

Risk factors of mortality for intensive care COVID-19 patients: A retrospective cohort study.

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Research Article

Keywords: COVID-19, interleukin-6, PaO₂/FiO₂, mortality, risk factor

Posted Date: October 9th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-90168/v1>

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Abstract

Aims: To identify the risk factors of mortality for coronavirus disease 19 (COVID-19) patients admitted to intensive care units (ICU), we conducted a retrospective analysis.

Methods: The demographic characteristics, laboratory findings and chest X-ray data of COVID-19 patients admitted to ICU of Huoshenshan Hospital from February 10 to April 10, 2020 were retrospectively analyzed. Student's t test and chi-square test were used to compare continuous variables, categorical variables respectively. Logistic regression model was used to seek risk factors of mortality.

Results: A total of 57 patients (38 males and 19 females) were included in this retrospective study, including 20 patients in deceased group and 37 patients in surviving group. Leukocyte count, neutrophil count, lymphocyte count, eosinophil count, neutrophil-to-lymphocyte ratio (NLR), urea nitrogen, lactate dehydrogenase (LDH), interleukin-6 (IL-6), C-reactive protein (CRP), arterial partial pressure of oxygen/oxygen concentration (PaO₂/FiO₂) and imaging findings were statistically different between the two groups. The multivariate logistic regression analysis identified IL-6 and PaO₂/FiO₂ as independent risk factors of mortality. The area of under curves (AUC) of IL-6 and PaO₂/FiO₂ were 0.9 (95%CI:0.823-0.977, p<0.0001) and 0.865 (95%CI:0.774-0.956, p<0.0001) respectively. The cut-off value of IL-6 was 25.69 pg/mL, the sensitivity was 95% and the specificity was 75.7%, while the cut-off value of PaO₂/FiO₂ was 167.79 mmHg, the sensitivity was 75.7% and the specificity was 85%.

Conclusion: Clinicians should pay enough attention to IL-6 and PaO₂/FiO₂, especially when IL-6>25.69 pg/ml and PaO₂/FiO₂<167.79 mmHg, and take active intervention measures as early as possible.

Introduction

Since the first case was diagnosed in Wuhan, China, COVID-19 which caused by severe acute respiratory syndrome coronavirus 2(SARS-Cov-2) has spread worldwide. Up to September 14, 2020, China has reported 85,202 infection cases and 4,634 deaths¹. Meanwhile, 28,918,900 cases of infection and 922,252 deaths have been reported globally².

The clinical manifestations of COVID-19 include asymptomatic infection, mild upper respiratory symptoms, and respiratory failure requiring advanced life support^{3,4}. The severity of COVID-19 was classified into mild, common, severe and critically ill according to the guidelines on the diagnosis and treatment of new coronavirus pneumonia published by the National Health Commission of China. A significant proportion of severe and critically ill patients required intensive care, and had high mortality rates. If patients with high risk of mortality can be identified early on ICU admission, it will help to focus treatment efforts on these patients and might reduce the mortality rate of COVID-19.

To identify the risk factors of mortality for COVID-19 patients in ICU, we retrospectively analyzed clinical data of 57 patients admitted to Huoshenshan Hospital in Wuhan, China. After analyzed by logistic regression model, we identified IL-6 and PaO₂/FiO₂ as independent risk factors.

Results

Demographic and Clinical data

From February 10 to April 10, 2020, 71 confirmed COVID-19 patients were admitted to the ICU, including 28 deaths and 43 survivors. As shown in **table 1**, after excluding patients with incomplete information, 20 cases (14 males, 6 females) in deceased group and 37 cases (24 males, 13 females) in surviving group were included. The mean time from illness onset to ICU admission was 29.07 days. No statistical difference was observed in age and sex between deceased group and surviving group. There was no statistically significant difference in underlying diseases, including hypertension, diabetes mellitus, coronary heart disease, cerebrovascular disease, COPD, and hepatic/renal insufficiency between the two groups (all $p > 0.05$). The most common symptom of COVID-19 patients was cough, followed by fever, dyspnea, chest tightness, fatigue, poor appetite, muscle soreness, which were all similar in the two groups (all $p > 0.05$). No statistically difference was observed in vital signs including body temperature, respiratory rate, heart rate, systolic blood pressure (SBP) and diastolic blood pressure (DBP) (all $p > 0.05$) at ICU admission.

Laboratory findings, chest X-ray severity and treatment strategies

As shown in **table 2**, deceased patients had higher leukocyte count ($p = 0.027$) and neutrophil count ($p = 0.014$), lower lymphocyte count ($p = 0.003$) and eosinophil count ($p = 0.001$) than those in surviving group. NLR was higher in deceased group (11.14 ± 5.1 vs 7.67 ± 4.85 , $p = 0.049$). Urea nitrogen was increased in deceased group compared to survivors (11.66 ± 9.54 vs 6.95 ± 4.11 , $p = 0.047$), indicating that patients in deceased group were more likely to be complicated with renal insufficiency. Moreover, LDH ($p = 0.001$), IL-6 ($p = 0.024$) and CRP ($p = 0.001$) level in deceased group were significantly higher than those in surviving group. There was no statistical difference in other indicators, including platelet, hemoglobin, albumin, globulin, white/globule ratio (A/G ratio), alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, serum electrolytes (sodium, potassium, chloride, calcium), cardiac index (myoglobin, hypersensitive troponin I, brain natriuretic peptide (BNP)), coagulation index (activated partial thromboplastin time (APTT), thrombin time, D-dimer), procalcitonin (PCT), etc. (all $p > 0.05$). Compared with surviving patients, oxygenation index (PaO₂/FiO₂) of deceased patients was much lower ($p < 0.0001$), whereas PaCO₂ level was not different ($p = 0.442$). In addition, chest X-ray severity was related to the prognosis of COVID-19 patients ($p = 0.01$). Among overall population, the proportion of patients receiving antiviral drugs, antibiotics and systemic corticosteroid was 21 (37%), 44 (77%), 22 (39%), respectively. Intravenous albumin use differed significantly between the two groups ($p = 0.002$). 3 patients received ECMO and 10 received CRRT, none of whom survived. Immunomodulatory drugs including

intravenous immunoglobulin and thymalfasin were used similarly. Moreover, some patients accepted tocilizumab, convalescent plasma, stem cell therapy.

Risk factors of mortality

From the clinical data and laboratory findings of these patients, we selected indicators with $p < 0.05$, including leukocyte count, neutrophil count, lymphocyte count, NLR, eosinophil count, urea nitrogen, LDH, IL-6, CRP, PaO₂/FiO₂, chest X-ray severity, and incorporated them into logistic regression model. As shown in **table 3**, the univariable logistic regression analysis showed that lymphocyte count, NLR, eosinophil count, LDH, IL-6, CRP, PaO₂/FiO₂ and chest X-ray severity were associated with death of COVID-19 patients. The above indicators were further incorporated into multivariable analysis. IL-6 (OR=1.013, 95%CI 1.001-1.025, $p = 0.028$) and PaO₂/FiO₂ (OR=0.955, 95%CI 0.915-0.996, $p=0.032$, respectively) were found to be independent risk factors of mortality for COVID-19 patients.

As shown in **figure 1**, The AUC of IL-6 and PaO₂/FiO₂ were 0.9 (95%CI:0.823-0.977, $p < 0.0001$) and 0.865 (95%CI:0.774-0.956, $p < 0.0001$) respectively. The cut-off value of IL-6 was 25.69 pg/mL, the sensitivity was 95% and the specificity was 75.7%, while the cut-off value of PaO₂/FiO₂ was 167.79 mmHg, the sensitivity was 75.7% and the specificity was 85%. Furthermore, we observed the variation trend of IL-6 in six patients (3 in deceased group and 3 in surviving group) who had tested plasma IL-6 for more than 5 times during hospitalization. The levels of IL-6 decreased gradually as the condition of patients improves in surviving group, while increasing when patients' condition deteriorated in deceased group (**Fig 2**).

Discussion

The SARS-CoV-2, known as the seventh human coronavirus, belonging to β coronavirus, is the pathogen of COVID-19. There are six coronaviruses infecting humans previously, including SARS-CoV-1 and middle east respiratory syndrome (MERS)-CoV in 2003 and 2012 respectively. But the global pandemic caused by SARS-CoV-2 is unprecedented. The mortality rates of SARS and MERS were more than 10% and 35% respectively^{5,6}, while it is approximately 3.12%-5.43% in hospitalized COVID-19 patients according to data from National Health Commission of the People's Republic of China and World Health Organization. Although the mortality rate of COVID-19 is lower than that of SARS and MERS, the overall number of deaths is higher due to the larger number of infections. Clinical data from Wuhan, China, indicate that approximately 17.7% to 32% of patients require ICU admission, and the mortality rate of critically ill patients is as high as 49% to 61.5%^{7,8}. Early identification of individuals at high risk of mortality might help reduce mortality of COVID-19.

Angiotensin-converting enzyme 2 (ACE2), expressed on pulmonary epithelial cells, vascular endothelial cells and macrophages, is the target receptor of SARS-COV-2⁹⁻¹¹. Decreased expression of ACE2 in the lungs may lead to acute lung injury^{12,13}. Cell apoptosis could induce local inflammatory response, which leads to the release of proinflammatory cytokines and chemokines into blood, including IL-1, IL-6, interferon Gamma (IFN- γ), Monocyte chemoattractant protein 1 (MCP1), IFN- γ -induced protein 10 (IP-10) and so on³. Under normal circumstances, this inflammatory response helps eliminating microorganism and facilitating patients recover. But excessive release of inflammatory cytokines, called cytokine release syndrome (CRS), can exacerbate inflammation response and damage lung tissues. Evidence shows that CRS plays an important role in the pathogenesis of COVID-19. Given the precise role of CRS in severe COVID-19, early recognition of this excessive inflammatory response and early intervention, such as glucocorticoids, immunoglobulin, and selective cytokine inhibitors, might help reducing severe COVID-19 mortality¹⁴. IL-6, one of the inflammatory cytokines significantly elevating in COVID-19 patients, is a key driver of the inflammatory process^{3,15}. Excessive IL-6 can lead to organ damage, such as increasing vascular permeability¹⁶ and decreasing myocardial contractility¹⁷, meanwhile serving as a biomarker for predicting disease severity¹⁸. A previous large retrospective cohort study showed that IL-6 was associated with death in COVID-19 patients¹⁹, which was consistent with our results.

IL-6 activates downstream JAK signaling pathway by binding to either trans-membrane (*cis*-signaling) or soluble (*trans*-signaling) IL-6R²⁰. Tocilizumab, a recombinant humanized monoclonal anti-IL-6R antibody, can bind to both trans-membrane and soluble IL-6R to inhibit IL-6-mediated *cis*- and *trans*-signaling²¹. Studies had shown the efficacy of tocilizumab against COVID-19^{22,23}. However, all of them are retrospective studies and the number of reported cases is small. Larger random control trials are needed in the future to confirm the therapeutic effect of tocilizumab on COVID-19.

As the most commonly used oxygenation index, PaO₂/FiO₂ is included in sepsis management guideline²⁴ and acute respiratory distress syndrome (ARDS)²⁵ although it may overestimate the incidence and underestimate the mortality of ARDS²⁶. In this study, oxygenation index PaO₂/FiO₂ was another independent predictor of COVID-19 death.

This study has several limitations. First, as a single-center retrospective study with relatively small sample size, the results needs to be validated by more studies. Second, because the imaging severity was not evaluated by computed tomography, the chest X-ray results might be inconsistent with real lung lesion. Third, not all laboratory tests were done in all patients, such as serum ferritin, T lymphocyte subpopulation.

In conclusion, IL-6 and PaO₂/FiO₂ are independent risk factors for predicting death in COVID-19 patients requiring intensive care, especially when IL-6 >25.69 pg/ml and PaO₂/FiO₂<167.79 mmHg. Clinicians should pay enough attention to these two indicators and take active intervention measures as early as possible in order to reduce mortality.

Methods

Study design and participants

After excluding patients with incomplete information, a total of 57 patients admitted to ICU in Huoshenshan Hospital from February 10 to April 10, 2020 were included in this single-center, retrospective study. All patients were confirmed SARS-CoV-2 infection by reverse transcription-polymerase chain reaction. Patients who admitted into ICU should satisfied any of the following criteria: 1. respiratory failure requiring mechanical ventilation; 2. unstable vital signs requiring electrocardiogram monitoring; 3. combining with other organ failure such as gastrointestinal bleeding, heart failure, renal failure, etc. This study was approved by the Ethics Committee of the Wuhan Huoshenshan Hospital and informed consents was obtained from all individual participants or their families included. All methods were performed in accordance with the relevant guidelines and regulations.

Data collection

All data were obtained from the electronic medical system and was independently collected by two researchers to check the accuracy of data. Detailed demographic information, underlying diseases, clinical symptoms, vital signs, laboratory findings, imaging severity and treatment strategies of all patients were recorded when they entered the ICU. Demographic information included age and sex. Underlying diseases included hypertension, diabetes mellitus, coronary heart disease, cerebrovascular disease (cerebral infarction / hemorrhage), chronic obstructive pulmonary disease (COPD) and hepatic/renal insufficiency, etc. Clinical symptoms included fever, cough, dyspnea, chest tightness, fatigue, poor appetite, and muscle soreness. Vital signs included body temperature, heart rate, respiratory rate, blood pressure, etc. Laboratory tests included blood routine, liver, kidney, heart, coagulation indexes, biological indicators related to inflammation or infection, oxygenation index (PaO₂/FiO₂), PaCO₂, etc. Some indicators had been tested several times during hospitalization but the most recent examination results were analyzed in this study. According to the lung lesion range, the chest X-ray finding were divided into mild, moderate, severe. Mild was defined as the lesion area involving 1-2 lung fields, moderate involving 3-4 lung fields and severe involving 5-6 lung fields. Therapeutic agents included antiviral drugs, antibiotics, corticosteroid, tocilizumab, convalescent plasma, immunoglobulin, albumin, thymalfasin. Life support treatments included high-flow nasal cannula oxygen therapy (HFNC), non-

invasive mechanical ventilation (NIV), invasive mechanical ventilation (IMV), extracorporeal membrane oxygenation (ECMO), continuous renal replacement therapy (CRRT).

Data analysis

Student's t test and chi-square test were used to compare continuous variables and categorical variables respectively. Continuous variables and categorical variables were expressed as mean \pm standard deviation (SD) and frequency respectively. The multivariate logistic regression model was used to identify independent risk factors of mortality. $P < 0.05$ [two-tailed] was considered statistically significant. All statistical analyses were performed using SPSS (version 25.0).

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Declarations

Acknowledgements

This work was supported by the grants from the National Natural Science Foundation of China (grant numbers 81970034 and 81770082).

Authors' contributions

Fang Zhang and Yong Song contributed to concept; Yanli Gu wrote the main manuscript text; Donghui Wang, Cen Chen and Wanjun Lu prepared the tables and figures; Hongbing Liu and Tangfeng Lv offered proposals and helped analyzing data; All authors reviewed the manuscript.

Additional Information:

Conflict of interests

The author(s) declare no competing interests.

Ethics approval

This study was approved by the Ethics Committee of the Wuhan Huoshenshan Hospital.

Consent to participate

Informed consent was obtained from all individual participants or their families included in the study.

Consent to publish

Not applicable

Tables

Table 1. Demographic information and clinical manifestations of COVID-19 patients admitted to ICU.

Characteristic	Total (n=57)	Deceased group (n=20)	Surviving group (n=37)	P value
Age, year	70.89±11.79	71.7±9.921	70.46±12.8	0.708
Sex, n(%)				0.775
Male	38(66.67)	14(70)	24(64.86)	
Female	19(33.33)	6(30)	13(35.14)	
Underlying disease, n(%)				
Hypertension	31(54.39)	11(55)	20(54.05)	1
Diabetes mellitus	14(24.56)	8(40)	6(16.22)	0.059
Coronary heart disease	5(8.77)	3(15)	2(5.41)	0.332
Cerebrovascular disease	9(15.79)	5(25)	4(10.81)	0.253
COPD	6(10.53)	1(5)	5(13.51)	0.41
Hepatic/renal insufficiency	7(12.28)	3(15)	4(10.81)	0.687
Symptoms, n(%)				
Fever	34(59.65)	11(55)	23(62.16)	0.778
Cough	41(71.93)	13(65)	28(75.68)	0.538
Dyspnea	34(59.65)	12(60)	22(59.46)	1
Chest tightness	16(28.07)	5(25)	11(29.73)	0.767
Fatigue	24(42.11)	11(55)	13(43.24)	0.77
Poor appetite	11(19.3)	3(15)	8(21.62)	0.73
Muscle soreness	7(12.28)	4(20)	3(11.11)	0.438
Vital Signs				
Temperature °C	36.55±0.42	36.66±0.52	36.49±0.35	0.154
Heart rate, beats per minute	91.12±16.36	96.5±17.08	88.22±15.41	0.068
Respiratory rate, beats per minute	24.6±6.26	26.05±6.13	23.81±6.27	0.2
Systolic blood pressure, mmHg	138.6±21.51	139.05±27.17	138.35±18.17	0.908
Diastolic blood pressure, mmHg	79.14±16.79	74.1±14.87	81.86±17.31	0.096
Time from illness onset to ICU admission	29.07±14.88	26.95±13.15	30.22±15.88	0.434

Data are presented as mean \pm SD or number (%)

Abbreviation: COPD=chronic obstructive pulmonary disease

Table 2. Laboratory findings, chest X-ray severity and treatment strategy of COVID-19 patients admitted to ICU.

	Total(n=57)	Deceased group(n=20)	Survived group(n=37)	P value
Laboratory findings				
Leucocyte count, *10 ⁹ /L	10.29±5.11	12.32±5.33	9.2±4.71	0.027
Neutrophil count, *10 ⁹ /L	8.89±5.17	11.14±5.1	7.67±4.85	0.014
Lymphocyte count, *10 ⁹ /L	0.81±0.39	0.63±0.25	0.91±0.42	0.003
NLR	14.57±12.41	11.14±5.1	7.67±4.85	0.049
Eosinophil count, *10 ⁹ /L	0.1±0.16	0.02±0.03	0.14±0.19	0.001
Hemoglobin, g/L	110.89±18.28	109.25±19.85	111.78±17.59	0.622
Platelet, *10 ⁹ /L	206.09±121.78	191.7±156.32	213.86±99.97	0.517
Albumin, g/L	33.01±3.99	31.71±3.96	33.71±3.88	0.07
Globulin, g/L	27.88±4.84	27.78±4.95	27.93±4.85	0.914
A/G ratio	1.23±0.28	1.18±0.33	1.26±0.26	0.371
ALT, IU/L	42.71±82.42	70.78±134.63	27.54±18.11	0.169
Creatinine μmol/L	86.11±86.17	118.75±133.36	68.46±35.38	0.113
Urea nitrogen, mmol/L	8.6±6.85	11.66±9.54	6.95±4.11	0.047
Serum sodium, mmol/L	4.28±0.74	4.434±0.85	4.1849±0.67	0.235
Serum potassium, mmol/L	142.47±14.47	145.37±22.96	140.81±5.5	0.392
Serum chloride, mmol/L	102.52±6.85	102.85±8.35	102.34±5.94	0.792
Serum calcium, mmol/L	2.07±0.16	2.02±0.16	2.1±0.15	0.05
Myoglobin, ng/ml	189.06±745.03	475.27±1206.73	28.06±67.01	0.135
Hypersensitive troponin I, ng/ml	0.15±0.73	0.39±1.26	0.04±0.08	0.283
BNP, pg/ml	312.61±758.87	541.28±1136.33	167.79±309.48	0.177
APTT, s	30.96±10.13	35.22±14.59	28.7±5.81	0.075
Thrombin time, s	16.85±8.24	19.67±13.68	15.37±1.38	0.188
D-dimer, mg/L	5.03±5.89	5.8±5.16	4.63±6.23	0.485
LDH, IU/L	336.05±152.47	426.65±174.07	288.24±116.1	0.001
IL-6, pg/ml	339.47±980.67	884.36±1529.86	44.94±81.59	0.024
CRP, mg/L	65.99±67.73	103.65±69.71	45.07±57.53	0.001

PCT, ng/ml	0.54±1.61	1.19±2.71	0.21±0.19	0.169
PaO ₂ /FiO ₂ , mmHg	212.2±145.46	117.41±46.22	263.9±155.07	<0.0001
PaCO ₂ , mmHg	42.3±13.82	44.47±19.55	40.77±7.75	0.442
Chest X-ray severity, %				0.01
Mild	20(37.04)	3(16.67)	17(47.22)	
Moderate	20(37.04)	6(33.33)	14(38.89)	
Severe	14(25.92)	9(50)	5(13.89)	
Treatment strategy, %				
Antiviral treatment	21(37)	9(45)	12(32)	0.397
Antibiotics	44(77)	18(90)	26(70)	0.111
Corticosteroid	22(39)	8(40)	14(38)	1
Intravenous immunoglobulin	10(18)	6(30)	4(11)	0.141
Intravenous albumin	32(56)	17(85)	15(41)	0.002
Thymalfasin	25(44)	12(60)	13(35)	0.096
HFNC	31(54)	12(60)	19(51)	0.587
NIV	13(23)	8(40)	5(14)	0.044
IMV	25(44)	20(100)	5(14)	<0.0001
ECMO	3(5)	3(15)	0(0)	0.039
CRRT	10(18)	10(50)	0(0)	<0.0001
Tocilizumab	17(30)	7(35)	10(27)	0.557
Convalescent plasma	12(21)	5(25)	7(19)	0.736
Stem cell therapy	4(7)	1(5)	3(8)	1

Data are presented as mean ± SD or number (%)

Abbreviations: NLR=neutrophil-to-lymphocyte ratio. ALT=alanine aminotransferase. AST=aspartate transaminase. A/G ratio=white/globule ratio. BNP=brain natriuretic peptide. APTT=activated partial thromboplastin time. LDH=lactate dehydrogenase. IL-6=interleukin-6. CRP=C-reactive protein. PCT=procalcitonin. PaO₂=arterial partial pressure of oxygen. FiO₂=oxygen concentration. PaCO₂=arterial partial pressure of carbon dioxide. HFNC= high-flow nasal cannula oxygen therapy. NIV=non-invasive mechanical ventilation. IMV=invasive mechanical ventilation. ECMO=extracorporeal membrane oxygenation. CRRT=continuous renal replacement therapy.

Table 3. Risk factors associated with mortality for intensive care COVID-19 patients.

Characteristic	Univariable OR (95%CI)	P value	Multivariable OR (95%CI)	P value
Leucocyte count, *10 ⁹ /L				
≤10	1(ref)			
>10	2.769(0.903-8.493)	0.075		
Neutrophil count, *10 ⁹ /L				
≤6.3	1(ref)			
>6.3	3.4(0.953-12.134)	0.059		
Lymphocyte count, *10 ⁹ /L	0.093(0.014-0.641)	0.016		
Eosinophil count, *10 ⁹ /L				
≥0.02	1(ref)			
<0.02	3.125(1.011-9.662)	0.048		
Urea nitrogen, mmol/L				
≤8.8	1(ref)			
>8.8	2.966(0.913-9.637)	0.071		
LDH, IU/L				
≤250	1(ref)			
>250	4.772(1.181-19.273)	0.028		
IL-6, pg/ml	1.009(1.003-1.015)	0.003	1.013(1.001-1.025)	0.028
CRP, mg/L				
≤10	1(ref)			
>10	10.739(1.285-89.717)	0.028		
NLR	1.095(1.026-1.168)	0.006		
PaO ₂ /FiO ₂ , mmHg	0.977(0.964-0.99)	0.001	0.955(0.915-0.996)	0.032
Chest X-ray severity				
Mild	1(ref)			
Moderate	2.429(0.512-11.511)	0.264		
Severe	10.2(1.971-52.775)	0.006		

Abbreviations: LDH=lactate dehydrogenase. IL-6=interleukin-6. CRP=C-reactive protein. NLR=neutrophil-lymphocyte ratio. PaO2=arterial partial pressure of oxygen. FiO2=oxygen concentration.

Figures

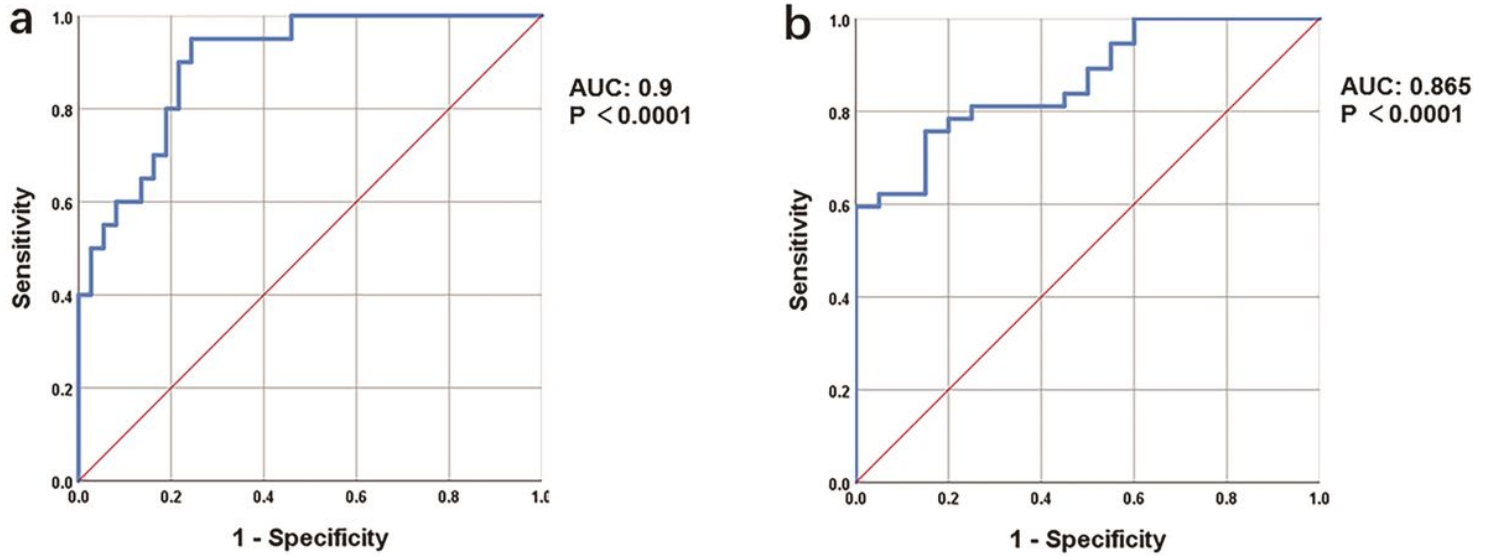


Figure 1

The AUC of IL-6 and PaO₂/FiO₂. (a) The AUC of IL-6 was 0.9 (95%CI:0.823-0.977, $p < 0.0001$), (b) The AUC of PaO₂/FiO₂ was 0.865 (95%CI:0.774-0.956, $p < 0.0001$).

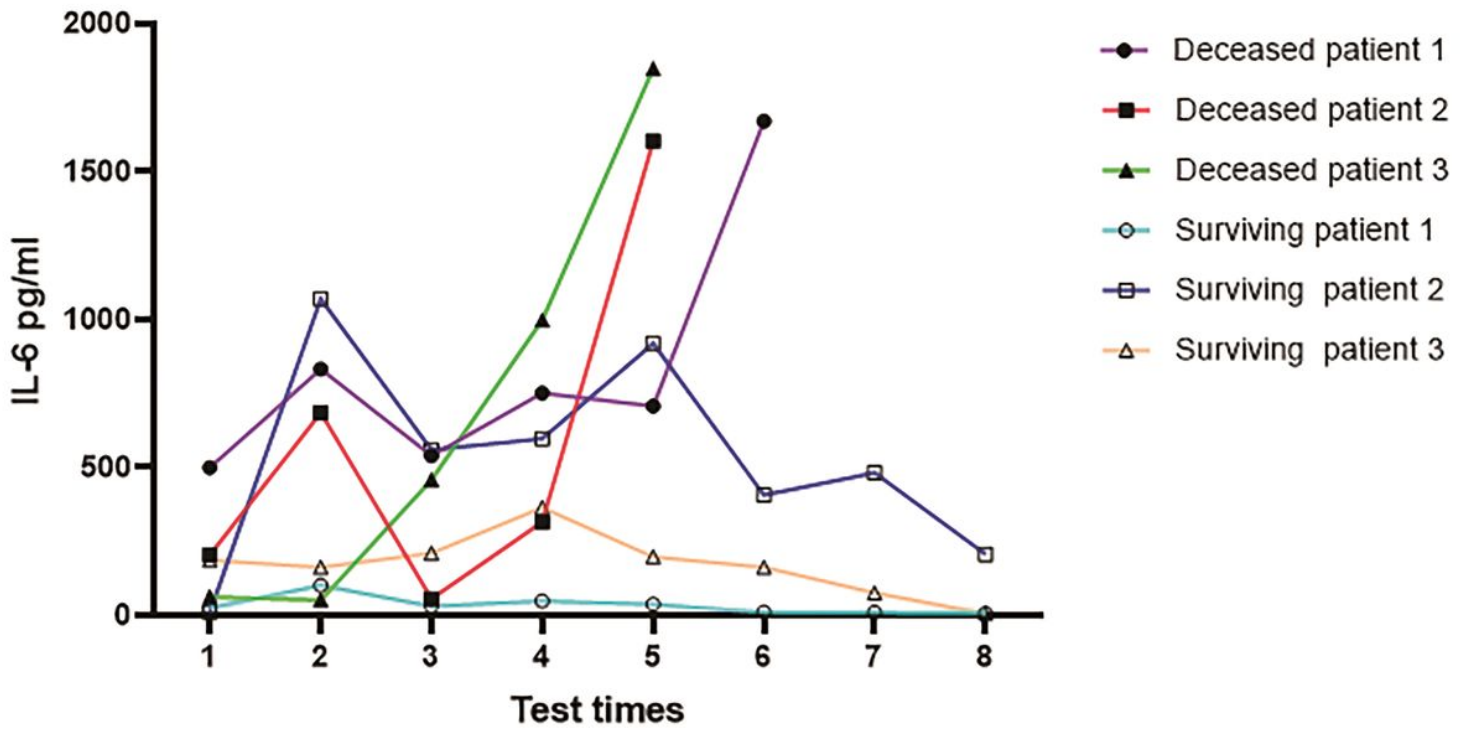


Figure 2

The variation trend of IL-6 levels in six patients (3 in deceased group and 3 in surviving group) during hospitalization.