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## The role of IL-6/lymphocyte ratio in the peripheral blood of severe patients with COVID-19

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**Abstract**

**Background:** To investigate the prognostic value of a novel immune-inflammatory index, the interleukin-6-to-lymphocyte ratio (IL-6/LY), with the clinical outcomes of severe coronavirus disease 2019 (COVID-19) cases.

**Methods:** A cohort study of COVID-19 patients in Tongji Hospital, from January 2020 to February 2020, was evaluated. Kaplan–Meier method and the log-rank test was performed to analyze survival data. Univariate and multivariate analyses were performed with COX proportional hazard regression model. The primary and secondary outcomes were in-hospital mortality and multiple organ dysfunction syndrome (MODS), respectively.

**Results:** Total 320 adult patients were enrolled in our analyses. Patients were divided into low IL-6/LY group and high IL-6/LY group based on the cutoff value with 2.50. The Kaplan-Meier survival curves showed that high-value group ( $IL-6/LY \geq 2.50$ ) had a greater risk of poor prognosis ( $P < 0.001$ , respectively). Multivariate analysis indicated that IL-6/LY was the independent risk predictor for in-hospital mortality (hazard ratio [HR]=3.404, 95% confidence interval [CI]=1.090-10.633,  $P=0.035$ ) and MODS development (HR, 4.143; 95%CI, 1.321-12.986,  $P=0.015$ ). Meanwhile, IL-6/LY was positively correlated with the MuLBSTA score ( $r=0.137$ ,  $P=0.031$ ), suggesting that IL-6/LY was associated with long-term mortality (90-day). Furthermore, kinetic analysis revealed that the dynamic changes of inflammatory immune indexes were related to the severity of the disease.

**Conclusions:** The elevated IL-6/LY was related with the increased risk of poor prognosis. Not only that, IL-6/LY could be used for risk stratification and early clinical identification of high-risk patients.

**Keywords:** Coronavirus disease 2019; Immune-inflammatory index; Interleukin-6; Lymphocyte; Prognosis

## 1. Introduction

In December 2019, the outbreak of coronavirus disease 2019 (COVID-19), caused by a novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread rapidly throughout the world [1]. Considering the present epidemic situation, the World Health Organisation (WHO) declared a global pandemic on March 11, 2020 [2]. The raging infectious disease has caused a serious threat to human health. This brings the global cumulative numbers to 110.7 million cases and over 2.4 million deaths since the start of the pandemic [3].

SARS-CoV-2 is a beta-coronavirus, similar to other two known virus: severe acute respiratory syndrome-CoV (SARS-CoV) and Middle East Respiratory Syndrome-CoV (MERS-CoV), which have caused potentially fatal infections over the last 20 years [4]. The whole genome sequencing indicated that SARS-CoV-2 was very closely related to SARS-CoV [5]. Although SARS-CoV-2 is less lethal than MERS-CoV and SARS-CoV, it has stronger interpersonal transmission ability [6, 7]. Most patients with COVID-19 were asymptomatic or presented mild to moderate symptoms, however, about 10-20% of cases developed severe symptoms, characterized by the rapid development of acute respiratory distress syndrome (ARDS), sepsis and/or multiple organ failure [2]. In particular, the elderly and those with comorbidities tended to develop severe symptoms [8], which might be due to their weaker immune function. Till now, the pathogenicity of COVID-19 has not been completely understood, and the underlying mechanism leading from mild to severe cases remains unclear.

Recently, it has been speculated that the cytokine storm and immune dysfunction was closely related to the rapid disease progression [9]. Researchers found that the levels of infection-related biomarkers played vital roles in severe cases of COVID-19[10]. Moreover, previous studies showed that lower lymphocyte counts, especially decreased levels of T lymphocyte subsets were linked to severe cases, accompanied with elevated levels of pro-inflammatory cytokines like interleukin-6 (IL-6) [11, 12] These suggested that immune dysfunction and cytokine dysregulation might be the key factors in the progression of the disease.

In the current situation, the identification of disease progression of COVID-19 mainly depends on the clinical manifestation, while effective biomarkers have not been proposed. It was important to find sensitive biomarkers to identify critically ill patients in a timely and effective manner. As mentioned above, elevated IL-6 levels and lymphopenia were correlated with severity of disease [11, 12]. The IL-6-to-lymphocyte ratio (IL-6/LY) based on the two factors may reflect the imbalance of inflammation response and immune dysfunction in the body more comprehensively. In our study, we investigated the predictive effect of the new immune-inflammatory complex index on the prognosis of COVID-19, in order to provide positive help for clinical risk assessment.

## **2. Materials and Methods**

### **2.1. Study population**

A total of 320 adult patients with severe COVID-19 pneumonia who were hospitalized in Sino-French New City Branch of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, from January 2020 to February 2020, were enrolled in our retrospective study. Diagnosis of confirmed

COVID-19 was based on the interim guidance issued by WHO [13]. The definitions of severe illness associated with COVID-19 were as follow: fever or suspected respiratory infection; plus one of the following: 1) respiratory rate  $> 30$  breaths/min; 2) severe respiratory distress; 3) or  $SPO_2 \leq 93\%$  on room air. Moreover, patients with suspected COVID-19, patients whose age was below 18 years old, or the patients died within 24 hours of admission were excluded.

The ethics Committee of Tongji Hospital approved this study (TJ-IRB20200362) and waived the requirement for written informed consent due to the massive contagion outbreak of this infectious disease.

## **2.2. Clinical data collection**

We reviewed the electronic medical records system in hospital and collected the clinical information of all participants, including age, sex, smoking history, past medical histories (such as coronary artery disease, hypertension and diabetes). In addition, the data of initial common symptoms were gathered at the time of admission. The treatments during hospitalization (like oxygen therapy, pharmacotherapy and invasive therapies) were included in our data as well. What's more, the complications were destined to record.

Venous blood samples were routinely collected from all patients during the time of hospitalization. The data were checked by two trained physicians independently. Laboratory findings included complete blood counts, coagulation function (prothrombin time, activated partial thromboplastin time, D-dimer), cardiac function (high sensitivity cardiac troponin I, N-terminal pro brain natriuretic peptide), liver

function (aminopherase, creatine kinase, lactate dehydrogenase), kidney function (urea nitrogen, creatinine), lipid profile and immuno-inflammatory indices.

### **2.3. Clinical outcomes**

The primary endpoint of our study was in-hospital mortality, which was identified as the all-cause death happened during hospitalization. The secondary endpoint was incidence of multiple organ dysfunction syndrome (MODS), which was identified as acute dysfunction or failure happened in more than one system simultaneously or sequentially because of the severe diseases (such as serious infection). Clinically, MODS was common in lung, kidney, liver, heart, central nervous system, immune system and hematologic system [14].

### **2.4. Statistical analysis**

The IL-6/LY was calculated as follow:  $IL-6/LY = IL-6 / \text{lymphocyte counts}$ . The neutrophil to lymphocyte ratio (NLR) was calculated as follow:  $N/L = \text{neutrophil counts} / \text{lymphocyte counts}$ . Continuous variables were described as mean  $\pm$  standard error and tested for normal distribution by the Kolmogorov-Smirnov test. Using independent samples *t* test or Mann-Whitney *U*-test to compare the continuous variables between groups. Categorical variables were described as frequency rates and percentages and compared with the chi-square test. The correlation between IL-6/LY and MuLBSTA score was tested by using Spearman correlation coefficient. The optimal cut-off point for IL-6/LY was calculated by receiver operating characteristic (ROC) curve. Kaplan–Meier method and the log-rank test was performed to analyze survival data. Univariate and multivariate analyses were conducted with COX proportional hazard regression model. Any variables examined in the univariate

analysis for which the P value was  $<0.10$  or several established risk factors were contained in the multivariate model. A P value  $<0.05$  was considered statistically significant. All data were analyzed using SPSS version 22.0 and Graphpad 6.0 software.

### 3. Results

#### 3.1. Baseline characteristics of COVID-19 patients

Totally, 320 severe patients with COVID-19 were enrolled in our study and they all met the diagnostic criteria of severe COVID-19 patients as described above. In accordance with the cut-off value of IL-6/LY, the whole population was divided into low IL-6/LY group (207 patients, 100 males) and high IL-6/LY group (113 patients, 40 males).

The demographics and clinical characteristics of study population were shown in **Table 1**. The patients in high IL-6/LY group were older, smoking more and with more comorbidities of coronary heart disease, diabetes and chronic lung disease ( $P<0.050$ , respectively). Additionally, more patients in the high IL-6/LY group experienced moderate to high-grade fever ( $P<0.050$ ), with longer days from onset to hospitalization ( $P=0.023$ ), more complications ( $P<0.001$ ), and higher occupancy ratio of oxygen therapy and invasive treatment applications ( $P<0.050$ , respectively). Conversely, patients in the low IL-6/LY group stayed longer in hospital ( $P<0.001$ ). The main clinical manifestations were dyspnea and mild-grade fever, and more patients in low IL-6/LY group received pharmacotherapy in hospital ( $P<0.050$ ).

The laboratory characteristics of the patients were summarized in **Table 2**. Higher levels of white blood cells, neutrophil counts, monocyte counts, prothrombin time, D-dimer, hypersensitive cardiac troponin I, NT-proBNP, ALT, AST, globulin,

triglyceride, creatine kinase, LDH, urea, creatinine, high-sensitivity C-reactive protein (Hs-CRP), ESR, ferritin, procalcitonin, IgA, IgG, IL-2R, IL-6, IL-8, IL-10, TNF- $\alpha$  and MulBSTA score were found in high IL-6/LY group patients ( $P < 0.050$ , respectively), comparing to those in low IL-6/LY group. However, the value of lymphocyte, platelet, albumin, total cholesterol, HDL-C, LDL-C, C3 and C4 was lower in high IL-6/LY group compared with that in low IL-6/LY group ( $P < 0.050$ , respectively).

Table 1 Demographics and clinical characteristics of study population

	All patients (n=320)	Low IL-6/LY group (n=207)	High IL-6/LY group (n=113)	P
Gender, (male), n (%)	140 (43.75)	100 (48.31)	40 (35.40)	0.026
Age, year	61.37 $\pm$ 0.86	57.87 $\pm$ 1.10	67.77 $\pm$ 1.15	<0.001
Smoking, n (%)	41 (12.81)	16 (7.73)	25 (22.12)	<0.001
<b>Comorbidity, n (%)</b>				
CHD	46 (14.38)	23 (11.11)	23 (20.35)	0.024
Hypertension	113 (35.31)	65 (31.40)	48 (42.48)	0.048
Diabetes	109 (34.06)	53 (25.60)	56 (49.56)	<0.001
Chronic lung disease	26 (8.13)	12 (5.80)	14 (12.39)	0.039
Chronic kidney disease	8 (2.5)	6 (2.90)	2 (1.77)	0.537
Chronic liver disease	14 (4.38)	7 (3.38)	7 (6.19)	0.240
Autoimmune diseases	8 (2.5)	7 (3.38)	1 (0.88)	0.172
Tumor	19 (5.94)	12 (5.80)	7 (6.19)	0.886
Cerebrovascular disease	16 (5.00)	7 (3.38)	9 (7.96)	0.072

Gastrointestinal disease	16 (5.00)	12 (5.80)	4 (3.54)	0.376
Time of illness onset, days	10.83±0.34	10.06±0.38	12.22±0.64	0.023
Hospital stays, days	14.49±0.42	15.89±0.48	11.93±0.75	<0.001
<b>Initial common symptoms, n (%)</b>				
Fever	281 (87.81)	179 (86.47)	102 (90.27)	0.322
Dyspnea	189 (59.06)	107 (51.69)	82 (72.57)	<0.001
Stomachache	31 (9.69)	22 (10.63)	9 (7.96)	0.441
Diarrhea	100 (31.25)	66 (31.88)	34 (30.09)	0.740
Chest distress	80 (25.00)	45 (21.74)	35 (30.97)	0.068
Chest pain	24 (7.5)	13 (6.28)	11 (9.73)	0.262
Palpitation	32 (10.00)	17 (8.21)	15 (13.27)	0.149
Dizziness	32 (10.00)	22 (10.63)	10 (8.85)	0.612
Headache	60 (18.75)	36 (17.39)	24 (21.24)	0.399
<b>Temperature, °C</b>				
High fever (39.1-41.0)	9 (2.81)	3 (1.45)	6 (5.31)	0.046
Moderate fever (38.1-39.0)	68 (21.25)	31 (14.98)	37 (32.74)	<0.001
Mild fever (37.3-38.0)	68 (21.25)	40 (19.32)	28 (24.78)	0.254
<b>Pharmacotherapy in hospital, n (%)</b>				
Antibiotic therapy	295 (92.19)	186 (89.86)	109 (96.46)	0.035
Antiviral therapy	213 (66.56)	146 (70.53)	67 (59.29)	0.042
GCS	219 (68.44)	126 (60.87)	93 (82.30)	<0.001
<b>Oxygen therapy in hospital, n (%)</b>				

NMV	153 (47.81)	68 (32.85)	85 (75.22)	<0.001
IMV	85 (26.56)	26 (12.56)	59 (52.21)	<0.001
<b>Other treatment in hospital, n (%)</b>				
CRRT	19 (5.94)	4 (1.93)	15 (13.27)	<0.001
ECMO	5 (1.56)	1 (0.48)	4 (3.54)	0.035
<b>Complications, n (%)</b>				
Death	145 (45.31)	55 (26.57)	90 (79.65)	<0.001
MODS	137 (42.81)	51 (24.64)	86 (76.11)	<0.001
ARDS	114 (35.63)	44 (21.26)	70 (61.95)	<0.001
DIC	75 (23.44)	19 (9.18)	56 (49.56)	<0.001
Secondary infection	42 (13.13)	14 (6.76)	28 (24.78)	<0.001
MACE	80 (25.00)	29 (14.01)	51 (45.13)	<0.001
AKI	53 (16.56)	11 (5.31)	42 (37.17)	<0.001
Spesis shock	52 (16.25)	20 (9.66)	32 (28.32)	<0.001
Myelosuppression	79 (24.69)	24 (11.59)	55 (48.67)	<0.001
GIB	14 (4.38)	2 (0.97)	12 (10.62)	<0.001
Liver function impairment	80 (25.00)	35 (16.91)	45 (39.82)	<0.001

Mean  $\pm$  SEM and n (%) are reported for continuous and categorical variables, respectively. standard error of the mean(SEM), interleukin-6 to lymphocyte ratio(IL-6/LY), coronary heart disease(CHD); glucocorticoids(GCS), noninvasive mechanical ventilation(NMV), invasive mechanical ventilation(IMV), continuous renal replacement therapy(CRRT), extracorporeal membrane oxygenation(ECMO), multiple organ dysfunction syndrome(MODS), acute respiratory distress syndrome(ARDS), disseminated intravascular coagulation(DIC), major adverse cardiac events(MACE), acute kidney injury(AKI), gastrointestinal bleeding(GIB).

Table 2 Laboratory characteristics of study population

	All patients (n=320)	Low IL-6/LY group (n=207)	High IL-6/LY group (n=113)	P
<b>Blood routine index</b>				
WBC, 10 <sup>9</sup> /L	7.56±0.27	5.99±0.25	10.44±0.53	<0.001
Neutrophil%, %	75.95±0.84	70.31±1.04	86.30±0.74	<0.001
Neutrophil, 10 <sup>9</sup> /L	6.22±0.28	4.55±0.25	9.28±0.52	<0.001
Lymphocyte%, %	16.12±0.64	20.44±0.79	8.21±0.56	<0.001
Lymphocyte, 10 <sup>9</sup> /L	0.90±0.04	1.04±0.06	0.65±0.03	<0.001
Monocyte%, %	6.88±0.22	7.83±0.29	5.14±0.29	0.252
Monocyte, 10 <sup>9</sup> /L	0.45±0.02	0.43±0.02	0.47±0.03	<0.001
Hemoglobin, mg/dL	124.73±1.34	124.91±1.59	124.41±2.46	0.931
Platelet, 10 <sup>9</sup> /L	193.25±5.09	204.74±6.33	172.22±8.23	<0.001
<b>Coagulation function</b>				
PT, sec	15.34±0.34	14.48±0.21	16.95±0.86	<0.001
APTT, sec	42.29±0.76	41.43±0.60	43.57±1.65	0.133
D-dimer, ug/mL FEU	4.85±0.42	2.98±0.40	8.39±0.84	<0.001
<b>Biochemical indexes</b>				
CTnI, pg/ml	616.36±199.58	168.54±97.51	1331.94±487.36	<0.001
NT-proBNP, pg/ml	2467.98±521.93	1449.30±531.33	4022.81±1023.28	<0.001
ALT, u/L	37.37±3.56	31.75±3.78	47.57±7.21	<0.001
AST (u/L)	48.30±5.41	33.43±1.91	75.27±14.53	<0.001
Albumin, g/L	33.30±0.30	34.83±0.33	30.51±0.50	<0.001

Globulin, g/L	34.17±0.36	33.41±0.45	35.56±0.58	<0.001
TC, mmol/l	3.57±0.05	3.66±0.06	3.42±0.08	0.008
TG, mmol/L	1.64±0.07	1.51±0.09	1.80±0.12	0.001
HDL-C, mmol/l	0.85±0.02	0.95±0.03	0.75±0.03	<0.001
LDL-C, mmol/l	2.18±0.06	2.30±0.07	2.05±0.11	0.014
CK, u/L	254.18±37.96	147.14±18.86	382.39±78.34	<0.001
LDH, u/L	427.50±16.44	334.58±13.65	597.58±33.86	<0.001
Urea, mmol/L	7.72±0.45	5.62±0.31	11.55±1.04	<0.001
Creatinine, mmol/L	95.75±5.04	89.05±6.76	107.96±6.98	<0.001

#### Immuno-inflammatory indices

Hs-CRP, mg/L	76.95±4.01	52.85±3.93	119.18±7.05	<0.001
ESR, mm/H	38.93±1.58	35.39±1.85	45.02±2.78	0.003
Ferritin, ug/L	1483.87±188.08	854.89±87.86	2366.85±421.14	<0.001
PCT, ng/mL	1.41±0.48	0.23±0.05	3.44±1.28	<0.001
Ig A, g/L	2.40±0.09	2.20±0.10	2.61±0.14	0.017
Ig G, g/L	12.43±0.29	11.71±0.35	13.21±0.47	0.010
Ig M, g/L	1.06±0.04	1.09±0.06	1.03±0.07	0.214
Alexin C3, g/L	0.83±0.02	0.87±0.02	0.79±0.03	0.007
Alexin C4, g/L	0.24±0.01	0.25±0.01	0.22±0.01	0.014
IL-1 $\beta$ , pg/ml	5.93±0.26	5.67±0.23	6.25±0.51	0.890
IL-2R, pg/ml	1008.15±51.85	716.46±59.66	1356.64±77.04	<0.001
IL-6, pg/ml	113.32±31.35	51.18±36.95	187.55±52.10	<0.001

IL-8, pg/ml	68.94±30.36	21.64±3.83	125.45±66.25	<0.001
IL-10, pg/ml	12.44±1.25	7.92±0.67	17.83±2.55	<0.001
TNF- $\alpha$ , pg/ml	11.70±0.63	9.13±0.63	14.76±1.10	<0.001
MuLBSTA score	7.88±0.21	7.46±0.25	8.65±0.37	0.024

Mean  $\pm$  SEM and n (%) are reported for continuous and categorical variables, respectively. standard error of the mean(SEM), not available(NA), interleukin-6 to lymphocyte ratio(IL-6/LY =), white blood cells count(WBC), prothrombin time(PT), activated partial thromboplastin time(APTT), Hypersensitive cardiac troponin I(CTnI), N-terminal pro brain natriuretic peptide(NT-proBNP), aspartate aminotransferase(AST), alanine aminotransferase(ALT), total cholesterol(TC), triglyceride(TG), high density lipoprotein cholesterol(HDL-C), low density lipoprotein cholesterol(LDL-C), creatine kinase(CK), lactate dehydrogenase(LDH), high-sensitivity C-reactive protein(Hs-CRP), erythrocyte sedimentation rate(ESR), procalcitonin(PCT =),immunoglobulin A(Ig A), immunoglobulin G(Ig G), immunoglobulin M(Ig M), interleukin-1 $\beta$ (IL-1 $\beta$ ), interleukin-2 receptor(IL-2R), interleukin-6(IL-6), interleukin-8(IL-8), interleukin-10(IL-10), tumor necrosis factor  $\alpha$ (TNF- $\alpha$ ).

### 3.2. Prognostic factors for clinical outcomes

The following categorical variables were entered in a forward stepwise COX regression analysis: age, sex, smoking history, coronary heart disease, hypertension, diabetes, the days of illness onset, blood routine index, coagulation dysfunction indicators, serum biochemical indices, inflammatory markers and cytokines. Elevated IL-6/LY (hazard ratio [HR], 3.404; 95% confidence interval [CI], 1.090-10.633, P=0.035) along with older age (HR, 1.034; 95%CI, 1.004-1.064, P=0.025), lower LY% (HR, 0.897; 95%CI, 0.846-0.952, P<0.001), lower hemoglobin (HR, 0.980; 95%CI, 0.968-0.992, P=0.002) and higher ferritin (HR, 1.000; 95%CI, 0.999-1.001, P=0.007) was associated with greater risk of in-hospital mortality according to multivariate

COX regression analysis. In addition, compared with other inflammatory markers (including NLR, Hs-CRP, procalcitonin and interleukins; all  $P>0.05$ ), IL-6/LY showed more significant predictability on in-hospital mortality (**Table 3**). Similarly, diabetes (HR, 3.353; 95%CI, 1.640-6.856,  $P=0.001$ ), lower hemoglobin (HR, 0.984; 95%CI, 0.972-0.997,  $P=0.016$ ), prolonged prothrombin time (HR, 1.050; 95%CI, 1.022-1.079,  $P<0.001$ ), higher NT-ProBNP level (HR, 2.424; 95%CI, 1.660-3.541,  $P<0.001$ ) and elevated IL-6/LY (HR, 4.143; 95%CI, 1.321-12.986,  $P=0.015$ ) was associated with higher likelihood of MODS development. As a matter of fact, among the numerous inflammatory factors considered in the computational model, IL-6/LY had the best predictive ability (**Table 4**).

As shown in **Figure 1 A**, compared with the ROC analysis of NLR (AUC=0.882, 95% CI, 0.844-0.920,  $P<0.001$ ; sensitivity=76.60%, specificity=85.70%), IL-6/LY had better performance with in-hospital mortality (AUC=0.919, 95% CI, 0.887-0.951,  $P<0.001$ ; sensitivity=84.10%, specificity=84.30%). As illustrated in **Figure 1 B**, such comparisons with NLR (AUC=0.869, 95% CI, 0.829-0.909,  $P<0.001$ ; sensitivity=79.60%, specificity=80.30%) suggested that the IL-6/LY had better prediction power of MODS development (AUC=0.900, 95% CI, 0.863-0.937,  $P<0.001$ ; sensitivity=83.50%, specificity=81.90%).

The Kaplan-Meier survival curves for high-value and low-value groups were shown in **Figure 2**. It was suggested that the high-value group ( $IL-6/LY \geq 2.50$ ) has a greater risk in poor prognosis ( $P<0.001$ , respectively).

Interestingly, we also found that IL-6/LY was positively correlated with the MuLBSTA score which was used to predict the mortality risk of viral pneumonia ( $r=0.137$ ,  $P=0.031$ ; **Figure 3**).

**Table 3** Predictors of in-hospital mortality in univariable and multivariable Cox regression analyses.

Variables	Univariable			Multivariable		
	HR	95% CI	P	HR	95% CI	P
Age	1.046	1.033 — 1.060	<0.001	<b>1.034</b>	<b>1.004 — 1.064</b>	<b>0.025</b>
Gender (male)	1.617	1.148 — 2.279	0.006			
Smoking	2.445	1.669 — 3.583	<0.001			
<b>Comorbidity</b>						
CHD	1.771	1.171 — 2.679	0.007			
Hypertension	1.999	1.440 — 2.776	<0.001			
Diabetes	2.620	1.889 — 3.634	<0.001			
Time of illness onset	1.039	1.012 — 1.066	0.004			
<b>Blood routine index</b>						
WBC	1.133	1.108 — 1.159	<0.001			

Neutrophil	1.138	1.114 — 1.164	<0.001			
Neutrophil%	1.095	1.075 — 1.115	<0.001			
Lymphocyte	0.121	0.070 — 0.207	<0.001			
Lymphocyte%	0.881	0.859 — 0.904	<0.001	<b>0.897</b>	<b>0.846 — 0.952</b>	<b>&lt;0.001</b>
Monocyte	1.538	1.042 — 2.270	0.030			
Monocyte%	0.826	0.783 — 0.871	<0.001			
Hemoglobin	0.993	0.987 — 1.000	0.038	<b>0.980</b>	<b>0.968 — 0.992</b>	<b>0.002</b>
Platelet	0.994	0.992 — 0.996	<0.001			
<b>Coagulation function</b>						
PT	1.036	1.024 — 1.048	<0.001			
D-Dimer	1.088	1.068 — 1.108	<0.001			
<b>Biochemical indexes</b>						
CTnI	1.369	1.164 — 1.611	<0.001			

NT-proBNP	2.319	1.964 — 2.739	<0.001			
ALT	1.003	1.001 — 1.005	<0.001			
AST	1.002	1.001 — 1.003	<0.001			
Albumin	0.873	0.846 — 0.900	<0.001			
Globulin	1.018	0.998 — 1.039	0.079			
HDL-C	0.087	0.037 — 0.208	<0.001			
LDL-C	0.571	0.419 — 0.778	<0.001			
CK	1.000	1.000 — 1.001	<0.001			
LDH	1.002	1.001 — 1.002	<0.001			
Creatinine	1.002	1.001 — 1.003	<0.001			
<b>Immuno-inflammatory indices</b>						
IL-6/LY	8.889	5.282 — 14.961	<0.001	<b>3.404</b>	<b>1.090 — 10.633</b>	<b>0.035</b>
NLR	1.041	1.034 — 1.048	<0.001			

Hs-CRP	1.009	1.007 — 1.011	<0.001			
ESR	1.006	0.999 — 1.013	0.122			
Ferritin	5.521	3.588 — 8.497	<0.001	<b>1.000</b>	<b>0.999 — 1.001</b>	<b>0.007</b>
PCT	1.028	1.015 — 1.040	<0.001			
Alexin C3	0.067	0.023 — 0.190	<0.001			
Alexin C4	0.003	0.001 — 0.049	<0.001			
IL-2R	1.000	1.000 — 1.001	<0.001			
IL-6	1.001	1.000 — 1.001	<0.001			
IL-8	1.000	1.000 — 1.001	0.006			
IL-10	1.012	1.008 — 1.017	<0.001			
TNF- $\alpha$	1.044	1.032 — 1.056	<0.001			

hazard ratio(HR), confidence interval(CI), coronary heart disease(CHD), white blood cell count(WBC), prothrombin time(PT), Hypersensitive cardiac troponin I(CTnI), N-terminal pro brain natriuretic peptide(NT-proBNP), alanine aminotransferase(ALT), aspartate aminotransferase(AST), high density lipoprotein cholesterol(HDL-C), low density lipoprotein cholesterol(LDL-C), lactate dehydrogenase(LDH), creatine kinase(CK), IL-6 to

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lymphocyte ratio(IL-6/LY), neutrophil to lymphocyte ratio(NLR), high-sensitivity C-reactive protein(Hs-CRP), erythrocyte sedimentation rate(ESR), procalcitonin(PCT), interleukin-2 receptor(IL-2R), interleukin-6(IL-6), interleukin-8(IL-8), interleukin-10(IL-10), tumor necrosis factor  $\alpha$ (TNF- $\alpha$ ).

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**Table 4** Predictors of MODS development in univariable and multivariable Cox regression analyses.

Variables	Univariable			Multivariable		
	HR	95% CI	P	HR	95% CI	P
Age	1.047	1.033 — 1.062	<0.001			
Gender (male)	1.640	1.152 — 2.335	0.006			
Smoking	2.630	1.788 — 3.867	<0.001			
<b>Comorbidity</b>						
CHD	1.752	1.141 — 2.691	0.010			
Hypertension	1.990	1.420 — 2.790	<0.001			
Diabetes	2.816	2.010 — 3.945	<0.001	<b>3.353</b>	<b>1.640 — 6.856</b>	<b>0.001</b>
Time of illness onset	1.033	1.005 — 1.062	0.020			
<b>Blood routine index</b>						
WBC	1.135	1.109 — 1.161	<0.001			

Neutrophil	1.140	1.115 — 1.167	<0.001			
Neutrophil%	1.096	1.076 — 1.116	<0.001			
Lymphocyte	0.103	0.058 — 0.183	<0.001			
Lymphocyte%	0.879	0.856 — 0.902	<0.001			
Monocyte	1.615	1.101 — 2.369	0.014			
Monocyte%	0.830	0.786 — 0.876	<0.001			
Hemoglobin	0.993	0.987 — 1.000	0.058	<b>0.984</b>	<b>0.972 — 0.997</b>	<b>0.016</b>
Platelet	0.994	0.992 — 0.996	<0.001			
<b>Coagulation function</b>						
PT	1.037	1.024 — 1.049	<0.001	<b>1.050</b>	<b>1.022 — 1.079</b>	<b>&lt;0.001</b>
D-Dimmer	1.087	1.067 — 1.108	<0.001			
<b>Biochemical indexes</b>						
CTnI	1.425	1.204 — 1.688	<0.001			

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NT-proBNP	2.421	2.035 — 2.881	<0.001	<b>2.424</b>	<b>1.660 — 3.541</b>	<b>&lt;0.001</b>
ALT	1.003	1.002 — 1.005	<0.001			
AST	1.002	1.001 — 1.003	<0.001			
Albumin	0.876	0.848 — 0.905	<0.001			
Globulin	1.016	0.994 — 1.038	0.153			
HDL-C	0.091	0.037 — 0.221	<0.001			
LDL-C	0.535	0.388 — 0.738	<0.001			
CK	1.000	1.000 — 1.001	<0.001			
LDH	1.002	1.002 — 1.003	<0.001			
Creatinine	1.002	1.001 — 1.003	<0.001			
<b>Immuno-inflammatory indices</b>						
IL-6/LY	8.487	5.032 — 14.314	<0.001	<b>4.143</b>	<b>1.321 — 12.986</b>	<b>0.015</b>
NLR	1.042	1.035 — 1.050	<0.001			

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Hs-CRP	1.009	1.007 — 1.011	<0.001
ESR	1.002	0.995 — 1.010	0.514
Ferritin	5.733	3.674 — 8.946	<0.001
PCT	1.029	1.016 — 1.041	<0.001
Alexin C3	0.074	0.025 — 0.221	<0.001
Alexin C4	0.004	0.001 — 0.073	<0.001
IL-2R	1.000	1.000 — 1.001	<0.001
IL-6	1.001	1.000 — 1.001	<0.001
IL-8	1.000	1.000 — 1.001	0.005
IL-10	1.013	1.008 — 1.017	<0.001
TNF- $\alpha$	1.046	1.034 — 1.058	<0.001

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hazard ratio(HR), confidence interval(CI), multiple organ dysfunction syndrome(MODS), coronary heart disease(CHD), white blood cell count(WBC), prothrombin time(PT), Hypersensitive cardiac troponin I(CTnI), N-terminal pro brain natriuretic peptide(NT-proBNP), alanine aminotransferase(ALT), aspartate aminotransferase(AST), high density lipoprotein cholesterol(HDL-C), low density lipoprotein cholesterol(LDL-C), lactate dehydrogenase(LDH), creatine kinase(CK), IL-6 to lymphocyte ratio(IL-6/LY), neutrophil to lymphocyte ratio(NLR), high-sensitivity

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C-reactive protein(Hs-CRP), erythrocyte sedimentation rate(ESR), procalcitonin(PCT), interleukin-2 receptor(IL-2R), interleukin-6(IL-6), interleukin-8(IL-8), interleukin-10(IL-10), tumor necrosis factor  $\alpha$ (TNF- $\alpha$ ).

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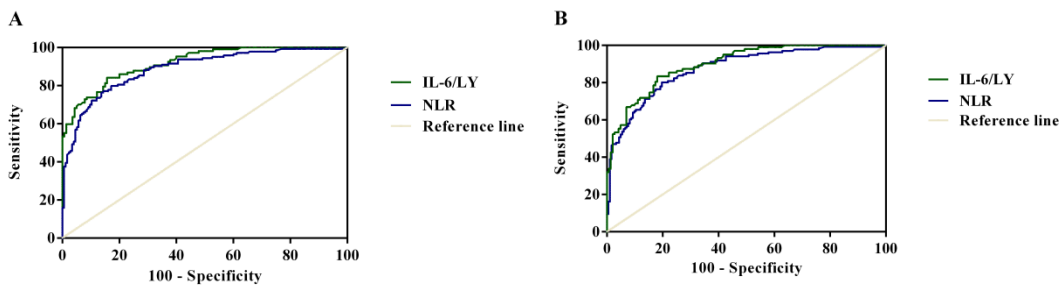


Figure 1. The effectiveness of IL-6/LY and NLR predictor for poor prognosis of COVID-19 by ROC curves.

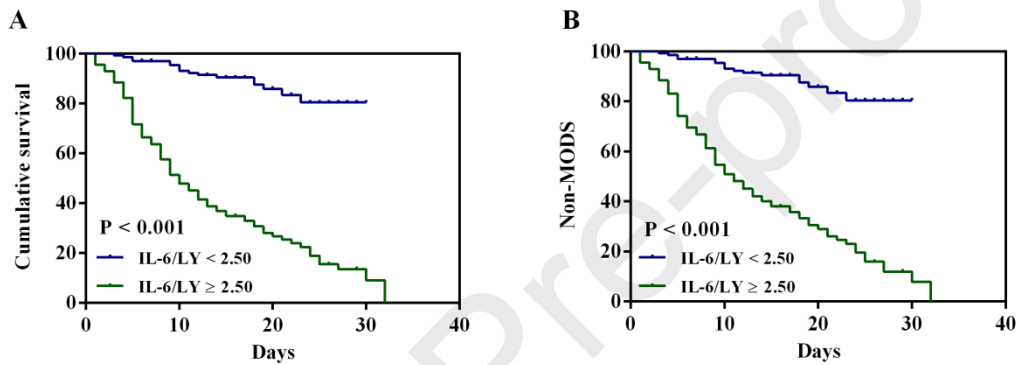


Figure 2. Kaplan-Meier cumulative survival curves for COVID-19 patients with in-hospital mortality and developed MODS according to the cutoff value of IL-6/LY.

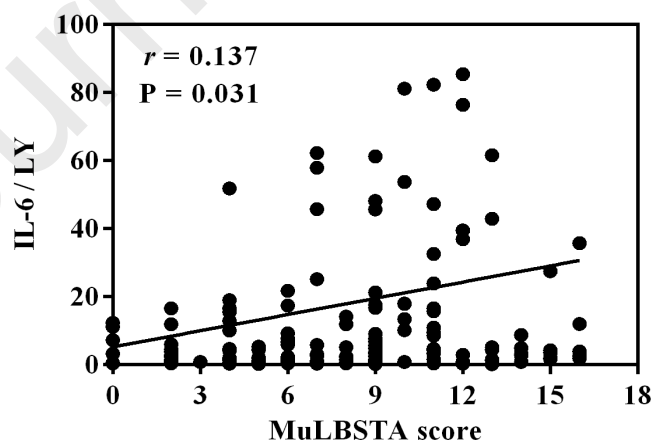


Figure 3. The correlation between IL-6/LY and MuLBSTA score ( $r=0.137$ ,  $P=0.031$ ).

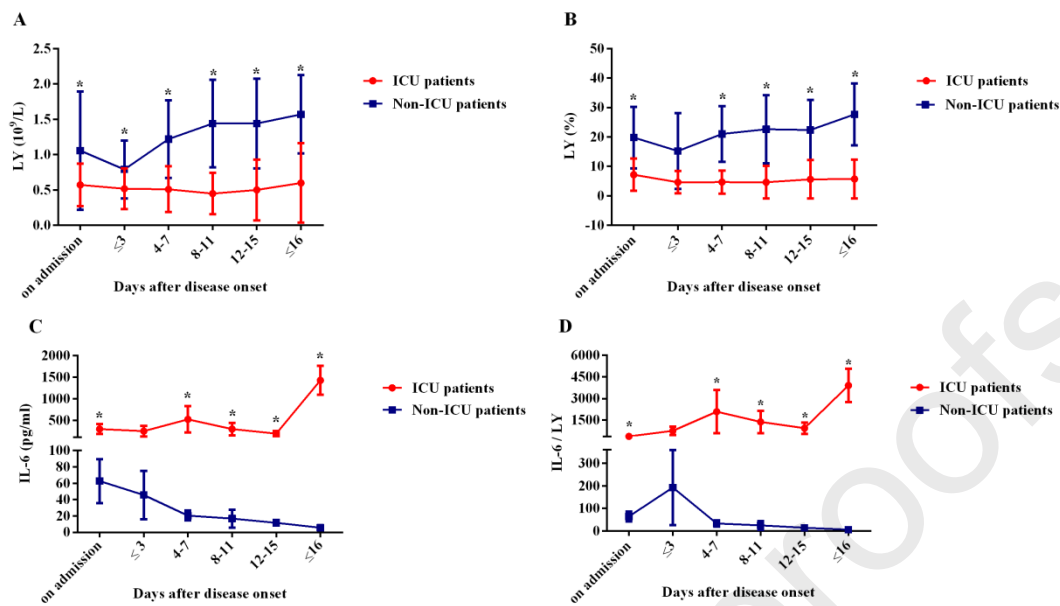


Figure 4. Kinetic analysis of LY, LY%, IL-6 and IL-6/LY in COVID-19 patients.

### 3.3. Dynamic changes of LY%, LY, IL-6 and IL-6/LY

Among our population, there were 105 intensive care patients and 215 non-intensive care patients. As the **Figure 4 A-B** showed, the blood LY% and LY were much lower in intensive care unit (ICU) group than those in non-ICU group on admission, and the difference was statistically significant ( $P < 0.001$ , respectively). Besides, the LY% and LY gradually declined during the first three days of hospitalization in non-ICU group, while since then, they increasingly rose to normal levels upon discharge ( $P < 0.001$ , respectively). In contrast, the above trend did not appear in ICU patients and both the LY% and LY still remained at a low level until discharge.

In addition, significantly increased in IL-6 level and IL-6/LY were observed in ICU group compared with those in non-ICU group at several time points except for the first three days in hospital (the day of at admission, four to seven days after admission, eight to eleven days after admission, twelve to fifteen days after admission,

before discharge, all  $P < 0.001$ ). The difference between ICU group and non-ICU group was significant at the time point of 4-7 days and became even greater before discharge (**Figure 4 C-D**).

#### 4. Discussion

In current study, we found that patients with elevated IL-6/LY ( $\geq 2.50$ ) was the independent risk factor for in-hospital mortality and the development of MODS in severe COVID-19 patients. Besides, our results showed that the age along with LY% were also the predictors of in-hospital mortality and the diabetes, prothrombin time, and NT-ProBNP were significant associated with higher likelihood of MODS development. Meanwhile, the dynamic changes of the inflammatory biomarkers could reflect the clinical severity in patients with COVID-19.

A series of evidences showed that the uncontrolled inflammatory response and immunity dysregulation were the prominent feature of critical ill COVID-19 patients [2, 15]. In addition, several other researches also proved that some seriously ill COVID-19 patients have increased cytokine profile similar to cytokine storm in severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) [16-18]. Cytokine storm stems from the coronavirus infected place and then spread throughout the organism by mass of inflammatory cells infiltration which in turn lead to acute lung injury, ARDS and death [17, 18]. It was reported that higher levels of inflammatory parameters, especially IL-6 could be shown in severe COVID-19 patients, which was consistent with previous studies [8, 19, 20]. IL-6 has multiple effects in regulating inflammation. Cifaldi et al. has reported that elevated IL-6 level was linked to impaired cytolytic function by overstimulating the immune system and finally might result in multiple organ failure [21].

Furthermore, significantly reduced of T cells counts have been found in severe COVID-19 patients in recent studies [22, 23]. Researchers identified that very few lymphocytes were infiltrated in the alveolar of damaged lung tissue [10, 24, 25]. A similar decrease in lymphocyte counts and the subset of T cells could be seen in SARS patients according to previous investigations [26, 27]. However, the exact mechanism of lymphopenia in severe COVID-19 patients remains still unclear. Previous body biopsies reported that the COVID-19 patients' secondary lymphoid tissues had been destroyed [10, 24, 25]. Zhang et al. speculated that lymphocytes were directly invaded by virus infection or indirectly damaged by cytokine storm which induced by immune response [24]. And a substantial decrease in lymphocytes revealed that the immune cells may be consumed by the viruses and the body's cellular immune function may be restrained [28, 29]. It suggested that COVID-19 infection can lead to immune dysfunction through affecting the subsets of T cells [30].

Through analyzing the immune cells and inflammatory cytokines in the severe COVID-19 patients, Zhou et al. noted that the Th1 cells (GM-CSF<sup>+</sup>IFN- $\gamma$ <sup>+</sup>) and inflammatory monocytes (CD14<sup>+</sup>CD16<sup>+</sup> with high expression of IL-6) existed particularly in ICU patients [31]. Therefore, lots of these pathogenic T cells and inflammatory monocytes may get into the pulmonary circulation and arouse inflammatory storm which probably prevents alveolar gas exchange and contributing to the high mortality of severe COVID-19 patients [32]. Given their weight during the course of COVID-19, our study developed a novel biomarker, named as IL-6/LY, in order to estimate condition, evaluate prognosis and conduct risk stratification. As we know, this was the first research for exploring the effect of IL-6/LY on predicting the clinical outcomes for COVID-19 cases.

According to existing research results, we proposed potential mechanisms of high IL-6/LY was resulted from the increased IL-6 and the decreased lymphocyte counts. Recent studies' results would give some explanations. Wan S et al found that patients with severe COVID-19 patients were more likely to have higher IL-6 levels than those mild COVID-19 cases [23]. It was also showed that lymphopenia was one of the important features of COVID-19 infection and which was also the common ground in most severe patients [1]. As shown in another study, IL-6 could suppress the T cell activation, which may explain the decrease of lymphocyte [33]. Furthermore, according to the study by Jing Liu et al, they revealed that the T cell counts were negatively associated with the examined cytokine levels (such as IL-6) [34]. Accordingly, the balance of IL-6 and lymphocyte played a crucial role in the immunoregulation of patients with COVID-19. When evaluating patients infected with COVID-19, inflammatory biomarkers might be useful to help clinicians start treatment and monitor closely. Compared to other biomarkers, people were often hesitant to use a inflammatory marker alone because it might be influenced by many factors. While IL-6/LY, consisted of two inflammatory components (IL-6 and lymphocyte), might reflect the immune dysregulation in COVID-19 patients more realistically and comprehensively. Still not only such, IL-6/LY could be analyzed rapidly and accurately in the light of the blood test at the time of admission. Our data suggested that IL-6/LY could serve as an indicator of poor prognosis of COVID-19. The dynamic changes of IL-6/LY in patients revealed that the magnitude of the immune response dysregulation was related to the severity of COVID-19 patients. Herby, the physicians could identify the specific subpopulations of COVID-19 patients who were at greater risk for unfavorable outcomes at an early stage.

What's more, in our study, the relationship between other immunoinflammatory parameters and poor prognosis were also evaluated. We found that individual variable (such as WBC, Hs-CRP, procalcitonin, ferritin and interleukins) had an influence on the occurrence of clinical outcomes partly. However, after adjustment for potential confounders, the results statistically supported the conclusions that the incidence of high IL-6/LY was significantly correlated with the poor prognosis of the disease.

Not only that, older age and comorbidities were proved to be in connection with severe COVID-19 [35]. Weina Guo et al suggested that COVID-19 patients with diabetes had a poor prognosis and diabetes was proposed as a risk factor for the progression of COVID-19 cases [36, 37]. Clinically, infected by SARS-CoV-2 caused multiple system organ failure, such as the hematologic system [38-40]. Previous studies showed that prothrombin time was positively correlated with 28-day mortality [41]. Besides, a retrospective study showed that NT-proBNP was an independent risk factor for in-hospital death in patients with severe COVID-19 [42]. In fact, these results were in consistent with our findings.

We have to acknowledge that there were some limitations in this study. Firstly, the retrospective design of the study set a limit to the convincement of our study. Due to the nature of our study, the results must be explained with caution, given the possibility of confounders. Secondly, because of the objective conditions, the patients were not followed up outside of hospital. And we did not study the relationship between IL-6/LY with the long-term outcomes. Thirdly, our sample size was small. Therefore, prospective clinical studies with larger population were needed.

## **5. Conclusion**

In conclusion, the elevated IL-6/LY was an independent risk factor for in-hospital mortality and the development of MODS in severe COVID-19 patients. The dynamic

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change of IL-6/LY was associated with the severity of the disease, which could predict the rapid progression and bad prognosis of COVID-19. Thus, more intensive attention should be paid to the immune dysregulation and systemic inflammatory response in severe case with COVID-19.

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### **Declaration of Competing Interest**

The authors declared that there is no conflict of interest.

### **CRedit authorship contribution statement**

**Hong Li:** Conceptualization, writing- original draft preparation. **Xiaoyan Chang:** Methodology, Resources. **Boyi Yang:** Project administration, writing-Review and Editing. **Jiabao Huang:** Investigation, data curation. **Wen Pan:** Data collection, validation. **Zhilong Si:** Formal analysis and software. **Cuntai Zhang:** Supervision. All authors read and approved the final manuscript.

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### Figure legends

Figure 1. The effectiveness of IL-6/LY and NLR predictor for poor prognosis of COVID-19 by ROC curves.

(A) ROC curves of IL-6/LY and NLR for in-hospital mortality (AUC=0.919, 95% CI, 0.887-0.951,  $P<0.001$ ; AUC=0.882, 95% CI, 0.844-0.920,  $P<0.001$ ). (B) ROC curves of IL-6/LY and NLR for MODS development (AUC=0.900, 0.863-0.937,  $P<0.001$ ; AUC=0.869, 95% CI, 0.829-0.909,  $P<0.001$ ).

IL-6/LY: interleukin-6 to lymphocyte ratio; NLR: neutrophil to lymphocyte ratio; COVID-19: coronavirus disease 2019; ROC: receiver operating characteristic curve; AUC: area under the curve; CI: confidence interval; MODS: multiple organ dysfunction syndrome.

Figure 2. Kaplan-Meier cumulative survival curves for COVID-19 patients with in-hospital mortality and developed MODS according to the cutoff value of IL-6/LY.

(A) Kaplan-Meier survival curves of in-hospital mortality (log-rank test:  $P<0.001$ ). (B) Kaplan-Meier survival curves of developed MODS (log-rank test:  $P<0.001$ ).

COVID-19: coronavirus disease 2019; MODS: multiple organ dysfunction syndrome; IL-6/LY: interleukin-6 to lymphocyte ratio.

Figure 3. The correlation between IL-6/LY and MuLBSTA score ( $r=0.137$ ,  $P=0.031$ ).

IL-6/LY: interleukin-6 to lymphocyte ratio.

Figure 4. Kinetic analysis of LY, LY%, IL-6 and IL-6/LY in COVID-19 patients.

The counts of LY (A), LY% (B), IL-6 (C), and IL-6/LY (D) in the peripheral blood of non-ICU COVID-19 patients (blue line) and ICU COVID-19 patients (red line) were

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analyzed at different time points during the time of hospitalization. Error bars, mean  $\pm$  SE; \*P<0.050.

LY: lymphocyte; LY%: lymphocyte percentage; IL-6: interleukin-6; IL-6/LY: interleukin-6 to lymphocyte ratio; ICU: intensive care unit; COVID-19: coronavirus disease 2019.

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## Highlights

1. Our study described the characteristic of patients between high IL-6/LY group and low IL-6/LY group in Tongji Hospital of Huazhong University of Science and Technology.
2. This was the first analysis to investigate the value of IL-6/LY, an new immune inflammation-based prognostic index based on IL-6 and lymphocyte counts, to predict in-hospital death and MODS in patients with COVID-19.
- 3 Our study showed that high IL-6/LY group has a grester risk in adverse outcomes according to the Kaplan-Meier analysis. It might be helpful for for clinical risk assessment.
4. Our results suggested that the dynamic change of IL-6/LY was associated with the severity of the disease, which could predict the rapid progression and bad prognosis of COVID-19. Thus, more intensive attention should be paid to the immune dysregulation and systemic inflammatory response in severe case with COVID-19.

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**CRedit authorship contribution statement**

**Hong Li:** Conceptualization, writing- original draft preparation. **Xiaoyan Chang:** Methodology, Resources. **Boyi Yang:** Project administration, writing-Review and Editing. **Jiabao Huang:** Investigation, data curation. **Wen Pan:** Data collection, validation. **Zhilong Si:** Formal analysis and software. **Cuntai Zhang:** Supervision. All authors read and approved the final manuscript.