The clinical implication of secondary pulmonary bacterial infection for the outcome of critically ill patients with Covid-19

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Abstract

Background Covid-19 is an emerging and evolving infectious and communicable diseases which gravely endanger the lives of critically ill patients with it. It is crucial to determine the clinical implication of secondary pulmonary bacterial infection for the outcome of critically ill patients with severe Covid-19.

Methods All critically ill patients with Covid-19(30 deceased and 35 discharged) between January 26, 2020 and March 15, 2020 in two ICUs of Jinyintan Hospital, Wuhan, China, were retrospectively reviewed, to investigate the clinical implication of secondary pulmonary bacterial infection in the prognosis of critically ill patients with severe Covid-19.

Results The fatality rate between patients with positive and negative sputum bacterial culture is 75.0%vs 33.3% (P = 0.003). The ROC analyses demonstrate that NLR[0.921(0.858–0.984)P<0.001], CRP[0.908(0.837–0.978)P<0.001],neutrophil[0.832(0.728–0.937)P<0.001],lymphocyte[0.858(0.755–0.960)P<0.001],leucocyte[0.753(0.626–0.879)P<0.001] and PCT [0.733(0.605–0.860)P = 0.001] have the discrimination power for the fatality. The Kaplan-Meier analyses show that the patients with negative sputum bacterial culture(P<0.001) have higher cumulative overall survival rates, in comparison with the opposite. The positive sputum bacterial culture is positively correlated with leukocyte(r = 0.706), CRP(r = 0.733), NLR(r = 0.554) and PCT(r = 0.549)(all P<0.001). A multivariate Cox regression analysis shows that sputum bacterial culture[15.36(4.291–54.980) P<0.001], CRP[2.022(2.013–2.030) P<0.001] and NLR[2.012(2.000-2.024) P = 0.045] are positively correlated with the fatality of the patients.

Conclusions The critically ill patients with severe Covid-19 who are complicated with secondary pulmonary bacterial infection may have an unfavorable outcome, in comparison with those who are not. Secondary pulmonary bacterial infection is an independent factor for the fatality of critically patients with Covid-19.

Introduction

Since December 2019, an unexpectedly emerging novel coronavirus that was denominated as SARS-CoV-2, has resulted in a pandemic of respiratory morbidity which was designated as Covid-19. The emerging and evolving Covid-19 has aroused global concern. It leads to a series of clinical manifestations from mild respiratory tract infection to severe pneumonia, multiple organ failure, and death. For critically ill patients with Covid-19, an admission into intensive care units (ICUs) is frequently indicated.[1–5] It has been reported that Covid-19 patients complicated with a secondary bacterial pneumonia are more severe.[6] Since Covid-19 is an infectious disease that gravely endanger the lives of critically ill patients, thereby it is extremely vital to determine the clinical implication of secondary pulmonary bacterial infection in critically ill ones with severe Covid-19, for the sake of prognostic assessment and therapeutic guidance.

Methods

Study design

All critically ill patients with Covid-19 died or being discharged between January 26, 2020 and March 15, 2020 in two ICUs of Wuhan Jinyintan Hospital were retrospectively reviewed, to explore the clinical roles of secondary pulmonary bacterial infection in critically ill patients with severe Covid-19. All included patients were 18 years of age or older. All the included patients were diagnosed with Covid-19,pneumonia and acute respiratory distress syndrome(ARDS), with or without septic shock, or multiple organ failure and the like, all of which were indicated for ICU admission. Due to the emerging and evolving nature of the Covid-19, no exclusion criteria was adopted in the patients' selection.

The diagnosis of Covid-19 was defined as a positive result on a reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay of a specimen collected with a nasopharyngeal and/or oropharyngeal swabs. ARDS was defined as an acute-onset hypoxemia which meant that the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (Pao2:Fio2) was less than 300 with bilateral pulmonary opacities on chest imaging that could not be explained by congestive heart failure or other forms of volume overload.[7] The criteria for discharge comprised the negative RT-PCR assay of SARS-CoV-2 twice, stable vital signs, improved pneumonia, and the absence of any organ failure or dysfunction.

The Demographics, clinical characteristics, clinical variables and therapeutic regimen of all the patients being studied were retrieved from the electronic medical record system of Wuhan Jinyintan Hospital and analyzed subsequently. Data were extracted by members of the research group and were reviewed by two independent investigators. The study protocol was reviewed and approved by the ethics committee of Wuhan Jinyintan Hospital. The informed consent from all patients being studied was waived by the ethics committee of Wuhan Jinyintan Hospital. The authors vouch for the accuracy and completeness of the data and analyses. No one who is not an author contributed to the writing of the manuscript.

Statistical analyses

Measurement data were presented as mean ± standard deviation or median with interquartile range according to whether or not they mainly conformed to normal distribution. Categorical data were presented as frequencies and percentages. Between-groups comparison was performed by using Student's t test. A trend line consisted of the first value after the admission into ICUs, the median value during the hospitalization, and the last one before the discharge or death was delineated for all the infectious hallmarks including leukocyte, neutrophil, lymphocyte, neutrophil to lymphocyte ratio (NLR), C-reactive protein (CRP), procalcitonin(PCT), interleukin-6(IL-6), and erythrocyte sedimentation rate (ESR), for both deceased and discharged patients, to explore the underlying discrepancy. A ROC curve analysis was performed to compare the discrimination power among all the infectious variables for the prediction of fatality. A Kaplan-Meier analysis was performed to compare the cumulative overall survival rates between the patients with the values below and above the cutoff of all infectious variables, and that between patients with positive and negative sputum bacterial culture. A Pearson correlation analysis was performed to reveal the correlation between sputum culture and serum infectious hallmarks. A univariate and a multivariate Cox regression analysis were performed to determine the correlation between all

variables and fatality. A P-value being less than 0.05 was defined as statistical significance. The statistics was performed by using SPSS 26.

Results

Demographics and characteristics of patients being studied

A total of 65 patients with critically severe Covid-19(30 deceased and 35 discharged) were finally collected. The overall fatality rate was 46.2%. The median age and female proportion were 61 (50–70) vs58 (46–68) and 12(40.0%) vs 9(25.7%) between the deceased and discharged patients. There was no pregnant woman in the patients being studied. The detailed demographics and clinical characteristics are summarized in Table 1.

Table 1
Demographics and clinical characteristics of the patients studied

	Deceased(n = 30)	Discharged(n = 35)	P value
Age, median (IQR) — yr	61(50–70)	58(46–68)	
Female-no. (%)	12(40.0)	9(25.7)	
Smoking history-no. (%)	15(50.0)	13(37.1)	
Comorbidities-no. (%)	4(13.3)	3(8.6)	
COPD	12(40.0)	4(11.4)	
Cardio vascular diseases	17(56.7)	5(14.3)	
Diabetes	4(13.3)	3(8.6)	
Cancer	5(16.7)	0(0)	
Chronic renal disease			
Fever-no. (%)	25(83.3)	21(60.0)	
RR > 24/min-no. (%)	30(100))	30(100)	
SBP < 90 mm Hg-no. (%)	16(53.3)	1(2.9)	
Median PaO2/FiO2(IQR)	125(85–173)	262(228–305)	
Median APACHE II(IQR)	27(17–35)	20(15–27)	
Complication	15(50.0)	1(2.9)	
Septic shock-no. (%)	8(26.7)	1(2.9)	
ARF-no. (%)	3(10.0)	0(0)	
DIC-no. (%)	21(70.0)	2(5.7)	
MOFS-no. (%)			
Leukocyte-×10^9 /L(IQR)	6.7(5.0-9.2)	6.7(4.7–9.5)	0.974
Leukocyte 1.	12.7(10.5–15.1)	7.6(5.8–10.4)	0.027
	16.1(11.8–22.6)	6.9(5.6–7.9)	<0.001
	7.5(2.9–9.9)	5.3(3.0-8.4)	0.005
	12.5(9.9–15.4)	5.4(3.6–7.5)	<0.001
	15.1(9.6–21.9)	4.4(3.3–5.5)	<0.001
	0.64(0.45–0.89)	0.94(0.71–1.15)	0.008
	0.52(0.34–0.83)	1.34(0.97–1.65)	0.001

Note: IQR: interquartile range; yr: years; no.: number; COPD: chronic obstructive pulmonary disease; RR: respiratory rate; min: minute; SBP: systolic blood pressure; mmHg: millimeter of mercury; PaO2: partial pressure of alveolar oxygen; FiO2: fraction of inspired oxygen; APACHE II: acute physiological and chronic health II score; ARDS: acute respiratory distress syndrome; ARF: acute renal failure; DIC: disseminated intravascular coagulation; MOFS: multiple organ failure syndrome; L: liter; NLR: neutrophil to lymphocyte ratio; CRP: C-reactive protein; mg: milligram; PCT: procalcitonin; ng: namogram; ml: milliliter;IL-6: interleukin-6; pg: picogram; ESR: erythrocyte sedimentation rate; mm: millimeter; h: hour; MV: mechanical ventilation; CRRT: continuous renal replacement therapy; ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit; P: positive; N:negative; KP: Klebsiella pneumonia; AB: Acinetobacter baumannii; MRSA: methicillin-resistant staphylococcus aureus; PA: Pseudomonas aeruginosa

Deceased(n = 30)	Discharged(n = 35)	P value
	0.54(0.28–0.91)	1.55(1.25–1.83) 0.001
Leukocyte 2.	12.1(5.9–17.7)	6.4(3.0-10.8) 0.150
Leukocyte 3.	24.3(16.9–32.2)	5.1(2.6–11.2) 0.001
Neutrophil-×109 /L(IQR)	25.5(13.1–34.9)	2.4(2.1–3.3) 0.001
Neutrophil 1.	100.0(34.5–160.0)	43.1(5.4-139.8) 0.046
Neutrophil 2.	84.4(60.7-105.8)	13.8(3.1–35.2) 0.001
Neutrophil 3.	104.6(59.4–160.0)	3.2(1.6–19.5) 0.001
Lymphocyte-$\times 10^9$/L(IQR)	0.1(0.05–0.28)	0.05(0.05–0.14) 0.023
Lymphocyte 1.	0.31(0.07–0.98)	0.05(0.05–0.12) 0.004
Lymphocyte 2.	0.44(0.08–3.10)	0.05(0.05–0.05) 0.001
Lymphocyte 3.	10.1(7.4–15.1)	11.0(7.4–17.1) 0.430
NLR(IQR)	10.5(7.1–17.2)	9.7(9.2–11.9) 0.230
NLR 1.	15.7(7.6–20.8)	8.6(6.8–11.3) 0.002
NLR 2.	48.8(25.5–71.5)	35.0(14.0-59.2) 0.008
NLR 3.	46.2(25.5–71.5)	40.5(15.0-59.7) 0.020
CRP-(mg/L) (IQR)	46.2(16.5–68.5)	35.0(10.0–57.0) 0.072
CRP 1.	30(100)	35(100)
CRP 2.	30(100)	35(100)
CRP 3.	8(26.7)	5(14.3)
PCT-(ng/ml) (IQR)	30(100)	35(100)
PCT 1.	14(46.7)	1(2.9)
PCT 2.	30(100)	35(100)
PCT 3.	8(26.7)	2(5.7)
IL-6-(pg/ml) (IQR)	4(13.3)	0(0)
	1(3.3)	0(0)

Note: IQR: interquartile range; yr: years; no.: number; COPD: chronic obstructive pulmonary disease; RR: respiratory rate; min: minute; SBP: systolic blood pressure; mmHg: millimeter of mercury; PaO2: partial pressure of alveolar oxygen; FiO2: fraction of inspired oxygen; APACHE II: acute physiological and chronic health II score; ARDS: acute respiratory distress syndrome; ARF: acute renal failure; DIC: disseminated intravascular coagulation; MOFS: multiple organ failure syndrome; L: liter; NLR: neutrophil to lymphocyte ratio; CRP: C-reactive protein; mg: milligram; PCT: procalcitonin; ng: namogram; ml: milliliter;IL-6: interleukin-6; pg: picogram; ESR: erythrocyte sedimentation rate; mm: millimeter; h: hour; MV: mechanical ventilation; CRRT: continuous renal replacement therapy; ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit; P: positive; N:negative; KP: Klebsiella pneumonia; AB: Acinetobacter baumannii; MRSA: methicillin-resistant staphylococcus aureus; PA: Pseudomonas aeruginosa

Deceased(n = 30)	Discharged(n = 35)	P value
IL-6 1.		
IL-6 2.		
IL-6 3.		
ESR-(mm/h) (IQR)		
ESR 1.		
ESR 2.		
ESR 3.		
Treatments		
Antiviral -no. (%)		
Antibiotics-no. (%)		
Antifungal-no. (%)		
Glucocorticoids-no. (%)		
MV -no. (%)		
Invasive		
Noninvasive		
Vasopressors -no. (%)		
CRRT -no. (%)		
ECMO -no. (%)		
From onset to ICU-days	5(3–8)	7(4–9)
ICU stay(IQR)-days	14(10–20)	25(16–32)

Note: IQR: interquartile range; yr: years; no.: number; COPD: chronic obstructive pulmonary disease; RR: respiratory rate; min: minute; SBP: systolic blood pressure; mmHg: millimeter of mercury; PaO2: partial pressure of alveolar oxygen; FiO2: fraction of inspired oxygen; APACHE II: acute physiological and chronic health II score; ARDS: acute respiratory distress syndrome; ARF: acute renal failure; DIC: disseminated intravascular coagulation; MOFS: multiple organ failure syndrome; L: liter; NLR: neutrophil to lymphocyte ratio; CRP: C-reactive protein; mg: milligram; PCT: procalcitonin; ng: namogram; ml: milliliter;IL-6: interleukin-6; pg: picogram; ESR: erythrocyte sedimentation rate; mm: millimeter; h: hour; MV: mechanical ventilation; CRRT: continuous renal replacement therapy; ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit; P: positive; N:negative; KP: Klebsiella pneumonia; AB: Acinetobacter baumannii; MRSA: methicillin-resistant staphylococcus aureus; PA: Pseudomonas aeruginosa

Deceased(n = 30)	Discharged(n = 35)	P value
Sputum culture-(P/N)	15/15	5/30 0.003
KP-no. (%)	7(46.7)	2(10.0)
AB-no. (%)	4(26.7)	1(5.7)
MRSA-no. (%)	2(13.3)	1(5.7)
PA-no. (%)	2(13.3)	1(2.9)
Blood culture-(P/N)	2/28	0/35
KP-no. (%)	1(3.3)	
MRSA-no. (%)	1 (3.3)	

Note: IQR: interquartile range; yr: years; no.: number; COPD: chronic obstructive pulmonary disease; RR: respiratory rate; min: minute; SBP: systolic blood pressure; mmHg: millimeter of mercury; PaO2: partial pressure of alveolar oxygen; FiO2: fraction of inspired oxygen; APACHE II: acute physiological and chronic health II score; ARDS: acute respiratory distress syndrome; ARF: acute renal failure; DIC: disseminated intravascular coagulation; MOFS: multiple organ failure syndrome; L: liter; NLR: neutrophil to lymphocyte ratio; CRP: C-reactive protein; mg: milligram; PCT: procalcitonin; ng: namogram; ml: milliliter;IL-6: interleukin-6; pg: picogram; ESR: erythrocyte sedimentation rate; mm: millimeter; h: hour; MV: mechanical ventilation; CRRT: continuous renal replacement therapy; ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit; P: positive; N:negative; KP: Klebsiella pneumonia; AB: Acinetobacter baumannii; MRSA: methicillin-resistant staphylococcus aureus; PA: Pseudomonas aeruginosa

Table 2
The Cox regression analyses of correlation between all variable and fatality in critically ill patients with Covid-19

Variables	Univariate	Multivariate
	HR(95%CI) P value	HR(95%CI) P value
Age(years)	1.055(1.018–1.151) P = 0.035	1.046(1.010–1.187)P = 0.577
Sex(male/female)	1.015(1.003–1.166)P = 0.177	
Leukocyte(× 10^9/L)	1.065(1.004–1.131) P = 0.036	1.073(1.005–1.144) P = 0.390
Neutrophil(× 10^9/L)	1.097(1.035–1.163) P = 0.002	1.088(1.043–1.199)P = 0.103
Lymphocyte(× 10^9/L)	0.427(0.203–0.898) P = 0.025	0.376(0.222–0.877)P = 0.775
NLR(× 10^9/L)	2.009(2.000-2.017) P = 0.041	2.012(2.000-2.024) P = 0.045
CRP(mg/L)	2.022(2.013–2.030) P□0.001	2.022(2.007–2.027) P = 0.001
PCT(ng/ml)	1.022(1.006–1.182) P = 0.499	
IL6(pg/ml)	1.143(1.110–1.253) P = 0.408	
ESR(mm/h)	1.115(1.041–1.331) P = 0.266	
Sputum culture(P/N)	7.158(3.205–15.988) P□0.001	15.36(4.291–54.980) P□0.001
Note: HR: hazard ratio; CI: confidence interval; NLR: neutrophil to lymphocyte ratio; CRP: C-reactive protein; PCT: procalcitonin; IL-6: interleukin-6; ESR: erythrocyte sedimentation rate; P: positive; N: negative		
Legend:		

The most pervasively detected bacteria with clinical significance from lower respiratory tract was klebsiella pneumoniae, followed by acinetobacter baumannii, methicillin-resistant staphylococcus aureus (MRSA) and pseudomonas aeruginosa. The overall incidence of positive bacterial sputum culture was 30.8% (20/65). The discrepancy of positive incidence in sputum bacterial culture was 15/30(50.0%) vs 5/35(14.3%). (P = 0.003) between the deceased and discharged patients. The comparison of fatality rate between the patients with positive and negative sputum culture was 75.0%vs 33.3%. (P = 0.003) Accordingly, the incidence of septic shock was 15(50.0%) vs 1(2.9%) between the deceased and discharged patients (P□0.001). There were two deceased patients who had positive blood culture with clinical significance. One was klebsiella pneumoniae, the other was MRSA. The antiviral regimen including oral lopinavir-retonavir, oral arbidol, α-interferon aerosol inhalation as well as traditional Chinese patent medicine lianhuaqingwen capsule were administered to all patients being studied. The antibiotics (100%vs100%) and glucocorticoids (methylprednisolone) (100%vs100%) usage rate were equal between the deceased and discharged patients. The top three most frequently used antibiotics for the deceased patients are meropenem(93.3%), moxifloxacin (73.3%) and cefoperazone sulbactam(50%), whereas the

top three most frequently used antibiotics for the discharged patients were moxifloxacin (68.6%), cefoperazone sulbactam (51.4%) and meropenem (42.9%). The selection of the anti-infectious agents was determined by the patients' attending physicians on the basis of patients' pathogenic culture, infectious markers, and infectious symptoms.

The divergent trends of infectious hallmarks between the deceased and discharged patients

From Fig. 1, it can be observed that the level of leukocyte and neutrophil of the deceased patients elevates uphill mildly, whereas those of the discharged patients declines tenderly downhill. The level of lymphocyte of the deceased patients nearly holds down all the way, whereas that of the discharged patients elevates uphill. The NLR of the deceased patients escalates uphill dramatically in the earlier stage of the hospitalization, then slightly rises in the later one, whereas that of the discharged patients gently slashes down. The level of CRP in the deceased patients is significantly higher than that of the discharged ones at the beginning and upswings after a slight downtrend, whereas that of the discharged patients falls all the way down. The level of PCT of the deceased patients is as good as that of the discharged ones at the beginning, then skyrockets all the way till the death of the patients, whereas that of the discharged patients holds down all the way. The two trend lines of IL-6 crosses each other in the earlier stage of the hospitalization, then diverges at the later stage. The two lines of ESR are not apparently separating. The statistical significance in the divergent trends of variables in between-groups are in Table 1.

The comparison of the discrimination power for the prediction of fatality among all the infectious hallmarks

A ROC curve analysis presented that the area under the curve(AUC)of NLR, CRP, neutrophil, leucocyte and PCT were[0.921(0.858–0.984)P□0.001], [0.908(0.837–0.978)P□0.001], [0.832(0.728–0.937)P□0.001], [0.753(0.626–0.879)P□0.001], and [0.733(0.605–0.860)P = 0.001], respectively. The sensitivity and specificity were 0.967 and 0.743, 0.967 and 0.543, 0.933 and 0.514, 0.800 and 0.743, 0.767 and 0.629, of NLR, CRP, neutrophil, leucocyte and PCT for the prediction of fatality, respectively. The cutoff value of NLR, CRP, neutrophil, leucocyte, and PCT were 9.505×10^9/L, 15.65 mg/L, 5.555×10^9/L, 9.685×10^9/L, and 0.075 ng/ml, for the prediction of fatality, respectively. As a contrast, IL-6[0.563(0.414–0.713) P = 0.382] and ESR [0.612(0.475–0.749) P = 0.122] did not demonstrate certain power for the prediction of fatality. (Fig. 2.) With respect to the ROC curve of lymphocyte, it could not be merged into the overall ROC curve, since its role in the outcome of Covid-19 is opposite to other variables. On analysis, the AUC of lymphocyte for the prediction of fatality was [0.858(0.755–0.960)P□0.001], with the sensitivity and specificity of 0.886 and 0.733, respectively.

The comparison of cumulative survival rates between the patients with the values below and above the cutoff of all variables

A Kaplan-Meier curve demonstrated that the patients with the values below the cutoff of leukocyte (P = 0.001), neutrophil (P = 0.019), NLR(P□0.001), and CRP(P□0.001), those with the value above the cutoff of lymphocyte(P□0.001), and those with negative sputum bacterial culture(P□0.001) had higher cumulative overall survival rates, in comparison with the opposite.(Fig. 3.) As a contrast, the cumulative survival rates did not differ statistically between the patients with the values below and above the cutoff in IL-6(P = 0.495) and ESR (P = 0.264).

The correlation between sputum culture and serum infectious hallmarks

A Pearson correlation analysis presented that a positive sputum bacterial culture is positively correlated with a higher level of leukocyte(r = 0.706) (P□0.001), CRP(r = 0.733) (P□0.001), NLR(r = 0.554) (P□0.001) and PCT(r = 0.549)(P□0.001). (Fig. 4.) As a contrast, a positive sputum bacterial culture was not correlated with any of neutrophil, lymphocyte, IL-6, and ESR.

The correlation between all variables and fatality

The univarirate Cox regression analyses showed that age [1.055(1.018–1.151)P = 0.035],leukocyte[1.065(1.0041.131)P = 0.036],neutrophil[1.097(1.0351.163)P = 0.002],lymphocyte[0.427(0.2030.898)P = 0.025],NLR[2.009(2.000-2.017)P = 0.041], CRP[2.022(2.013–2.030) P□0.001] and sputum culture[7.158(3.205–15.988) P□0.001] were correlated with the fatality. A subsequent multivariate Cox regression analysis showed that sputum culture[15.36(4.291–54.980) P□0.001], NLR [2.012(2.000-2.024) P = 0.045] and CRP [2.022(2.013–2.030) P□0.001] remained to be correlated with fatality.

Discussion

In this retrospective study, it has been revealed that the fatality rate in critically ill Covid-19 patients with positive sputum bacterial culture was higher than that of the patients with negative results. The infectious hallmarks such as leukocyte, neutrophil, lymphocyte, NLR, CRP, and PCT were diverging evidently especially at the later stage of the hospitalization between the deceased and discharged patients. NLR, CRP, neutrophil, lymphocyte, leucocyte and PCT could be used to anticipate the fatality of critically ill patients with Covid-19. The patients with the values below the cutoff of leukocyte, neutrophil, NLR, and CRP, those with the value above the cutoff of lymphocyte, and those with negative sputum bacterial culture had higher cumulative overall survival rates, in comparison with the opposite. The positive sputum culture was positively correlated with infectious hallmarks including leukocyte, CRP, NLR and PCT. Sputum bacterial culture, CRP and NLR were independently correlated with the fatality of critically ill patients with Covid-19. The critically ill patients with severe Covid-19 who were complicated with secondary pulmonary bacterial infection may had an unfavorable outcome, in comparison with those who were not.

Being consistent with the statistical fatality rate among critically ill patients with Covid-19 being reported by Guan et al.[2] and Bhatraju et al,[8] the fatality rate of patients with critically severe Covid-19 in the ICUs of Wuhan Jinyintan Hospital is 46.2%. The reason for such high fatality consists in that this patient population represented the most severe cases at the early stage of the Covid-19 outbreak, ever since the blockade of Wuhan city. At that moment, Covid-19 was a newly emerging and contagiously uncharted disease, which had not been experienced before by any of the clinicians in Wuhan or those who reinforced Wuhan from all over the country, resulting in the unsatisfactory therapeutic response for critically ill patients. Besides, the unprepared medical resource was overwhelmed by the abrupt emergence of numerous patients with Covid-19 including a multitude of critically ill cases. In addition, there has been no efficacious iatreusis for Covid-19 to date, let alone at the incipient stage of the outbreak.

In the study of Dong, et al,[6] cases who were complicated with a secondary bacterial pneumonia were more severe in comparison with those without it, being consistent with our study, in which secondary pulmonary bacterial infection is an independent factor for the fatality of critically ill patients with Covid-19. The results of the current study are also consistent with those in the study of Guan et al,[2] Qin et al[9] and Li et al,[10] in which severe cases were prone to have lymphocytopenia and leukocytosis. Analogously, in the report of Qin et al,[9] and Liu et al,[11] an elevated NLR was frequently encountered in severe cases and was an independent risk factor for the in-hospital mortality of Covid-19 patients. The results of the present study are as well consistent with the study of Tan et al,[12] and Wang et al,[13] in which CRP was positively correlated with pulmonary lesion, disease development, and disease severity. To summarize, our study suggests that the Covid-19 patients with secondary bacterial infection and elevated infectious hallmarks such as leukocyte, NLR, CRP and PCT, have higher fatality rate by contrast with the opposite. Leukocytosis and elevated CRP as well as PCT have been already regarded as the hallmarks of bacterial infection,[14–16] being confirmed once again by the positive correlation between sputum bacterial culture and serum infectious hallmarks in our study. Taken together, it strongly suggests that the secondary pulmonary bacterial infection is an adverse factor for the outcome of critically ill patients with Covid-19.

Although glucocorticoids may induce leukocytosis[17] and secondary bacterial infection,[18] since its usage rate were equal between the deceased and discharged patients, plus the uprising CRP and PCT in the deceased patients, it still indicated that the deceased patients with Covid-19 were more apt to supervene secondary pulmonary bacterial infection with time, in comparison with the discharged patients, despite Covid-19 is a viral infection at the initial stage of disease. Eventually, the discrepancy of positive incidence in sputum bacterial culture between the deceased and discharged patients answer for the anomaly in the serum infectious hallmarks. In addition, in view of the antibiotics usage rate were also equal between the deceased and discharged patients, the occurrence of secondary bacterial infection was not interfered by the antibiotic therapy. It was reported that secondary bacterial infections could be predisposed for patients with influenza viral infections. The mechanisms of secondary bacterial infections include multiple processes mediated by interactions amongst viruses, bacteria, and the immune system of host. Antiviral immune responses induced by viruses are associated with dysbiosis in

the respiratory tract, which may subsequently compromise immunological function against secondary bacterial infection, or multiply the proliferation of underlying pathogenic bacterial loads.[19] Meanwhile, the induced inflammation by influenza virus can mutate genome-wide nasal gene responses to the carriage of pneumococcus, besides the promoted level of cytokines by the viral infection.[20] The current study verified that the analogue could likewise happen to the critically ill patients with Covid-19.

This study suffers from several limitations. First of all, it is a retrospective study due to the emergency nature of the Covid-19, resulting in unavoidable bias which may interfere with the results of study. Secondly, the sample size of this study is not considerable, since it was a single-centered study which only concerned the most critically ill patients with Covid-19. The last but not least, due to all patients we reviewed were unanimously critically ill ones, the conclusion may not be applicable to the patients with mild conditions.

In conclusion, we report through the present study that the critically ill patients with severe Covid-19 who are complicated with secondary pulmonary bacterial infection may have an unfavorable outcome, in comparison with those without it. Secondary pulmonary bacterial infection is an independent factor and a danger signal for the unfavorable outcome of critically ill patients with Covid-19. It may suggest that the implementation of potent antibiotic regimen could be of vital importance for the cure of critically ill Covid-19 patients with secondary pulmonary bacterial infection, despite Covid-19 is a disease caused by viral infection. Such findings may be helpfully informative for the prognostic assessment and therapeutic guidance in critically ill patients with severe Covid-19.

Abbreviations

ICU
intensive care unit
ARDS
acute respiratory distress syndrome
RT-PCR
reverse-transcriptase–polymerase-chain-reaction
NLR
neutrophil to lymphocyte ratio
CRP
C-reactive protein
PCT
procalcitonin
IL-6
interleukin-6
ESR
erythrocyte sedimentation rate
ROC

receiver operating characteristic
MRSA
methicillin-resistant staphylococcus aureus
AUC
area under the curve

Declarations

Ethics approval and consent to participate

The study protocol was reviewed and approved by the ethics committee of Wuhan Jinyintan Hospital. (Approval Number: KY-2020-06.01)

Consent for publication

Not applicable

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

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Author Contributions

WX, MX and YFZ have full access to all of the data in this study and take responsibility for the integrity of the data and the accuracy of the data analyses. All authors contributed substantially to the study design, data collection, data analysis and data interpretation, and the manuscript writing. All authors have read and approved the final version of the article before the submission.

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Figures

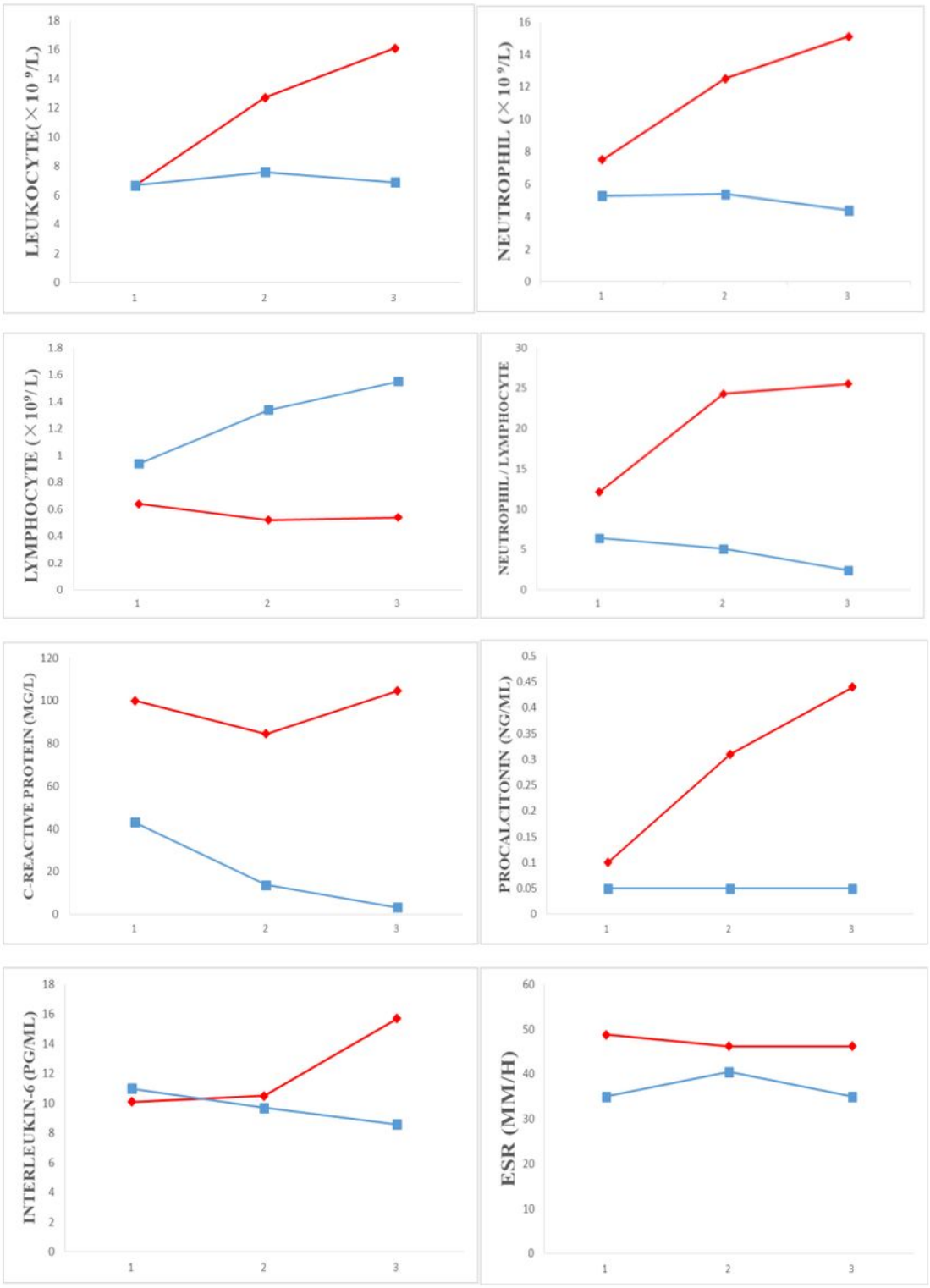
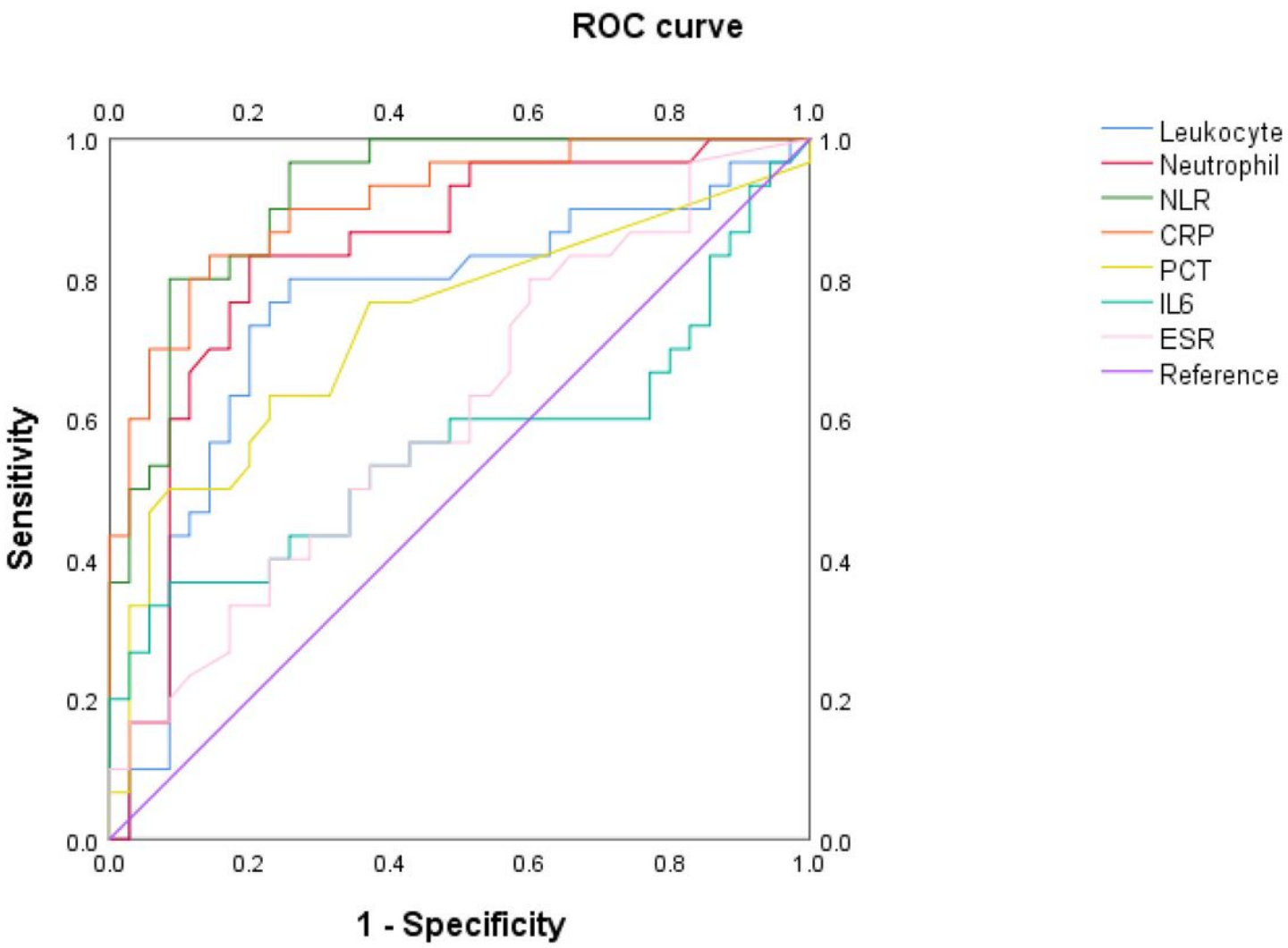


Figure 1

Divergent overall trend of infectious hallmarks between the deceased and discharged patients with critically ill Covid-19 Note: red line: the deceased patients; blue line: the discharged patients; 1: the first value after the admission into ICUs for each parameter; 2: the median value during the hospitalization for each parameter; 3: the last value before the discharge or death for each parameter; L: liter; mg: milligram; ng: nanogram; ml: milliliter; pg: picogram; mm: millimeter; h: hour



Variables	AUC(95% CI)	Sensitivity	Specificity	Cutoff value	P value
Leukocyte($\times 10^9$/L)	0.753(0.626-0.879)	0.800	0.743	9.685	＜0. 001
Neutrophil($\times 10^9$/L)	0.832(0.728-0.937)	0.933	0.514	5.555	＜0.001
NLR($\times 10^9$/L)	0.921(0.858-0.984)	0.967	0.743	9.505	＜0.001
CRP(mg/L)	0.908(0.837-0.978)	0.967	0.543	15.65	＜0.001
PCT(ng/ml)	0.733(0.605-0.860)	0.767	0.629	0.075	0.001
IL6(pg/ml)	0.563(0.414-0.713)	0.433	0.686	10.66	0.382
ESR(mm/h)	0.612(0.475-0.749)	0.800	0.400	24.50	0.122

Figure 2

The comparison of the discrimination power for the prediction of fatality among all the infectious hallmarks Note: ROC: receiver operating characteristic; AUC: area under the curve; NLR: neutrophil to lymphocyte ratio; CRP: C-reactive protein; PCT: procalcitonin; IL-6: interleukin-6; ESR: erythrocyte sedimentation rate

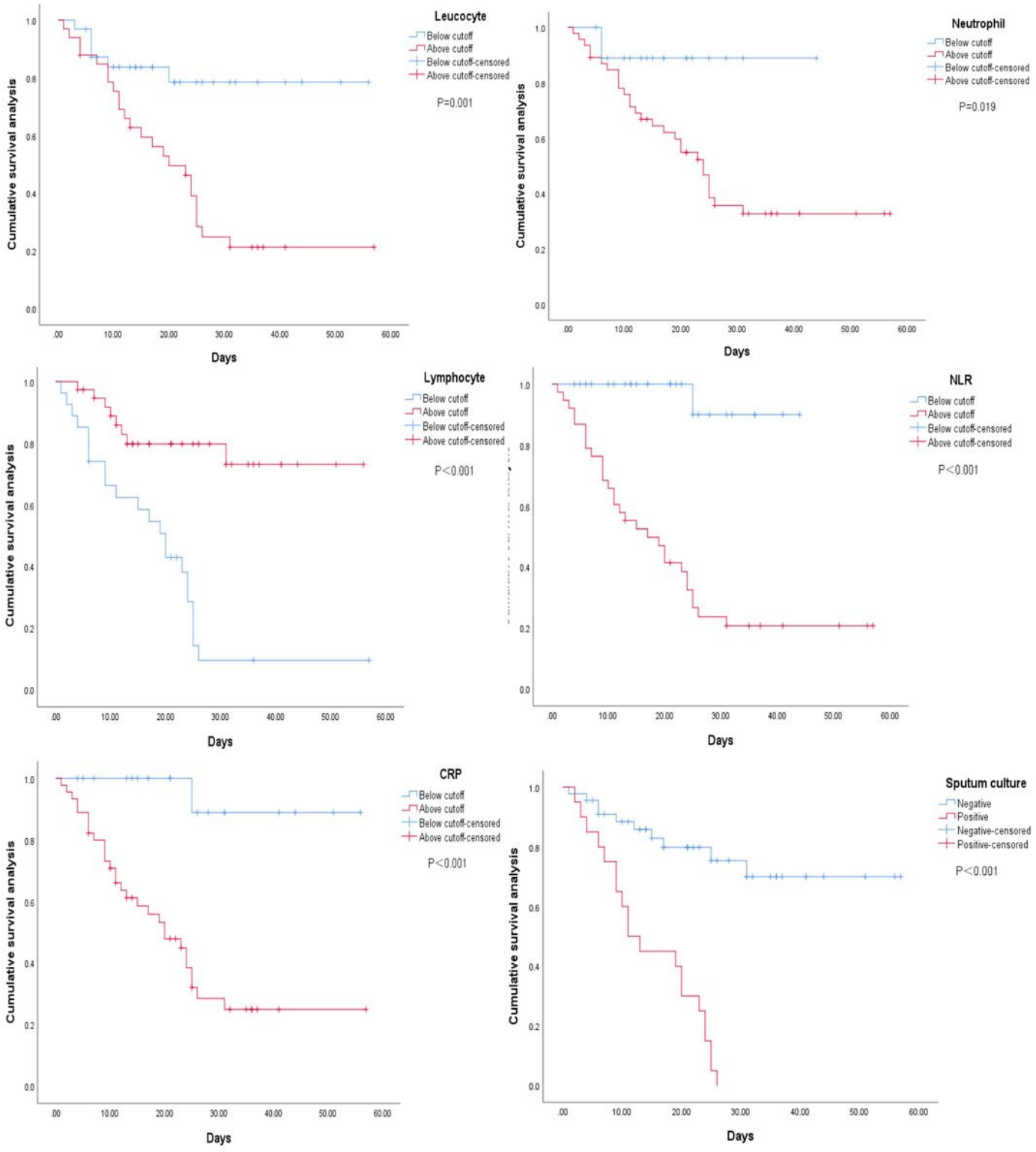


Figure 3

The comparison of cumulative survival rates between the patients with the values below and above the cutoff of all variables NOTE: NLR: neutrophil to lymphocyte ratio; CRP: C-reactive protein

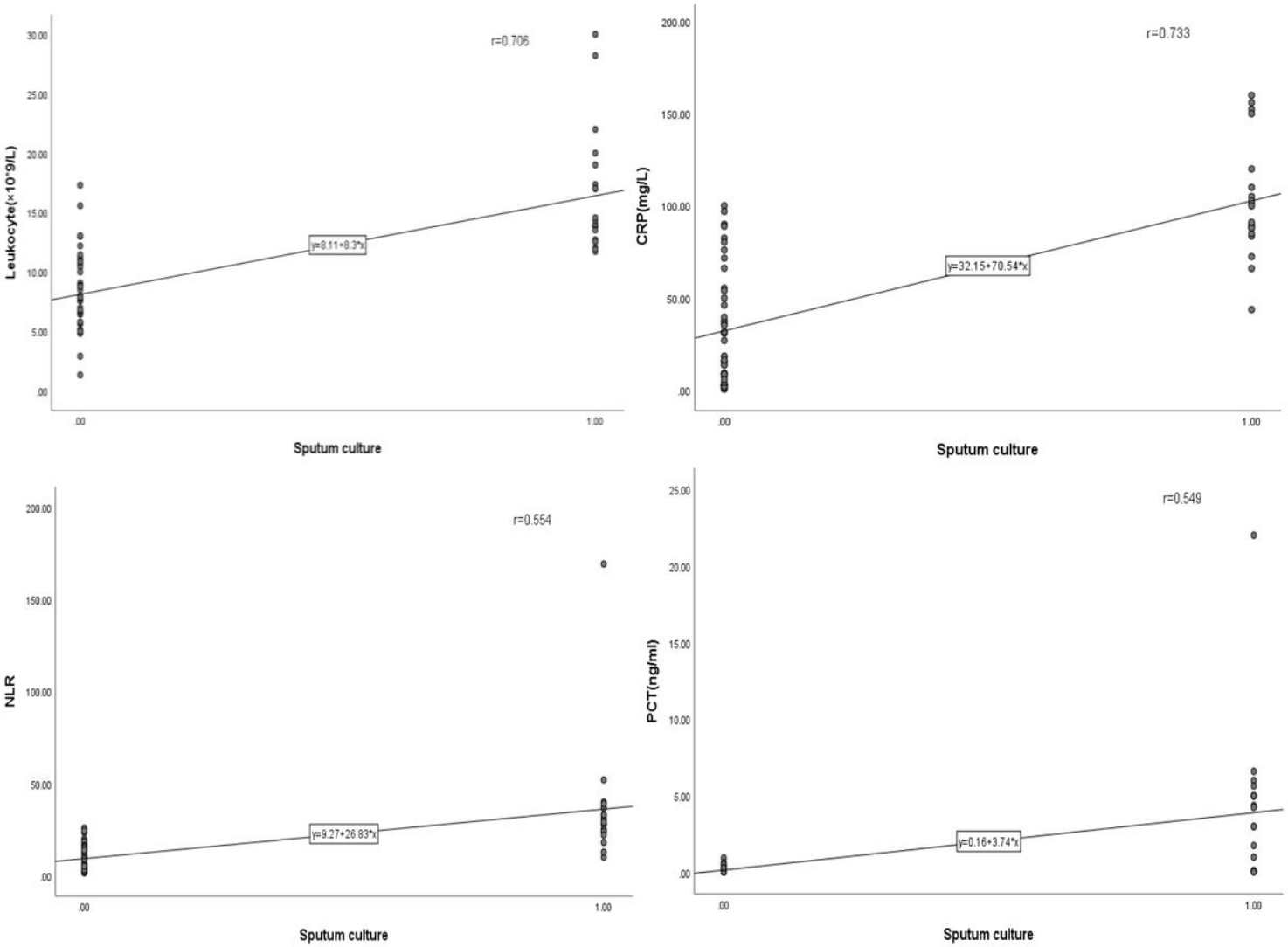


Figure 4

The correlation between sputum culture and serum infectious hallmarks Note: NLR: neutrophil to lymphocyte ratio; CRP: C-reactive protein; PCT: procalcitonin; Abscissa scale: 0: negative sputum culture; 1: positive sputum culture