

Predictive Value of Lactate Dehydrogenase to Albumin Ratio (LAR) in Patients With Coronavirus Disease 2019 (COVID-19)

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Research Article

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Abstract

Background

Coronavirus Disease-2019 (COVID-19) is an emerging acute infectious disease that was first discovered in Wuhan, Hubei Province, China. Since then, it has quickly spread to over one hundred cities around the world. Therefore, it is crucial to identify the risk factors of in-hospital mortality and disease severity for COVID-19 patients.

Methods

We firstly proposed a biomarker ratio, lactate dehydrogenase(LDH) to albumin ratio (LAR) may be more reliable to assess the predictive value of LAR for in-hospital mortality and early identification of critical COVID-19 patients. A retrospective study was conducted including patients (≥ 18 years old) with laboratory-confirmed COVID-19 infection who had been discharged or had died from 1 February to 29 February, 2020.

Results

The study included 321 patients with COVID-19. The median age of the 321 patients was 63.0 (IQR 51.0-70.0), ranging from 19 to 95 years old and 180 (56.1%) patients were male. 142 (44.2%) patients had 1 or more coexisting comorbidity. The most common symptoms on admission were fever(289[90%]) and cough(258[80.4%]). In multivariable logistic regression, only older age (OR, 1.11; 95% CI, 1.05-1.16), WBC count (OR, 1.26; 95% CI, 1.11-1.44), lymphocyte count (OR, 0.78; 95% CI, 0.62-0.99) and LAR (OR, 1.29; 95% CI, 1.18-1.40) were found to be significantly associated with in-hospital death. ROC analysis showed that LAR had a higher AUC (0.917) and the highest specificity(84.0%) and sensitivity(84.6%). Furthermore, the results showed that LAR had a higher AUC (0.931) to differentiate critical from mild patients and had a sensitivity of 87.7% and a specificity of 82.1%. Besides, LAR had an AUC (0.861) to differentiate critical from severe patients and had a sensitivity of 86.0% and a specificity of 73.8% and the role of LAR to distinguish severe from mild patients was the worst.

Conclusions

To the best of our knowledge, this study is the first for us to explore the predictive value of LAR for in-hospital mortality and disease severity. A high LAR appears to predict higher odds of mortality and differentiate critical patients from mild or severe COVID-19 patients.

Background

Coronavirus Disease-2019 (COVID-19) is an emerging acute infectious disease that was first discovered in Wuhan, Hubei Province, China. Since then, it has quickly spread to over one hundred cities around the world. By December 1, 2020, more than 60 million people were infected with COVID-19, including more than 1.53 million deaths. The virus is considered to be transmitted human-to-human by close contact and

respiratory droplets, and people of all ages are susceptible to this virus(1, 2). The clinical characteristics of COVID-19 patients have been shown in recent studies(1, 2). The main common clinical symptoms at the onset of the patients were dry-cough, fever, fatigue or myalgia. However, COVID-19 is capable of causing a series of illness ranging from asymptomatic infection to organ dysfunction such as acute respiratory distress syndrome (ARDS), acute liver injury, acute cardiac injury, acute kidney injury requiring intensive care unit (ICU) admission and even death also occur in the severe cases. However effective drugs are lacking and management remains mainly supportive. The majority of these mildly infected individuals had a good prognosis(1, 3), while it was reported that the in-hospital mortality was very high among severe and critical patients(4). According to published data focus on COVID-19, the overall mortality rate was between 2.3% and 28.3%(5, 6). Meanwhile, the mortality rate was up to 49% among critical individuals(6). Therefore, it is crucial to identify the risk factors of in-hospital mortality and disease severity for COVID-19 patients.

Several studies indicated that older patients with comorbidities, many laboratory biomarkers (such as peripheral blood inflammatory cells, cardiac troponin I, D-dimer, cytokines) and biomarker ratio (such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), IL-2R/lymphocytes and lymphocyte-to-C-reactive protein ratio (LCR)) were related with clinical progression and mortality of COVID-19(7–11). Meanwhile, several studies have shown that increased lactate dehydrogenase and reduced serum albumin levels were risk factors associated with severity and in-hospital death(12–14), but the predictive role is still controversial among different studies. Based on the above, we proposed a biomarker ratio, lactate dehydrogenase to albumin ratio (LAR), may be more reliable than the predictive effect of either lactate dehydrogenase or albumin. Therefore, the purpose of our study was initiated to assess the predictive value of LAR for in-hospital mortality and early identification of critical COVID-19 patients.

Methods

Study design and patients

This was a retrospective study of all patients who were diagnosed with a laboratory-confirmed COVID-19 infection from 1 February to 29 February, 2020 in the Tongji hospital affiliated to Huazhong University of Science and Technology. Patients were tracked until discharge from the hospital or death. We treated this cohort of patients with the latest version of the guidelines of Diagnosis and Treatment of Pneumonitis caused by the novel coronavirus. COVID-19 infection was confirmed by real-time RT-PCR testing of throat-swab specimens or respiratory specimens. Laboratory investigations and chest computed tomography scans were also done for all inpatients. The treating physicians determined the frequency of related examinations. The medical interventions included antiviral therapy, antibiotics, corticosteroid therapy, oxygen support, renal replacement therapy and other corresponding treatment. Patients younger than 18 years were excluded. This study was approved by the Ethics Commission of 1st hospital affiliated to Jilin University (No. 2020–405). Given the particularity of patients with COVID-19, the requirement for informed consent was waived.

Data collection

Data on the following parameters were collected from the medical records: demographic data: age, gender, underlying comorbid conditions (chronic heart disease, chronic lung disease, chronic kidney disease, chronic liver disease, hypertension, diabetes mellitus, and carcinoma), clinical symptoms at the onset of illness (fever, cough, sputum production, chest pain, myalgia or arthralgia, fatigue and confusion), laboratory results and outcomes (discharge or death). All COVID-19 patients were evaluated of different illness severity after admission, according to the guidelines of diagnosis and treatment for COVID-19 (Trial 6th edition) set by the National Health Commission of China. The COVID-19 is clinically classified as mild, severe and critically ill patients: mild patients had a fever, respiratory symptoms and radiological imaging showed pneumonia; severe patients were defined if any of the following items was met: (1) shortness of breath with respiration rate ≥ 30 times per minute, (2) blood oxygen saturation $\leq 93\%$ at resting time, (3) $\text{PaO}_2/\text{FiO}_2 \leq 300$ mmHg; critically ill patients were defined as those who required mechanical ventilation, shock and/or concomitant organ failure needing intensive care unit treatment. The discharge criteria included the following aspects: (1) normal temperature for more than 3 days; (2) significant subjective improvement in respiratory symptoms; (3) significant improvement in acute exudative inflammation of lung; (4) negative nucleic acid test at less twice (with the sampling interval ≥ 1 day). All the collected information was checked for missing or invalid data. Two researchers also independently reviewed the data collection forms to double check the data collected.

Statistical analysis

Continuous variables were expressed as mean \pm standard deviation (SD) or median and interquartile ranges (IQR) and categorical variables were presented as number (%). The chi-square (χ^2) test was used to compare categorical variables. For normally and abnormally distributed continuous data, the independent sample *t*-test and Mann-Whitney U test were used, respectively. Multivariable logistic regression models were used to explore the risk factors associated with in-hospital mortality. The area under the receiver operating characteristic (ROC) curve was used to analyze the ability of LAR for predicting in-hospital mortality and distinguishing severity of COVID-19. The area under the curve (AUC), sensitivity and specificity were recorded. The odds ratio (OR) and 95% confidence interval (CI) were obtained for each variable. The difference was considered statistically significant when $P < 0.05$. All statistical analysis were performed using SPSS19.0 software (SPSS Inc, Chicago, USA).

Results

The study population included 321 patients with COVID-19. The demographic, clinical characteristics and laboratory biomarkers are shown in Table 1. The median age of the 321 patients was 63.0 (51.0–70.0) years, ranging from 19 years to 95 years and 180 (56.1%) patients were male (Table 1). Of the 321 patients, 142 (44.2%) had 1 or more coexisting comorbidity (Table 1). Chronic heart disease (35[10.9%]), diabetes (14[10.1%]), chronic lung disease (14[4.4%]), hypertension (85[26.5%]), diabetes mellitus (58[18.1%]) were the most common coexisting comorbidity (Table 1). The most common symptoms on

admission were fever (289[90%]) and cough (258[80.4%]), followed by sputum production (117[36.4%]) and fatigue (114[35.5%]) (Table 1).

The results of demographic, clinical characteristics and laboratory biomarkers in survivor and non-survivor groups are compared in Table 1. In univariable analysis, age, male, coexisting comorbidity, fever, sputum production, shortness of breath, and confusion were significantly different between survivor and non-survivor group (Table 1). We observed that white blood cell count, neutrophil count, aspartate aminotransferase, total bilirubin, creatinine, and lactate dehydrogenase were significantly increased, while lymphocyte count and platelet count were significantly decreased in non-survivors compared with survivors. We then further calculated the ratio of lactate dehydrogenase to albumin and found that the value of LAR was remarkably increased in non-survivors (Table 1). For exploring the risk factors of in-hospital death, when all statistically significant variables were analyzed according to multivariable logistic regression, only older age (OR, 1.11; 95% CI, 1.05–1.16), WBC count (OR, 1.26; 95% CI, 1.11–1.44), lymphocyte count (OR, 0.78; 95% CI, 0.62–0.99) and LAR (OR, 1.29; 95% CI, 1.18–1.40) were found to be significantly associated with in-hospital death (Table 2).

Table 1

Demographic, clinical characteristics and laboratory biomarkers of patients with COVID-19 pneumonia on admission

Characteristics	Total (n = 321)	Survivors (n = 269)	Non-survivors (n = 52)	P value
Age(years)	63.0(51.0–70.0)	61.0(50.0-68.5)	69.0(63.25-79.0)	< 0.001
Sex, n (%)				< 0.001
Male	180(56.1)	138(51.3)	42(80.8)	
Female	141(43.9)	131(48.7)	10(19.2)	
Comorbidity, n (%)				< 0.001
Yes	142(44.2)	106(39.4)	36(69.2)	
No	179(55.8)	163(60.6)	16(30.8)	
Types of comorbidity, n (%)				
Chronic heart disease	35(10.9)	25(9.3)	10(19.2)	0.035
Chronic lung disease	14(4.4)	6(2.2)	8(15.4)	< 0.001
Chronic kidney disease	6(1.9)	2(0.7)	4(7.7)	0.001
Chronic liver disease	5(1.6)	5(1.9)	0	0.322
Hypertension	85(26.5)	70(26.0)	15(28.8)	0.673
Diabetes mellitus	58(18.1)	47(17.5)	11(21.2)	0.528
Carcinoma	6(1.9)	5(1.9)	1(1.9)	0.975
Clinical symptoms				
Fever(temperature \geq 37.3°C)	289(90.0)	237(88.1)	52(100)	0.009
Cough	258(80.4)	219(81.4)	39(75.0)	0.287
Sputum production	117(36.4)	105(39.0)	12(23.1)	0.029
Shortness of breath	91(28.3)	56(20.8)	35(67.3)	< 0.001
Chest pain	85(26.5)	71(26.4)	14(26.9)	0.937
Myalgia	84(26.2)	75(27.9)	9(26.2)	0.112

Data are presented as mean \pm SD, median (IQR) and n (%). P values were calculated by χ^2 test, independent sample t-test, or Mann-Whitney U test. Abbreviation: COVID-19 = coronavirus diseases 2019. ALT = alanine aminotransferase. AST = aspartate aminotransferase. LDH = lactate dehydrogenase. LAR = lactate dehydrogenase to albumin ratio.

Characteristics	Total (n = 321)	Survivors (n = 269)	Non-survivors (n = 52)	P value
Arthralgia	46(14.3)	43(16.0)	3(5.8)	0.054
Fatigue	114(35.5)	95(35.3)	19(36.5)	0.866
Confusion	11(3.4)	0	11(21.2)	< 0.001
Laboratory findings				
White blood cell count, 10 ⁹ /L	5.78(4.62–7.72)	5.5(4.4–7.2)	9.4(5.8–15.3)	< 0.001
Neutrophil count, 10 ⁹ /L	4.14(2.8–5.9)	3.8(2.6–5.4)	8.1(4.8–12.6)	< 0.001
Lymphocyte count, 10 ⁹ /L	1.08(0.7–1.5)	1.2(0.8–1.6)	0.6(0.5–0.8)	< 0.001
Haemoglobin, g/L	127.4 ± 17.5	127.9 ± 16.0	125.1 ± 24.1	0.435
Platelet count, 10 ⁹ /L	212.0(160.0-295.0)	223.0(172.0-308.0)	162.0(121.0-215.0)	< 0.001
ALT, U/L	24.0(16.0–37.0)	24.0(15.5–36.0)	27.0(19.0-46.8)	0.053
AST, U/L	28.0(19.5–42.5)	26.0(19.0-36.5)	44.5(31.0-69.3)	< 0.001
Total bilirubin, µmol/L	9.1(7.1–12.1)	8.6(6.8–11.7)	10.4(8.3–15.7)	< 0.001
Creatinine, µmol/L	70.0(58.0–86.0)	66.0(56.5–81.5)	92.5(71.8–149.0)	< 0.001
Albumin, g/L	35.0 ± 5.4	36.1 ± 4.8	29.2 ± 4.7	< 0.001
LDH, U/L	282.0(211–402.0)	255.0(204.5-340.5)	530.0(431.0-671.3)	< 0.001
LAR	7.9 (5.7–12.8)	7.1(5.4–10.0)	18.6(14.0-25.2)	< 0.001
Data are presented as mean ± SD, median (IQR) and n (%). P values were calculated by χ^2 test, independent sample t-test, or Mann-Whitney U test. Abbreviation: COVID-19 = coronavirus diseases 2019. ALT = alanine aminotransferase. AST = aspartate aminotransferase. LDH = lactate dehydrogenase. LAR = lactate dehydrogenase to albumin ratio.				

Table 2
Multivariable logistic regression analysis for risk factors associated with in-hospital death

Characteristics	Multivariable OR (95% CI)	P value
Age	1.11(1.05–1.16)	< 0.001
WBC count	1.26(1.11–1.44)	< 0.001
Lymphocyte count	0.78(0.62–0.99)	0.044
LAR	1.29(1.18–1.40)	< 0.001
Abbreviation: LAR = lactate dehydrogenase to albumin ratio.		

Then, all statistically significant variables were taken as candidates for ROC analysis and the optimal cut-off values calculated by the ROC analysis, and the areas under the curve(AUC) was presented in Fig. 1. ROC analysis showed that LAR had a higher AUC (0.917) than age (0.722), WBC count (0.779), lymphocyte count (0.188) to predict in-hospital death (Table 3). The optimal cut-off values were 12.3 for LAR and the highest specificity and sensitivity were 84.0% and 84.6%.

Table 3
Areas under the curve (AUC) of Age, WBC count, Lymphocyte count and LAR

Test Result Variable(s)	Area	Std. Error [†]	Asymptotic Sig. [‡]	Asymptotic 95% Confidence Interval	
Age	0.722	0.037	< 0.001	0.650	0.794
WBC count	0.779	0.039	< 0.001	0.703	0.855
Lymphocyte count*	0.812	0.034	< 0.001	0.879	0.956
LAR	0.917	0.020	< 0.001	0.879	0.956
The test result variables: Age, WBC count, Lymphocyte count, LAR has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased. [†] Under the nonparametric assumption. [‡] Null hypothesis: true area = 0.5. Lymphocyte count* means lymphocyte count after negative calculation. Abbreviation: LAR= lactate dehydrogenase to albumin ratio.					

Furthermore, to evaluate whether LAR plays a role in predicting disease severity, we also perform another ROC analysis. First, we divided the clinical classification of COVID-19 into three groups with different severity of illness : mild (n = 184), severe (n = 80) and critical (n = 57) patients. The results showed that LAR had a higher AUC (0.931) to differentiate critical from mild patients and had a sensitivity of 87.7% and a specificity of 82.1% (Fig. 2a). Besides, LAR had an AUC (0.861) to differentiate critical from severe patients and had a sensitivity of 86.0% and a specificity of 73.8%(Fig. 2b) and the role of LAR to distinguish severe from mild patients was the worst(Fig. 2c).

Discussion

This retrospective study included 321 COVID-19 patients and the total in-hospital mortality was 16.2%. And our study identified several risk factors for death in adults hospitalized with COVID-19 in Wuhan. In particular, older age, elevated WBC count, decreased lymphocyte count on admission were associated with higher odds of in-hospital death. Additionally, we found a new biomarker ratio, LAR was associated with higher odds of in-hospital death and critical illness.

In previous studies, older age has been identified as a significant independent predictor of in-hospital mortality in Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) (15–17). Similarly, several recent studies about COVID-19 also confirmed that COVID-19 was shown to tend to infect older age patients(13). Older age may be associated with coexisting comorbidities and thus increasing the in-hospital death rate. In the non-survivor group, most of the patients(69.2%) had one or more coexisting comorbidity. Our study showed that deceased patients had higher WBC count of $9.4(5.8–15.3) \times 10^9/L$ compared to $5.5(4.4–7.2) \times 10^9/L$ ($P < 0.001$) and had lower lymphocyte count level of $0.6(0.5–0.8) \times 10^9/L$ compared to those who survived ($1.2[0.8–1.6] \times 10^9/L$) ($P < 0.001$). Previous studies also showed similar results(18, 19). Our data indicated that the increase in white blood cell count is driven by elevated neutrophil count which may be related with concomitant infections. With the virus infection(such as SARS, MERS-CoV And COVID-19), it was suspected that lymphocytes are essential to eliminating virally infected cells that result in the apoptosis of lymphocytes, especially CD4 + T lymphocytes and CD8 + T lymphocytes(20).

According to researches, the pathogenic mechanism of COVID-19 might cause cytokine storm syndromes and pulmonary tissue damage by a strong immune response. LDH is a cytoplasmic glycolytic enzyme found in almost every tissue and serum LDH was associated with a systemic inflammatory response in many pulmonary diseases and cancer prognosis(21–23). Several recent studies indicated that high LDH level was risk factors for in-hospital mortality and was used as predictor of the disease severity in COVID-19 patients(5, 24, 25). The potential mechanism may be that the elevated LDH level was related with lung and tissue damage and systemic inflammatory response in severe COVID-19 patients(24). Previous studies indicated that low serum albumin has been also associated with adverse outcomes in COVID-19 patients(26, 27). Albumin is a water-soluble protein which is associated with nutritional status and systemic inflammatory response. However, the current study results about LDH and albumin were not consistent. LDH and albumin are both routinely tested laboratory markers in clinical practice, which makes them easily available. Just like the LCR is typically used as a prognostic marker for cancer, the LAR is first used as a potential prognostic marker for esophageal squamous cell carcinoma^[21]. To the best of our knowledge, we have firstly proposed LAR may be an effective predictor for in-hospital mortality and early identification of critical COVID-19 patients. LAR may serve to highlight a relatively elevated LDH or decreased albumin and have a better predictive effect. In our study, we found LAR (OR, 1.29; 95% CI, 1.18–1.40) was significantly associated with mortality in COVID patients and had a higher AUC (0.917) than age(0.722), WBC count(0.779), lymphocyte count(0.188) to predict in-hospital death. The optimal cut-off values were 12.3 for LAR and the highest specificity and sensitivity were 84.0% and

84.6%. In multivariable logistic regression, LDH and albumin were not independent risk factors for in-hospital mortality. Thus, LAR may be more sensitive and specific in reflecting systemic inflammation than LDH or albumin. Besides, the role of LAR showed higher sensitivity(87.7%) and specificity(82.1%) in differentiating critical patients from mild or severe patients and health-care workers could pay more attention to critical patients and improve survival rate.

Several notable limitations should be mentioned in this study. First, this study is a retrospective research and not all clinical characteristics and laboratory biomarkers have been obtained, such as cytokines and coagulation markers. Therefore, the role of LAR might be underestimated in predicting in-hospital death and disease severity. Second, laboratory biomarkers were measured on admission and continuous monitoring and comparison is limited. Finally, the validity of the predictive value of LAR derived from our cohort remains tentative and further validation from multicenter research is necessary.

Conclusions

To the best of our knowledge, this study is the first for us to explore the predictive value of LAR for in-hospital mortality and disease severity. A high LAR appears to predict higher odds of mortality and differentiate critical patients from mild or severe COVID-19 patients. However, further large-scale studies are needed to evaluate the benefits of LAR in COVID-19.

Abbreviations

COVID-19: Coronavirus Disease-2019

LDH: lactate dehydrogenase

LAR: lactate dehydrogenase to albumin ratio

ARDS: acute respiratory distress syndrome

ICU: intensive care unit

NLR: neutrophil-to-lymphocyte ratio

PLR: platelet-to-lymphocyte ratio

LCR: lymphocyte-to-C-reactive protein ratio

SD: standard deviation

IQR: median and interquartile ranges

ROC: receiver operating characteristic

AUC: area under the curve

OR: odds ratio OR

CI: confidence interval

MERS: Middle East respiratory syndrome

SARS: severe acute respiratory syndrome

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Commission of 1st hospital affiliated to Jilin University (No. 2020–405).

Consent for publication

Given the particularity of patients with COVID-19, the requirement for informed consent was waived.

Availability of data and materials

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

Competing interests

The authors declare no conflict of interest.

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Authors' contributions

Mingqing Liu, Luping Zhang and Hong Xu performed study design; Nan Zhang contributed to the acquisition of data; Yingli Zhang and Xiaoming Xu contributed to analysis and interpretation of data; Fengming Ni and Tantan Ma contributed to the literature search. Fengming Ni and Tantan Ma contributed

to statistical analysis; Mingqing Liu and Luping Zhang drafted and revised manuscript; Hong Xu and Nan Zhang contributed to critical review of the manuscript. All authors revised the manuscript and approved the final version.

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Figures

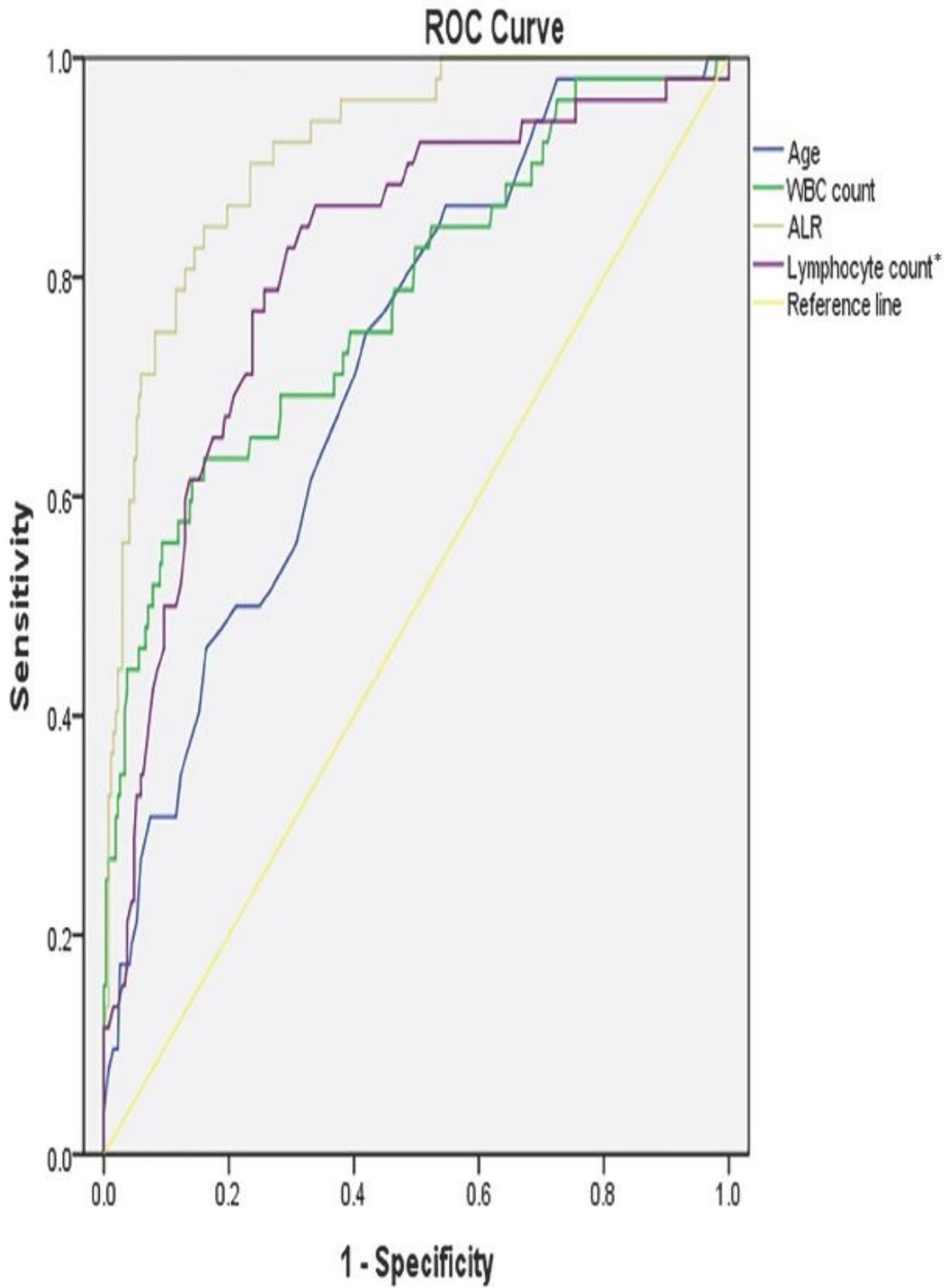


Figure 1

ROC curve was used to predict in-hospital death in patients with Coronavirus diseases 2019(COVID-19). Legend: Lymphocyte count* means lymphocyte count after negative calculation

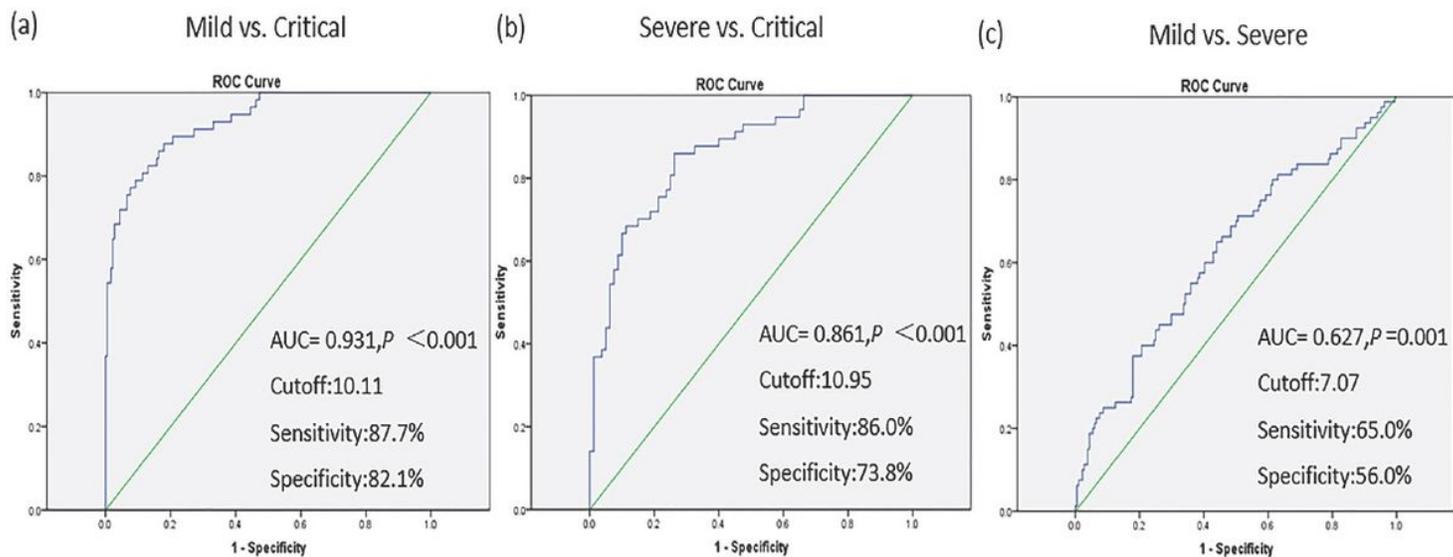


Figure 2

ROC analysis showing the performance of LAR among COVID-19 patients with different severity of illness. Legend: Abbreviation: ROC=Receiver operating characteristic. LAR= lactate dehydrogenase to albumin ratio. COVID-19= coronavirus diseases 2019.