A simple algorithm helps early identification of SARS-CoV-2 infection patients with severe progression tendency

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Research Article

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Abstract

Objectives We aimed to develop a simple algorithm helps early identification of SARS-CoV-2 infection patients with severe progression tendency.

Methods 322 SARS-COV-2 infection patients were respectively enrolled. The univariable and multivariable analysis were computed to identify the independent predictors of severe progression, and the prediction model was established based on independent predictors. The areas under the ROC curves (AUROCs) were used to evaluate the diagnostic performances.

Results Of 322 confirmed SARS-COV-2 infection patients, 11 were diagnosed as severe cases on admission, 15 developed to severe cases after admission, and 296 were non-severe cases. The multivariable analysis identified age (OR=1.061, *p*=0.028), lactate dehydrogenase (LDH) (OR=1.006, *p*=0.037), and CD4 count (OR=0.993, *p*=0.006) as the independent predictors of severe progression. Consequently, the age-LDH-CD4 algorithm was derived as (age×LDH)/CD4. The AUROC of the age-LDH-CD4 model was significantly higher than that of single CD4 count, LDH, or age (0.92, 0.85, 0.80, and 0.75, respectively). The age-LDH-CD4 model ≥ 82 has high sensitive (81%) and specific (93%) for the early identification of patients with severe progression tendency following SARS-CoV-2 infection.

Conclusions The age-LDH-CD4 model is a simple algorithm for early identifying cases with severe progression tendency in SARS-CoV-2 infection patients, and warrants further validation.

Introduction

Since November 2019, an outbreak of 2019 novel coronavirus disease (COVID−19) in Wuhan, Hubei province, China, caused by a novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV−2), and the rapidly spread has caused a major public health issue and attracted enormous attention around the world [1]. As of March 12th, 2020, there have been 80,955 confirmed cases and 3,162 deaths in China, and 118,326 confirmed cases and 4,292 deaths globally [2].

In previous studies, the clinical characteristics of SARS-CoV−2 infection patients have been described in detail [3−5]. Most patients were mild and often experienced fever, cough, and fatigue after an incubation period of median 3−7 days, and then recovered in 2−3 weeks [6]. 17%−32% of patients developed severe cases, and might progress rapidly to complications including acute respiratory distress syndrome, shock, secondary infection, acute cardiac injury, and acute kidney injury [3−5]. The reported proportion of severe cases were 17% [4], 26.1% [5], and 32% [3], and the mortalities were 4.3% [5], 11.0% [4], and 14.6% [3], respectively, in Wuhan, China.

Although the first patient of SARS-CoV−2 infection in the United States responding well to remdesivir [7], there were no clinically effective antiviral drugs for SARS-CoV−2 infection [8]. Early identification of patients with severe progression tendency is urgently needed not only to guide appropriate supportive

care and promptly access to the intensive care unit (ICU), but also for physicians to evaluate the prognosis of patients. However, to date, there is no clinically available method to early identify SARS-CoV–2 infection patients with severe progression tendency.

In this study, we designed a simple algorithm helps early identification of patients with severe progression tendency, based on 322 laboratory-confirmed SARS-CoV–2 infection patients, and aimed to provide a clinically available method to regulate the large flow of SARS-CoV–2 infection patients between primary health care and ICU.

Patients And Methods

Patients

We retrospectively enrolled 322 laboratory-confirmed SARS-CoV–2 infection patients, who hospitalized in Shanghai Public Health Clinical Center, Shanghai, China, a designated tertiary teaching hospital for the treatment of confirmed SARS-CoV–2 infection patient, between January 20th 2020 and February 23th 2020. Patients were grouped into severe (n = 26) and non-severe (n = 296). Of 26 severe cases, 11 were diagnosed as severe cases on admission, and 15 developed to severe cases after admission.

Informed consents were obtained from all patients and the study was approved by the ethics committee of Shanghai Public Health Clinical Center. The clinical diagnosis and treatment complied with the Helsinki declaration.

Diagnostic Criteria

Laboratory confirmation of SARS-CoV–2 infection was achieved by the Chinese Center for Disease Prevention and Control. A confirmed case was defined as a positive result with SARS-COV–2 nucleotides by real-time reverse-transcriptase polymerase-chain-reaction assay for nasopharyngeal swab specimens [9], according to the protocol established by World Health Organization [10]. Severe cases were defined as any one of the followings: (1) Respiratory distress, respiratory rates ≥ 30/min; (2) Pulse oxygen saturation ≤ 93% in a resting state; (3) Oxygenation index (PaO2/FiO2) ≤ 300 mmHg; (4) Require mechanical ventilation; (5) Shock; (6) Combined with other organ failures and needed treatment in ICU.

Data collection

The age, gender, and underlying disorders were extracted from the electronic medical records. The laboratory findings on admission including complete blood count, lymphocyte subpopulation, C-reactive protein (CRP), procalcitonin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl-transpeptidase, lactate dehydrogenase (LDH), total bilirubin, creatinine, creatine kinase, and D-dimer were obtained with data collection forms.

Statistical analysis

The normality test was performed for continuous variables using the Kolmogorov-Smirnov test. Normal distribution variables, non-normal distribution continuous variables, and categorical variables, were showed as means and standard deviations, medians and interquartile ranges (IQR), and counts and percentage, respectively. T-tests, Mann-Whitney-tests, and chi-square tests were applied to normal distribution variables, non-normal distribution continuous variables, and categorical variables, respectively. The Pearson correlation analysis was performed to show the correlation between two variables. The univariable and multiple analyze were performed to identify the independent predictors of cases with severe progression. The areas under the receiver operating characteristic (ROC) curves (AUROC) were used to estimate the predictive accuracy, and compared using Delong test [11]. The optimal cut-offs were obtained by maximizing Youden index. All statistical analyses were conducted with SPSS software version 15.0 (SPSS Inc. USA) and MedCalc software version 16.1 (MedCalc Software, Belgium).

Results

Baseline Characteristics

The baseline characteristics of enrolled patients were presented in Table 1. The median age was 51 years (IQR, 36–64), 51.8% were males, and 33.2% had underlying disorder. The age (65 *vs.* 49 years, $p<0.001$) and proportion of male (76.9% *vs.* 49.8%, $p = 0.008$) in severe cases (n = 26) were significantly higher than that in non-severe cases (n = 296). Moreover, underlying disorders were more common in severe cases as compared with non-severe cases (69.2% *vs.* 30.1%, $p<0.001$).

Severe cases had significantly higher CRP (53 *vs* 8 mg/L, $p<0.001$), procalcitonin (0.16 *vs* 0.03 ng/mL, $p<0.001$), AST (45 *vs* 23 U/L, $p<0.001$), LDH (399 *vs* 224 U/L, $p<0.001$), total bilirubin (10.3 *vs* 8 umol/L, $p = 0.001$), blood urea nitrogen (5.10 *vs* 4.37 mmol/L, $p = 0.025$), creatinine (80 *vs* 63 umol/L, $p = 0.002$), creatine kinase (220 *vs* 78 U/L, $p<0.001$), and D-dimer (1.2 *vs* 0.41 ug/mL, $p<0.001$); but significantly lower lymphocyte count (0.65×10^9 *vs* 1.14×10^9 cells/L, $p<0.001$), CD3 (323 vs 773 cell/ul, $p<0.001$), CD8 (124 vs 264 cell/ul, $p<0.001$), CD4 (159 *vs* 452 cell/ul, $p<0.001$), and CD45 count (586 vs 1120 cell/ul, $p<0.001$) compared with non-severe cases.

Correlation between Baseline Data and Severe Progression

Variables associated with severe progression were showed in Table 2. The severe progression positively correlated with LDH ($r = 0.39$, $p<0.001$), procalcitonin ($r = 0.39$, $p<0.001$), CRP ($r = 0.35$, $p<0.001$), D-dimer ($r = 0.32$, $p<0.001$), creatine kinase ($r = 0.31$, $p<0.001$), age ($r = 0.27$, $p<0.001$), underlying disorder ($r = 0.27$, $p<0.001$), AST ($r = 0.25$, $p<0.001$), total bilirubin ($r = 0.18$, $p = 0.001$), creatinine ($r = 0.17$, $p = 0.002$), male ($r = 0.15$, $p = 0.008$), and blood urea nitrogen ($r = 0.12$, $p = 0.026$); and negatively correlated with CD4 ($r = -0.34$, $p<0.001$), CD3 ($r = -0.33$, $p<0.001$), CD8 ($r = -0.32$, $p<0.001$), CD45 ($r = -0.31$, $p<0.001$), and lymphocyte count ($r = -0.30$, $p<0.001$).

Independent Predictors of Patients with Severe Progression

The independent predictors of patients with severe progression were showed in Table 3. Univariate analysis showed that age, male, underlying disorder, D-dimer, white blood cell, lymphocyte, CRP, CD3, CD4, CD45, AST, LDH, total bilirubin, and creatinine were associated with severe progression (all $p<0.05$). Multivariable analysis identified age (OR = 1.061, 95%CI, 1.007–1.119, $p = 0.028$), CD4 count (OR = 0.993, 95%CI, 0.987–0.998, $p = 0.006$), and LDH (OR = 1.006, 95%CI, 1.000–1.012, $p = 0.037$) as the independent predictors.

Develop a Simple Algorithm Early Identifying Patients with Severe Progression Tendency

In Table 2, we found that age and LDH had a positive correlation with severe progression ($r > 0$, $p<0.001$), and CD4 count was negatively correlated ($r < 0$, $p<0.001$). In Table 3, we found that age, LDH, and CD4 count were the independent predictors of severe progression. In order to improve the prediction performance using age, LDH, and CD4 count, a simple algorithm was derived as: age (years) × LDH (U/L)/ CD4 (cell/ul).

AUROCs Comparison of The age-LDH-CD4 Model and Single Index (age, LDH, or CD4)

Based on the fact that only the patients developed severe cases during hospitalization after admission could be counted for prediction. Therefore, ROC curve analysis was only performed in 15 patients who developed severe cases after admission (Figure 1). Pairwise comparison of AUROCs was presented in Table 4. The AUROC of age-LDH-CD4 model (0.92, 95%CI 0.88 to 0.95) was significantly higher than that of CD4 count (0.85, 95%CI 0.81 to 0.89, $p = 0.005$), LDH (0.80, 95%CI 0.75 to 0.84, $p = 0.025$), and age (0.79, 95%CI 0.74 to 0.83, $p<0.001$).

Cut-off Values of age-LDH-CD4 Model and Single Index (age, LDH, or CD4)

The cut-off values were showed in Table 5. According to maximizing the Youden index, the optimal cut-off values were 82 for age-LDH-CD4 model (the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) was 82%, 81%, 49%, and 98%, respectively), 295 for CD4 count (the sensitivity, specificity, PPV, and NPV was 77%, 81%, 25%, and 98%, respectively), 60 for age (the sensitivity, specificity, PPV, and NPV was 81%, 72%, 20%, and 98%, respectively), and 300 for LDH (the sensitivity, specificity, PPV, and NPV was 81%, 83%, 29%, and 98%, respectively), respectively.

Discussion

The current SARS-CoV–2 outbreak is the third epidemic caused by coronavirus in the 21st century, following severe acute respiratory syndrome and Middle East respiratory syndrome. At present, the epidemiological and clinical characteristics of SARS-CoV–2 infection have been reported [3–5]. However, there is still a lack on the risk factors of severe progression following SARS-CoV–2 infection. Early identification of patients with severe progression tendency has important significance for regulating the large flow of SARS-CoV–2 infection patients between primary health care and ICU. Patients had no severe

progression tendency can be treated in primary health care and general ward, whereas those had severe progression tendency needed to be redirected to ICU for specialized management.

This study developed a simple algorithm, named age-LDH-CD4 model, to early identify patients with severe progression tendency following SARS-CoV–2 infection. The age-LDH-CD4 model based on three routine parameters: age, LDH, and CD4 count. In this study, the age-LDH-CD4 model ≥ 82 has high sensitive (81%) and specific (93%) for the early identification of patients with severe progression tendency following SARS-CoV–2 infection. Therefore, the age-LDH-CD4 ≥ 82 could be used for screening patients who needed treatment in ICU. The NPV of age-LDH-CD4 model is 98%, suggesting just 2% of patients with age-LDH-CD4 < 82 developed to severe cases, therefore could be treated in primary health care or general isolation ward.

In this study, patients with age > 60 years, LDH > 300 U/L, or CD4 count < 295 cell/ul had more likely to develop to severe cases following SARS-CoV–2 infection. The results were consistent with previous studies. Wang et al reported that patients treated in the ICU were older (median age, 66 years vs 51 years) compared with patients not treated in the ICU [5]. Guan et al reported that patients in severe subgroups had higher age than patients in non-severe subgroups (mean difference, 7.0, 95%CI, 4.4 to 9.6) [12]. Chan et al also found older patients (aged >60 years) had more lymphopenia and increased LDH levels [13].

In this study, severe cases occurred in 8% of SARS-CoV–2 infection patients, which was lower than that reported in Wuhan, Hubei provinces, China (17%–32%) [3–5]. As of March 12th 2020, 3 patients dead, a markedly lower fatality rate (0.9 %) compared with that reported in Wuhan (4.3%–14.6%) [3–5]. The lower severe rate and fatality rate attributed to the early effective measures (early discovery, early isolation, early diagnosis, and early treatment) were undertaken in Shanghai at the beginning of outbreaks.

This study has some limitations. First, this study is a single-center study, because Shanghai Public Health Clinical Center is the only SARS-CoV–2 designated hospital for laboratory-confirmed adult patients in Shanghai, China. Second, the retrospective design might have caused selective bias [14]. Third, we cannot provide a validation cohort in a short time, because the outbreaks had been controlled in Shanghai.

In summary, this study showed that SARS-CoV–2 infection had a low severe rate and fatality rate once the measures (early discovery, early reporting, early quarantine and early treatment) were undertaken at the beginning of outbreaks. The age, LDH, and CD4 count were the independent predictors of severe progression following SARS-CoV–2 infection. The age-LDH-CD4 algorithm is a simple and accurate index for the early identification of patients with severe progression tendency following SARS-CoV–2 infection, and warrants further validation.

Declarations

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Conflict of Interest

The authors declare no competing financial and/or non-financial interests.

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Role of the Sponsor

The funding organizations are public institutions and had no role in the design and conduct of the study; collection, management, and analysis of the data; or preparation, review, and approval of the manuscript.

Declarations

The supporting data can be accessed from Liang Chen (corresponding author), E-mail: chenliang@shphc.org.cn

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Tables

Table 1 Baseline Characteristics

	Total (n=322)	Severe (n=26)	Non-severe (n=296)	P value
Age (years)	51 (36-64)	65 (63-76)	49 (36-63)	<0.001
Male, n (%)	167 (51.8%)	20 (76.9%)	147 (49.8%)	0.008
Underlying disorder, n (%)	107 (33.2%)	18 (69.2%)	89 (30.1%)	<0.001
WBC (10^9/L)	4.8 (3.9-6.0)	5.4 (3.6-10.2)	4.8 (4.0-5.9)	0.295
Lymphocyte count (10^9/L)	1.11 (0.79-1.49)	0.65 (0.48-0.87)	1.14 (0.84-1.52)	<0.001
Platelet count (10^9/L)	179 (143-224)	157 (121-211)	181 (144-226)	0.188
CD3 count (cell/ul)	727 (504-1027)	323 (181-542)	773 (550-1054)	<0.001
CD8 count (cell/ul)	250 (159-388)	124 (62-173)	264 (171-404)	<0.001
CD4 count (cell/ul)	428 (299-633)	159 (110-304)	452 (313-650)	<0.001
CD45 count (cell/ul)	1089 (750-1460)	586 (431-799)	1120 (800-1505)	<0.001
C-reactive protein (mg/L)	9 (2-26)	53 (26-87)	8 (2-22)	<0.001
Procalcitonin (ng/mL)	0.03 (0.02-0.06)	0.16 (0.06-0.62)	0.03 (0.02-0.05)	<0.001
ALT (U/L)	22 (15-34)	26 (19-39)	22 (15-33)	0.067
AST (U/L)	24 (19-33)	45 (26-53)	23 (19-32)	<0.001
GGT (U/L)	25 (17-42)	28 (21-68)	25 (16-42)	0.119
LDH (U/L)	229 (193-293)	399 (336-499)	224 (192-270)	<0.001
Total bilirubin (umol/L)	8.2 (6.6-10.5)	10.3 (8.6-13.8)	8 (6.5-10.4)	0.001
BUN (mmol/L)	4.41 (3.55-5.46)	5.10 (4.04-9.80)	4.37 (3.55-5.36)	0.025
Creatinine (umol/L)	63 (51-76)	80 (57-117)	63 (51-75)	0.002
Creatine kinase (U/L)	82 (57-130)	220 (113-417)	78 (55-118)	<0.001
D-dimer (ng/mL)	0.43 (0.29-0.79)	1.2 (0.74-2.23)	0.41 (0.28-0.69)	<0.001

WBC, white blood count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl-transpeptidase; LDH, lactate dehydrogenase; BUN, blood urea nitrogen;

Table 2 Correlation between baseline data and severe progression

Variables	correlation coefficient (r)	P value
Lactate dehydrogenase (U/L)	0.39	<0.001
Procalcitonin (ng/mL)	0.39	< 0.001
C-reactive protein (mg/L)	0.35	<0.001
D-dimer (ng/mL)	0.32	< 0.001
Creatine kinase (U/L)	0.31	<0.001
Age (years)	0.27	< 0.001
Underlying disorder	0.27	< 0.001
Aspartate aminotransferase (IU/L)	0.25	<0.001
Total bilirubin (umol/L)	0.18	0.001
Creatinine (umol/L)	0.17	0.002
Male	0.15	0.008
Blood urea nitrogen (mmol/L)	0.12	0.026
CD4 count (cell/ul)	-0.34	<0.001
CD3 count (cell/ul)	-0.33	<0.001
CD8 count (cell/ul)	-0.32	<0.001
CD45 count (cell/ul)	-0.31	<0.001
Lymphocyte count (10^9/L)	-0.30	< 0.001

The Pearson correlation coefficient (r value) was used to perform correlation analysis between clinical data and severe progression. $P < 0.05$ was considered statistically significant.

Table 3 Independent predictors of severe progression

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P	OR (95% CI)	P
Age (years)	1.086 (1.048-1.126)	<0.001	1.061 (1.007-1.119)	**0.028**
Male	3.379 (1.319-8.652)	0.011	1.152 (0.245-5.411)	0.857
Underlying disorder	2.628 (1.805-3.826)	<0.001	1.125 (0.532-2.380)	0.757
D-dimer (ng/mL)	1.115 (1.027-1.211)	0.009	0.967 (0.865-1.082)	0.562
White blood count (10^9/L)	1.187 (1.041-1.353)	0.011	1.154 (0.917-1.454)	0.223
Total lymphocyte (10^9/L)	0.132 (0.041-0.425)	0.001	9.406 (0.143-619.476)	0.294
C-reactive protein (mg/L)	1.048 (1.032-1.063)	<0.001	1.019 (0.998-1.039)	0.072
CD3 (cell/ul)	0.997 (0.996-0.999)	<0.001	0.999 (0.995-1.003)	0.656
CD8 (cell/ul)	0.999 (0.997-1.002)	0.535		
CD4 (cell/ul)	0.991 (0.987-0.994)	<0.001	0.993 (0.987-0.998)	**0.006**
CD45 (cell/ul)	0.998 (0.997-0.999)	<0.001	1.000 (0.998-1.002)	0.963
Platelet (10^9/L)	0.997 (0.990-1.004)	0.360		
Alanine aminotransferase (U/L)	1.010 (0.993-1.027)	0.267		
Aspartate aminotransferase (U/L)	1.017 (1.003-1.032)	0.020	1.005 (0.978-1.033)	0.716
γ-glutamyl-transpeptidase (U/L)	1.007 (0.997-1.017)	0.145		
Lactate dehydrogenase (U/L)	1.011 (1.007-1.015)	<0.001	1.006 (1.000-1.012)	**0.037**
Total bilirubin (umol/L)	1.119 (1.042-1.202)	0.002	1.003 (0.871-1.155)	0.966
Blood urea nitrogen (mmol/L)	1.000 (0.996-1.003)	0.836		

Creatinine (umol/L)	1.025 (1.012-1.038)	<0.001	1.012 (0.986-1.039)	0.371
Creatine kinase (U/L)	1.000 (1.000-1.001)	0.123		

Multivariate analysis were fitted by including the factors associated with the severe progression in the univariable analyses (p <0.05), and p < 0.05 was considered statistically significant. Multivariable analysis identified age (*p*=0.028), CD4 count (*p*=0.006), and LDH (*p*=0.037) as the independent predictors.

Table 4 AUROCs Comparison of age-LDH-CD4 model and single index (age, LDH, or CD4)

	Patients developed severe cases after admission (n=15)	
	AUROC	(95% CI)
Age-LDH-CD4 Model	0.92	(0.88-0.95)
CD4 (cell/ul)	0.85	(0.81-0.89)
LDH (U/L)	0.80	(0.75-0.84)
Age (years)	0.79	(0.74-0.83)
Age-LDH-CD4 Model *vs* CD4	*p=0.005*	
Age-LDH-CD4 Model *vs* LDH	*p=0.025*	
Age-LDH-CD4 Model *vs* Age	*P<0.001*	

Age-LDH-CD4 Model = (age × LDH)/ CD4 count; LDH, lactate dehydrogenase. The AUROC of age-LDH-CD4 model was significantly higher than that of CD4 count, LDH, and age.

Table 5 Cut-off values of age-LDH-CD4 model and single index (age, LDH, or CD4)

	Cut-off	Se (%)	Sp (%)	PPV (%)	NPV (%)	+LR	-LR
Age-LDH-CD4 Model	82	81	93	49	98	10.87	0.21
CD4 (cell/ul)	295	77	81	25	98	3.86	0.29
Age (years)	60	81	72	20	98	2.88	0.27
LDH (U/L)	300	81	83	29	98	4.69	0.23

Age-LDH-CD4 Model = (age × LDH)/ CD4 count; LDH, lactate dehydrogenase; Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; +LR, positive likelihood ratio; -LR, negative likelihood ratio.

Figures

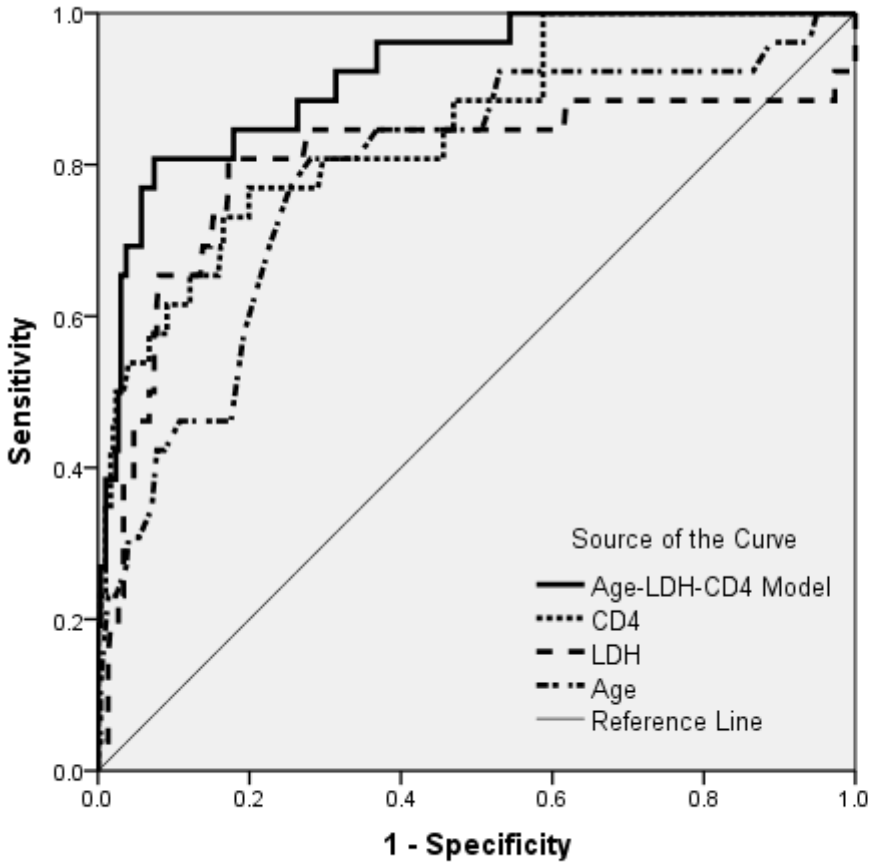

Figure 1

ROC curves of age-LDH-CD4 model and single index (age, LDH, or CD4) Based on the fact that only the patients developed to severe cases during hospitalization after admission could be counted for prediction. Therefore, ROC curve analysis was only performed in 15 patients who developed to severe cases after admission. The AUROC of age-LDH-CD4 model was significantly higher than that of CD4 count, LDH, and age.