(%)				
Fever	239(80.0)	18(90.0)	7(100.0)	0.233
Cough	151(50.5)	9(45.0)	2(28.6)	0.472
Fatigue	63(21.1)	5(25.0)	2(28.6)	0.825
Expectoration	63(21.1)	7(35.0)	1(14.3)	0.306
Headache	26(8.7)	1(5.0)	0(0.0)	0.612
Dyspnea	2(0.7)[a]	3(15.0)[b]	2(28.6)[a,b]	< 0.001
Others	128(42.8)	4(20.0)	4(57.1)	0.095

*P values are less than 0.05 for data with the same superscript letter on the same line.

Abbreviations: PM, persistent mild-ordinary group; S/C, severe/critical; MA, mild-ordinary-at-admission; SA, severe-at-admission group; SD: Standard Deviation; IQR: Interquartile Range; CHD: Coronary Heart Disease; COPD: Chronic Obstructive Pulmonary Disease;

Evaluation of potential predictive indicators

Laboratory findings at admission were the earliest value of candidate parameters of PM Group and MA group in their mild-ordinary stage, and of SA group in their severe stage (Table 2). While both PM Group and MA group were in mild-ordinary stage at admission, there were significant differences in CD4 T cell (507.9 vs. 248.2/μl, $p < 0.001$), FDP(1.8 vs. 9.4 μg/ml, $p < 0.001$), LDH(243.6 vs. 344.6 U/L, $p < 0.001$), albumin (41.1 vs. 37.3 g/L, $p < 0.001$), eGFR(113.0 vs. 89.9 ml/min/1.73 m^2, $p < 0.001$), CRP(17.2 vs. 69.4 mg/L, $p < 0.001$), PCT(0.04 vs. 0.36 ng/ml, $p < 0.001$), NT-proBNP(72.5 vs. 369.3 pg/ml, $p < 0.001$), myoglobin (14.8 vs. 80.6 ng/ml, $p < 0.001$) between them at admission. These parameters showed differences before the obvious deterioration of clinical condition, indicating a potential predictive value.

Table 2
Laboratory findings on admission of cases with SARS-CoV-2 infection

	PM Group (n = 299)	S/C Group (n = 27)		P Value
		MA group (n = 20)	Severe-critical on admission (n = 7)	
Blood routine and lymphocyte classification				
WBC, 10^9/ml	5.1 ± 2.0	5.5 ± 2.5	6.7 ± 4.8	0.104
Neutrophils, 10^9/ml	3.5 ± 2.4	3.9 ± 2.5	5.6 ± 4.6	0.060
Lymphocyte, 10^9/ml	1.2 ± 0.5[a]	1.0 ± 1.1	0.6 ± 0.4[a]	0.004
Platelet, 10^9/ml	190.4 ± 65.3	161.1 ± 46.0	188.9 ± 97.9	0.151
Haemoglobin, g/L	136.1 ± 17.4	130.1 ± 37.6	147.0 ± 19.8	0.125
CD8 + T cell, /μl	306.7 ± 182.2	370.9 ± 889.5	118.0 ± 95.1	0.119
CD4 + T cell, /μl	507.9 ± 256.1 [a,b]	248.2 ± 178 [a]	199.9 ± 171.3 [b]	< 0.001
Coagulation Profile				
Prothrombin Time, s	13.6 ± 4.0	12.8 ± 3.1	14.4 ± 1.3	0.586
APTT, s	41 ± 26.2	42.1 ± 12.2	43.2 ± 14.2	0.959
D-dimer, μg/ml	0.7 ± 1.3[a]	1.8 ± 4.3[b]	8.3 ± 8.1[a,b]	< 0.001
FDP, μg/ml	1.8 ± 5.4[a,b]	9.4 ± 33.1[a,c]	32.6 ± 57.5[b,c]	< 0.001
Liver, Kidney Function and Electrolytes				
ALT, U/L	27.5 ± 20.0	26.9 ± 16.3	45.1 ± 23.8	0.068
AST, U/L	28.4 ± 20.9[a]	36.0 ± 13.9	52.6 ± 26.5[a]	0.003

Data were shown as mean ± standard deviation

*P values are less than 0.05 for data with the same superscript letter on the same line.

Abbreviations: PM, persistent mild-ordinary group; S/C, severe/critical; MA, mild-ordinary-at-admission; SA, severe-at-admission group; WBC, White blood cell; APTT, Active Partial Thromboplastin Time; FDP, Fibrinogen Degradation Product; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; LDH, Lactate dehydrogenase; TBIL, total bilirubin; eGFR: estimated Glomerular Filtration Rate; ESR, erythrocyte sedimentation rate; CRP, C Reaction Protein; NT-proBNP: N-terminal pro-B-type natriuretic peptide;

	PM Group (n = 299)	S/C Group (n = 27)		P Value
		MA group (n = 20)	Severe-critical on admission (n = 7)	
LDH, U/L	243.6 ± 80.2[a,b]	344.6 ± 97.0[a,c]	454.7 ± 126.1[b,c]	< 0.001
Creatine Kinase, U/L	145.8 ± 413.6[a]	222.8 ± 165.0[b]	776.0 ± 952.9[a,b]	< 0.001
Albumin, g/L	41.1 ± 4.4[a,b]	37.3 ± 4.2[a]	34.6 ± 4.0[b]	< 0.001
TBIL, umol/L	13.9 ± 46.6	10.5 ± 5.9	15.1 ± 6.1	0.945
Creatine, umol/L	65.3 ± 20.7[a]	78.7 ± 40.8[b]	116.8 ± 122.5[a,b]	< 0.001
eGFR,ml/min/1.73 m^2	113.0 ± 26.6[a]	89.9 ± 23.2[a]	97.1 ± 48.3	< 0.001
Inflammatory Indicators				
ESR, mm/h	59.8 ± 38.3	58.9 ± 30.0	71.6 ± 37.6	0.714
CRP, mg/L	17.2 ± 22.2[a,b]	69.4 ± 54.0[a]	52.9 ± 38.6[b]	< 0.001
Procalcitonin, ng/ml	0.04 ± 0.03[a,b]	0.36 ± 0.64[a]	0.26 ± 0.42[b]	< 0.001
Cardiac Biomarker				
NT-proBNP, pg/ml	72.5 ± 113.6[a,b]	369.3 ± 551[a,c]	591.5 ± 799.9[b,c]	< 0.001
Myoglobin, ng/ml	14.8 ± 37.0[a,b]	80.6 ± 111.9[a,c]	145.5 ± 172.4[b,c]	< 0.001
Troponin T, ng/ml	0.07 ± 0.52	0.06 ± 0.05	0.06 ± 0.04	0.997

Data were shown as mean ± standard deviation

*P values are less than 0.05 for data with the same superscript letter on the same line.

Abbreviations: PM, persistent mild-ordinary group; S/C, severe/critical; MA, mild-ordinary-at-admission; SA, severe-at-admission group; WBC, White blood cell; APTT, Active Partial Thromboplastin Time; FDP, Fibrinogen Degradation Product; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; LDH, Lactate dehydrogenase; TBIL, total bilirubin; eGFR: estimated Glomerular Filtration Rate; ESR, erythrocyte sedimentation rate; CRP, C Reaction Protein; NT-proBNP: N-terminal pro-B-type natriuretic peptide;

Table 3
Summary of all indicators' performances.

	Correlation	Differentiation	Early-warning	Feasibility
LDH	+++	+++	+++	+++
Procalcitonin	+++	++	+++	+++
NT-proBNP	+++	++	+++	+++
Myoglobin	+++	+	+++	+++
D-dimer	+++	++	+++	++
FDP	++	++	+++	+++
C-reaction protein	++	+	+++	++
White blood cell	++	+	±	±
Lymphocytes	++	+	+	+
CD4 T cell	++	+	+++	+++
Troponin T	++	+	±	±
CD8 T cell	++	+	±	±
Creatine Kinase	++	±	+	+
eGFR	++	±	+++	+++
ALT	+	±	±	±
Platelet	±	±	±	±

Abbreviations: LDH, Lactate dehydrogenase; FDP, Fibrinogen Degradation Product; NT-proBNP: N-terminal pro-B-type natriuretic peptide; eGFR: estimated Glomerular Filtration Rate; ALT, Alanine aminotransferase.

The level of D-dimer, CRP at admission were above normal range both in the PM group and the MA group; the levels of LDH, NT-proBNP, myoglobin, CD4 T cell, eGFR, FDP and PCT were beyond normal range only in the MA group but remained normal in the PM group (Table 2, Fig. 2D, 2G, 2J, 2L, 2M), indicating a nature warning effect of the upper limit of normal of these parameters.

Evaluations of potential follow-up indicators

To evaluated the correlation of laboratory findings and the disease severity, we plotted value-stage curves and calculated spearmen coefficients of 16 candidate parameters (Fig. 2, Fig. 3). Top 5 parameters with highest spearmen coefficient were LDH, PCT, NT-proBNP, myoglobin and D-dimer (Spearman coefficient: 0.488, 0.453, 0.414, 0.412, 0.407, $p < 0.001$; Fig. 3).

In order to evaluate the diagnostic performance of the above 5 parameters in differentiating the severity of COVID-19, we conducted the ROC analysis (Fig. 4). Comparing between mild-ordinary stage and severe/critical stage (Fig. 4A), LDH had the best performance, with the highest ROC AUC of 0.951. With a cutoff value of 385.5 U/L, the sensitivity of LDH in differentiating severe COVID-19 was 49.7% and the specificity was 95.3%. PCT ranked second, with the ROC AUC of 0.905. With a cutoff value of 0.055 ng/ml, PCT had a sensitivity of 74.1% and a specificity of 79.2%. ROC AUC of D-dimer, NT-proBNP and FDP was less than 0.90. Comparing between mild-ordinary and severe stages (Fig. 4B), only LDH had the ROC AUC of over 0.90 (0.927). With a cutoff value of 345 U/L, the sensitivity of predicting severe cases was 48.2% and the specificity was 92.3%.

Discussion

This study is the first clinical study to describe the correlation and evolution of various laboratory parameters with the clinical severity and progression of COVID-19 based on clinical stages but not an absolute course of disease. Through multi-dimensional comparison of various parameters, we have found LDH as an indicator of both predictive and follow-up value in COVID-19 cases.

Although there have been many studies describing the clinical characteristics of COVID-19 patients and multiple possible prognostic indicators, we should pay attentions to the research methodology and process when evaluating those indicators. First, admission should not be used as a starting point for follow-up when evaluating prognostic indicators. Laboratory parameters are supposed to reflect the patient's clinical condition, but the patient's admission time is determined by many non-medical accidental factors. Therefore, analysis of the parameters at admission of all patients[3,5–7] undermines their correlations of the disease severity. Secondly, it is also inappropriate to follow up the laboratory parameters with an absolute course of disease. For example, in Zhou's article[3], the curve of D-Dimer and lymphocytes stayed relatively flat in first 7 days since the onset-of symptoms and began to rise significantly after that. This is consistent with Zhou’s finding that non-survivors of COVID-19 progressed to sepsis on the average of seven days. In another words, the non-survivors experienced several stages of the disease, i.e. mild, severe and even critical ill, in the first seven days and stayed in critical stages in the following 14 days. Therefore, the significantly elevated part of the curve described the patients in critical stage and these indicators were related to death, but not early predictors for disease progression. Third, predictors should show abnormalities earlier than the deterioration of the clinical condition manifested by the patient's symptoms and signs. The right way to find those indicators is to compare the parameters of severe cases in their mild stage to the persistent mild patients[4]. It is common to compare admission findings of the severe cases to the mild ones. However, as previously mentioned, many patients were seriously ill when they were admitted to the hospital. This kind of comparison would show the difference between severe and mild patients but not risk factors for developing severe cases. Fourth, for indicators that appear abnormal in most persistent mild cases, even if they also showed statistical differences to severe ones, it may have limited clinical application value for clinicians. These indicators need to

establish a cut-off specific for COVID-19, and it is also affected by technical factors such as laboratory examinations, resulting a higher threshold for acceptance and application in clinical practice.

We summarized a “CDEF” rule for indicators, namely correlation, differentiation, early-warning, and feasibility. We measured the correlation by Spearman analysis and found that LDH, PCT, NT-proBNP, MYO and D-dimer correlated well to the severity of COVID-19. The ability of differentiating the clinical conditions was quantified as the AUC value of the ROC curve, and we noted the superior performance of LDH in differentiating between mild and severe patients. Early-warning was to show abnormalities even in the mild stage of the disease, therefor helping clinicians to find high-risk patients who might deteriorate. One way to achieve feasibility was to warn the clinicians when the indicators become abnormal, i.e. beyond the normal range, rather than another unestablished cutoff. In this study, CRP and D-dimer levels were above the upper limit of normal both in mild and severe cases although there were significant differences between mild and severe cases. Thus, above-normal CRP or D-dimer had the difficulty to indicate the disease progression.

Lactate dehydrogenase is a cytoplasmic glycolytic enzyme found in almost every tissue. Its elevation generally indicates tissue damage. Raised LDH is a common finding in patients infected with MERS-CoV[8, 9], H7N9[10, 11] and H5N1[12]. It is reported to be independent factors of mortality for patients with severe acute respiratory syndrome[13] and H1N1 infection[14]. It is also one of the biomarkers most strongly associated with ARDS mortality[15,16]. Our research did not combine LDH with other indicators. The first reason is that LDH's ROC AUC for predicting severity of COVID-19 is more than 0.95. The combination of other indicators that are inferior to LDH is of limited significance for improving prediction performance. The main significance of the early predictors is to identify high-risk patients in order to allocate medical resources more rationally and improve the prognosis, but not predicting the prognosis itself. Therefore, we believe that even if LDH alone may slightly inferior to indicator combination in the predicting accuracy, it can greatly improve the convenience in clinical practice. What’s more, the present indictor combination or workflow of COVID-19[17, 18] still lack large-scale clinical verification, while LDH has been widely proved to be an important marker to indicate the progress of the disease[3,4,5,6,17,18]. Our research further shows that LDH has outstanding practical predictive performance for disease progression from many aspects.

This study has some limitations. First, we did not measure viral load and some patients lacked cytokine testing, which could be factors related to the severity of the disease. Second, we did not test the LDH isoenzymes due to limited resources. LDH isoenzyme analysis in the future may help to identify the source of increased LDH.

In conclusion, LDH was found to be a superior indicator of disease status among COVID-19 patients and had the potential to optimize the clinical management strategy.

List Of Abbreviations

COVID-19: Coronavirus disease 2019

WHO: World Health Organization

SPHCC: Shanghai Public Health Clinical Center

WBC: white blood cell

ALT: alanine aminotransferase

EGFR: estimated glomerular filtration rate

FDP: fibrin degradation products

CK: creatine kinase

TnT: troponin T

NT-proBNP: N-terminal pro-B-type natriuretic peptide

LDH: lactase dehydrogenase

CRP: C-reactive protein (CRP)

PCT: procalcitonin (PCT)

ROC: receiver operating characteristics

AUC: area under the curve

Declarations

Ethics approval and consent to participate:

An ethical approval was obtained from the Ethics Review Board of the Huashan hospital, Fudan University

Consent for publication:

Not appliable.

Availability of data and materials:

The data that support the findings of this study are available from the corresponding author on reasonable request.

Competing interests

All authors declare no competing interests.

Funding:

This study was not funded.

Authors' contributions

Conception or design of the work: XZ, YL, YH, WZ.

Data collection and patient care: YH, ZW, XZ, YL

Data analysis and interpretation: XZ, YL, JA, HW, HZ.

Drafting the article: YL, XZ, JA, HW.

Critical revision of the article: YH, WZ.

Final approval of the version to be published: All of the authors.

Acknowledgements

We thank all physicians that participated in this study for patient enrollment and follow-up and show the greatest appreciation to all health workers for their valuable input to the control of diseases.

References

1. Liang X, Feng Z, Li L. *Guidance for Corona Virus Disease 2019: Prevention, Control, Diagnosis and Management*. People's medical publishing house; 2020.
2. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*. 2020. Doi: 10.1056/NEJMoa2002032.
3. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *The Lancet*. 2020;395(10229):1054-1062.
4. Shi J, Li Y, Zhou X, Zhang Q, Ye X, Wu Z, et al. Lactate dehydrogenase and susceptibility to deterioration of mild COVID-19 patients: a multicenter nested case-control study. *BMC Medicine*. 2020;18(1):168.
5. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med*. 2020. Doi: 10.1001/jamainternmed.2020.0994.
6. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. *JAMA*. 2020;323(11):1061-1069.

7. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, et al. Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol*. Published online March 27, 2020.
8. Alsolamy S. Middle East Respiratory Syndrome: Knowledge to Date*. *Critical Care Medicine*. 2015;43(6):1283–1290.
9. Al Ghamdi M, Alghamdi KM, Ghandoora Y, Alzahrani A, Salah F, Alsulami A, et al. Treatment outcomes for patients with Middle Eastern Respiratory Syndrome Coronavirus (MERS CoV) infection at a coronavirus referral center in the Kingdom of Saudi Arabia. *BMC Infect Dis*. 2016;16:174.
10. Shi J, Xie J, He Z, Hu Y, He Y, Huang Q, et al. A detailed epidemiological and clinical description of 6 human cases of avian-origin influenza A (H7N9) virus infection in Shanghai. *PLoS ONE*. 2013;8(10):e77651.
11. Mei Z, Lu S, Wu X, Shao L, Hui Y, Wang J, et al. Avian influenza A(H7N9) virus infections, Shanghai, China. *Emerging Infect Dis*. 2013;19(7):1179-1181.
12. Oner AF, Bay A, Arslan S, Akdeniz H, Sahin H, Cesur Y, et al. Avian Influenza A (H5N1) Infection in Eastern Turkey in 2006. *New England Journal of Medicine*. 2006;355(21):2179-2185.
13. Choi KW, Chau TN, Tsang O, Tso E, Chiu M, Tong W, et al. Outcomes and prognostic factors in 267 patients with severe acute respiratory syndrome in Hong Kong. *Ann Intern Med*. 2003;139(9):715-723.
14. Xi X, Xu Y, Jiang L, Li A, Duan J, Du B, et al. Hospitalized adult patients with 2009 influenza A(H1N1) in Beijing, China: risk factors for hospital mortality. *BMC Infect Dis*. 2010;10:256.
15. Terpstra ML, Aman J, van Nieuw Amerongen GP, Groeneveld ABJ. Plasma biomarkers for acute respiratory distress syndrome: a systematic review and meta-analysis*. *Crit Care Med*. 2014;42(3):691-700.
16. Hoeboer SH, Oudemans-van Straaten HM, Groeneveld ABJ. Albumin rather than C-reactive protein may be valuable in predicting and monitoring the severity and course of acute respiratory distress syndrome in critically ill patients with or at risk for the syndrome after new onset fever. *BMC Pulm Med*. 2015;15:22.
17. Yan L, Zhang H-T, Goncalves J, Xiao Y, Wang M, Guo Y et al. An interpretable mortality prediction model for COVID-19 patients. *Nature Machine Intelligence*. 2020;2(5):283-288.
18. Liang W, Liang H, Ou L, Chen B, Chen A, Li C, et al. Development and Validation of a Clinical Risk Score to Predict the Occurrence of Critical Illness in Hospitalized Patients With COVID-19. *JAMA Intern Med*. 2020. Doi: 10.1001/jamainternmed.2020.2033.

Figures

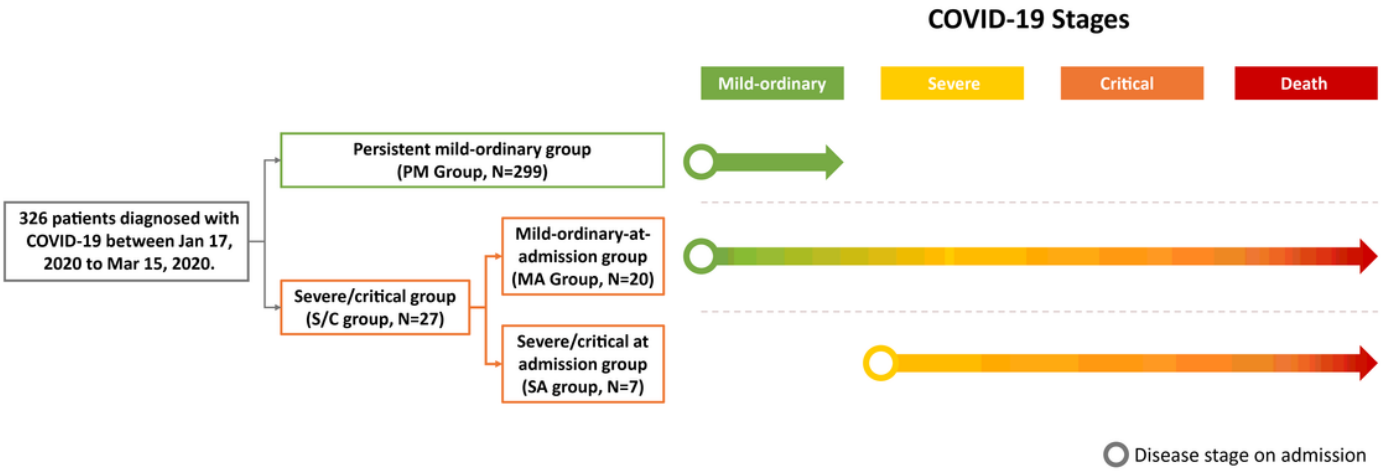

Figure 1

Study design and flow chart of this study.

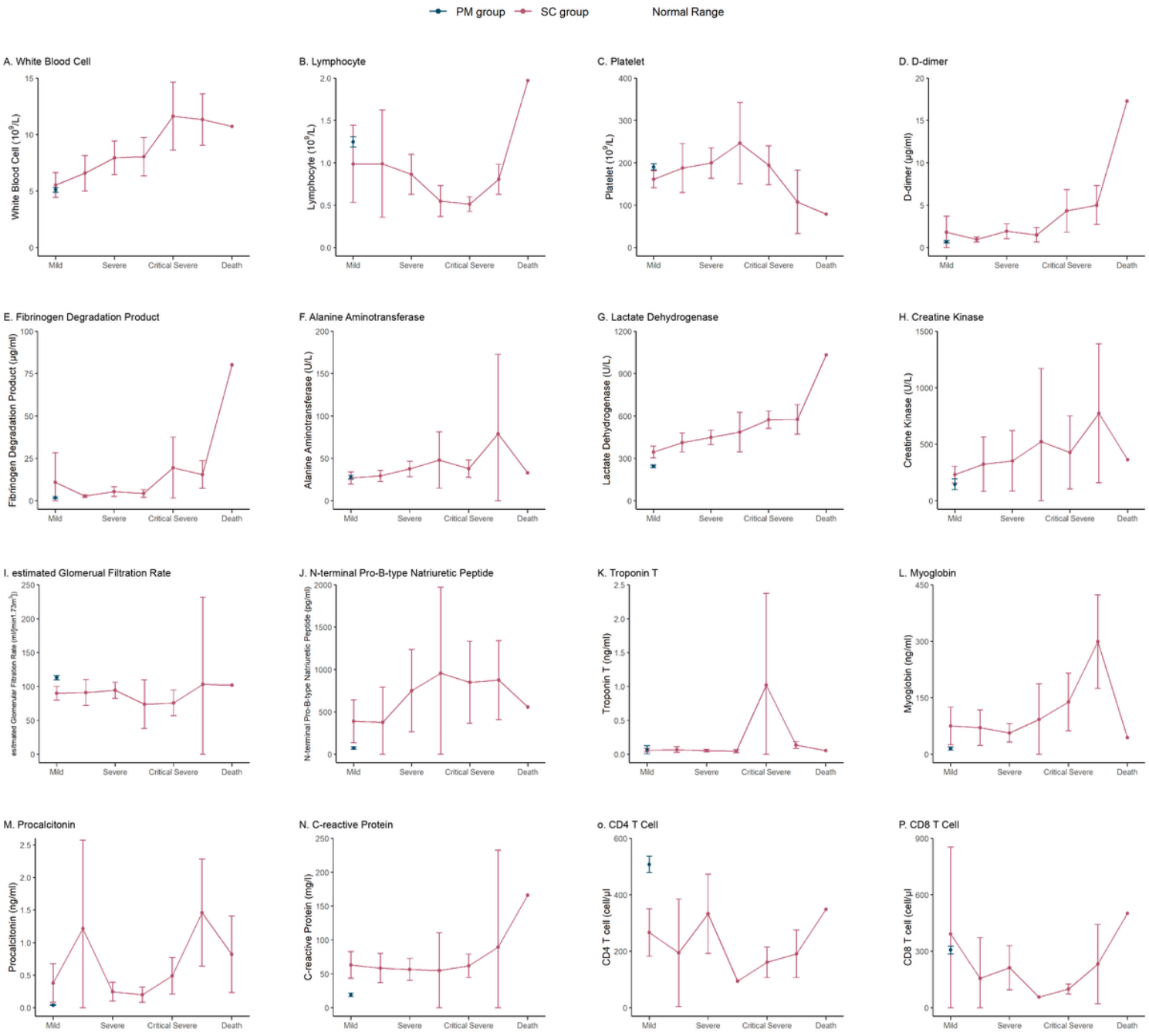

Figure 2

The value-stage curve of 16 candidate indicators. (A) White blood cell; (B) lymphocyte; (C) Platelet; (D) D-dimer; (E) fibrin degradation products; (F) alanine aminotransferase; (G) lactase dehydrogenase; (H) creatine kinase; (I) estimated glomerular filtration rate; (J) N-terminal pro-B-type natriuretic peptide; (K) troponin T; (L) myoglobin; (M) procalcitonin; (N) C-reactive protein; (O) CD 4 T cell; (P) CD8 T cell.

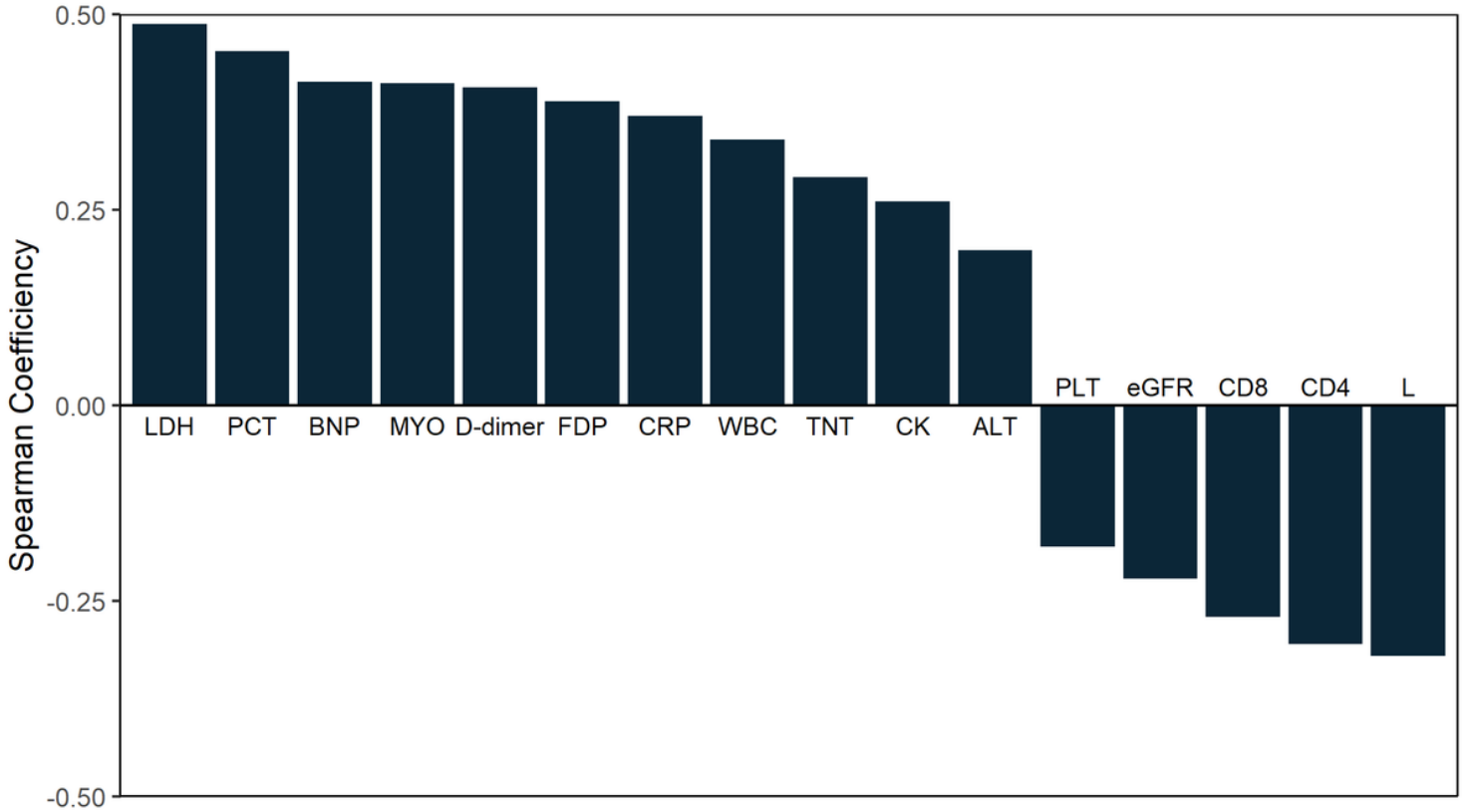

Figure 3

Spearman coefficient of 16 candidate indicators. Abbreviation: LDH, lactase dehydrogenase; PCT, procalcitonin; BNP, N-terminal pro-B-type natriuretic peptide; MYO, myoglobin; FDP, fibrin degradation products; CRP, C-reactive protein; WBC, white blood cell; TnT, troponin T; CK, creatine kinase; ALT, alanine aminotransferase; PLT, platelet; eGFR, estimated glomerular filtration rate; L, lymphocyte;

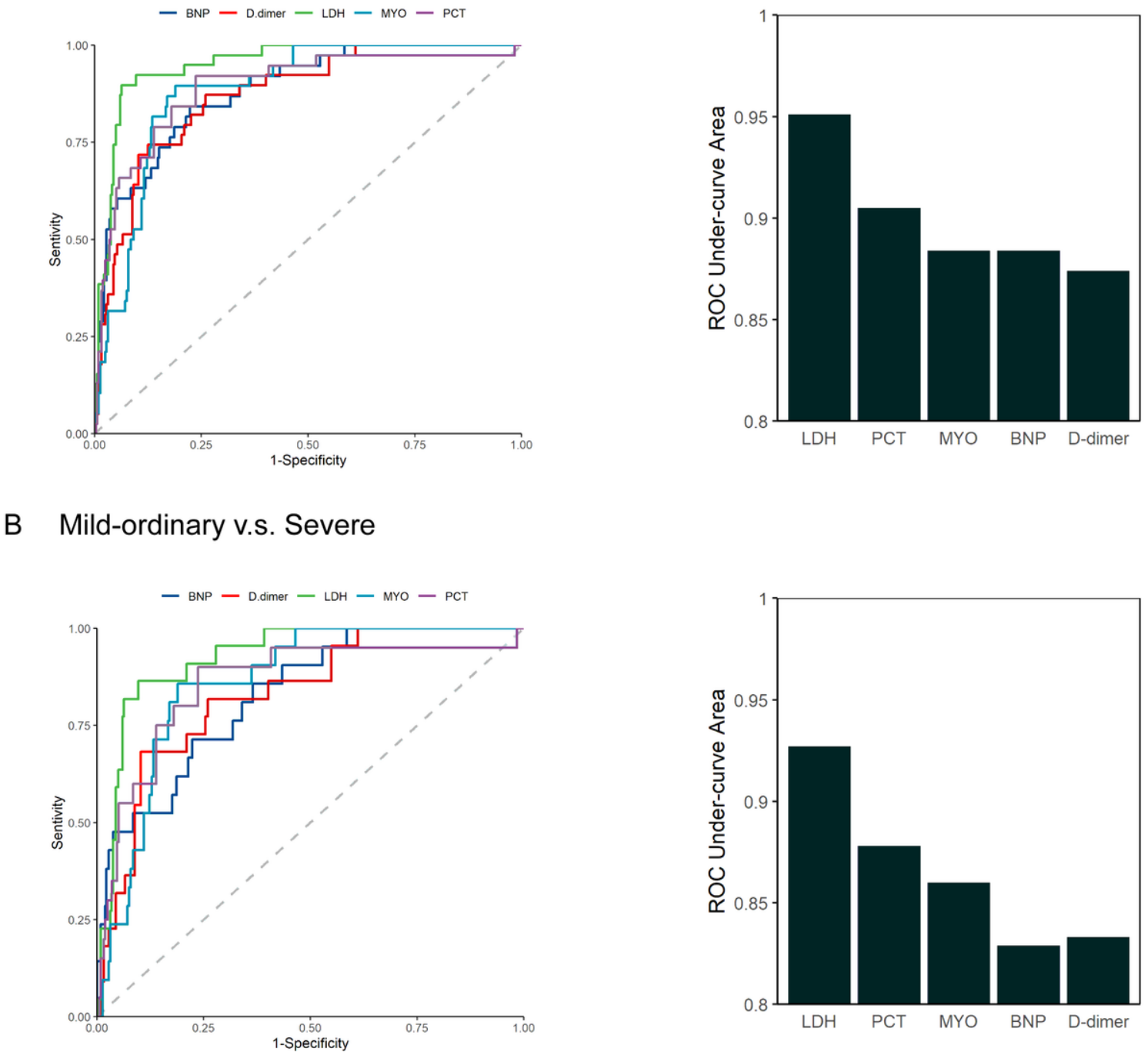

Figure 4

ROC curve of sensitivity versus specificity for NT-proBNP, D-dimer, LDH, MYO and PCT. (A) ROC curve and AUC for the differentiation between mild-ordinary and severe-critical group. (B) ROC curve and AUC for the differentiation between mild-ordinary and severe group. Abbreviation: ROC, receive operating characteristics; NT-proBNP, N-terminal pro-B-type natriuretic peptide; LDH, lactase dehydrogenase; MYO, myoglobin; PCT, procalcitonin; AUC, area under curve;