Systemic Immune-Inflammatory Index predicts prognosis of patients with COVID-19: a retrospective study

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Research

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Abstract

Background Our study aimed to investigate the prognostic value of a novel inflammatory index, systemic immune-inflammation index (SII), with the clinical outcomes of patients infected with coronavirus disease 2019 (COVID-19).

Methods We evaluated a cohort study of COVID-19 patients (18–95 years old) in Tongji Hospital of Huazhong University of Science and Technology from January 28th 2020 to February 29th 2020. The enrolled patients were divided into two groups (including low-SII group and high-SII group) according to the cut-off point which is analyzed by receiver operating characteristic (ROC) curve. Univariate and multivariate COX regression analysis were performed to identify the factors associated with the outcomes of patients with COVID-19 infection. The primary and secondary outcome were in-hospital mortality and the development of acute respiratory distress syndrome (ARDS), respectively.

Results A number of 326 adult patients (43.87% males, 61.22 ± 0.86 years) were enrolled in the final analyses. There were 147 cases (45.09%) died in hospital and 116 patients (35.58%) developed ARDS. ROC curve analysis indicated that the SII had a greater prediction accuracy in predicting the in-hospital mortality (area under the curve [AUC] = 0.789, sensitivity = 69.90%, specificity = 70.80%) and the development of ARDS (AUC = 0.736, sensitivity = 67.80%, specificity = 71.10%). Kaplan-Meier analysis revealed that patients in high-SII group had a greater risk of adverse clinical outcomes (all $P < 0.001$). The multivariate Cox regression analysis indicated that elevated SII was found as the risk predictor of in-hospital mortality (hazard ratio [HR] = 2.839, 95% confidence interval [CI] = 1.116–7.222, $P = 0.028$) and the developed ARDS (HR = 6.832, 95%CI = 2.583–18.074, $P < 0.001$). Additional significant independent predictor for adverse outcomes was the lymphocyte proportion. What's more, it suggests that the invasive mechanical ventilation performed in the early stage of the disease progression may be beneficial for patients.

Conclusion SII, a novel biomarker, might be a remarkable prognostic indicator to assess the in-hospital mortality and the development of ARDS in patients with COVID-19 and help for clinical risk assessment.

Introduction

Since December 2019, the coronavirus disease 2019 (COVID-19) has caused rapid outbreak in worldwide [1]. Because of the present epidemic situation, COVID-19 has been declared as a global pandemic by World Health Organization (WHO) [2]. The raging pneumonia has affected dozens of countries and regions and constructed a serious threat to human life and healthy. By May 14, 2020, total number of the globally confirmed patients with COVID-19 reached to 4,248,389 with 294,046 (6.65%) deaths [3].

Severe Acute Respiratory Syndrome Coronavirus − 2 (SARS-CoV-2), the pathogens of COVID-19, belongs to the β genus CoV. The other two known β-CoVs are severe acute respiratory syndrome-CoV (SARS-CoV) and Middle East Respiratory Syndrome-CoV (MERS-CoV), which caused to potentially fatal respiratory infections [4]. Comparing to SARS-CoV and MERS-CoV, the new virus caused relative lower mortality rate,

however, it is much more infectious [5]. The primary way that SARS-CoV-2 appears to spread is mainly by close person-to-person contact via droplets [6]. The clinical features of COVID-19 covered from asymptomatic or mild symptoms, to severe cases with acute respiratory distress syndrome (ARDS) or organ failure [7]. The underlying mechanism of the disease is still unclear. Preliminary studies showed that system inflammatory response played an important role in the progression of the disease [8, 9]. According to Matthew Zirui Tay et al research, for the immune system damage and the uncontrolled inflammatory response brought to human, COVID-19 could cause damage and functional impairment of major organs [10]. Therefore, it is essential to find sensitive biomarkers, which associate with the inflammatory status and are predictive for the prognosis of COVID-19 patients.

Recently, an innovative predictable marker named systemic immune-inflammation index (SII) was proposed [11]. SII, on the basis of lymphocyte, neutrophil and platelet counts, is an inflammation-related indicator and can reflect the immune and inflammation status of organism [12]. Previous studies have indicated SII to be predictive factors for prognosis of tumors and other inflammatory diseases [13, 14]. However, there are few reports about the role of SII in reflecting the inflammatory situation and predicting the prognosis of patients with COVID-19. Hence, the present study investigated the relationship between SII and the severity of COVID-19 disease and hope to make a contribution to clinical work.

Materials And Methods

Study design and Subjects

This retrospective cohort study enrolled 326 adult patients aged 18 to 95 who were diagnosed with COVID-19 in Sino-French New City Branch of TongJi Hospital of Huazhong University of Science and Technology from January 28th 2020 to February 29th 2020. Cases were diagnosed with COVID-19 based on the interim guidance from WHO [15]. Patients were excluded if they were 1) cases of juveniles (aged below 18 years old); 2) diagnosed as suspected cases; 3) or died during 24 hours after admission to hospital. Participants were assigned to two groups: low-SII group (190 cases) and high-SII group (136 cases).

The study was reviewed and approved by the Ethics Committee at the hospital (TJ-IRB20200362) and in accordance with the Helsinki Declaration. The requirement for Written informed consent was waived by the Ethics Commission of the designated hospital for COVID-19 treatment due to the outbreak of this infectious disease.

Clinical Data collection

Data on demographic characteristics, previous history, symptoms and vital signs at admission, days of hospitalization, coexisted infection, laboratory parameters, radiological examinations, comorbidities, treatment and outcomes were collected retrospectively from the electronic medical records system. Laboratory parameters included complete blood count, coagulation function, liver and kidney function,

lipid profile, blood electrolytes, cardiac function, immunoglobulins, inflammatory factors. All data were archived onto a local server and reviewed by trained physicians.

The primary and secondary outcomes were in-hospital mortality and the developed ARDS, respectively. ARDS induced by COVID-19 infection was defined according to the guidance of WHO [15], which is 1) within 1 week, patient developed new onset or aggravated symptoms on the basis of the existing respiratory system injury; 2) chest imaging suggested an unexplained decrease in pulmonary transmittance; 3) the respiratory failure developed dramatically for some unclear reason; 4) with oxygenation impairment in adults.

Statistical analysis

SII was calculated with the formula: SII = platelet counts × neutrophil counts / lymphocyte counts [11]. Continuous variables were expressed as mean ± standard error, while categorical variables were expressed as frequencies and percentages. Statistical comparisons between groups were performed using the independent group t test or the Mann-Whitney U test depending on parametric or non-parametric values for continuous variables. Chi-square test was conducted to compare the different categorical variables. A receiver operating characteristic (ROC) curve analysis was adopted to determine the optimal cut-off point for SII. The Kaplan-Meier analysis was performed to construct the survival curve and the log-rank test was used to compare the differences. Univariate and multivariate analyses were performed using COX proportional hazard regression model. Clinical factors probably associated with prognosis [16, 17] and variables with $p < 0.10$ in univariate analysis were included for stepwise multivariate regression analysis. Hazard ratios (HR) value and 95% confidence interval (CI) were further calculated. P value < 0.05 was considered a statistically significant difference. All data were statistically analyzed using SPSS 22.0 and Graphpad 6.0 software.

Results

Demographic and clinical characteristics of the study population

A total of 326 participants (43.87% males, 61.22 ± 0.86 years old) with SARS-CoV-2 were finally included in this study. Baseline characteristics of the patients were divided into two groups according to the cut-off value determined in ROC curve: high-SII group (136cases, 36.76%, 66.43 ± 1.09 years old) and low-SII group (190cases, 48.95% males, 57.49 ± 1.18 years old).

In Table 1, diabetes mellitus was the most common comorbidity in high-SII group, followed by hypertension and coronary heart disease. The common symptoms on admission presented the significant differences between two groups in dyspnea (75.74% vs 47.37%, $P < 0.001$), chest distress (37.50% vs 15.26%, $P < 0.001$), chest pain (12.50% vs 3.68%, $P = 0.003$) and consciousness disorders (8.09% vs 2.11%, $P = 0.011$). Most high-SII group patients used arbidol for antiviral therapy and the difference was statistically significant (62.50% vs 26.84%, $P < 0.001$). Followed by oseltamivir (2.94% vs 1.58%, $P = 0.403$) and lopinavir/ritonavir (5.15% vs 4.21%, $P = 0.691$). Meanwhile, low-SII group patients

received most combined antiviral therapy (40.53% vs 26.47%, $P = 0.008$). More people in high-SII group were treated with glucocorticoids (GCS) ($P < 0.001$) and immune globulin ($P = 0.002$). The application of oxygen therapy (noninvasive mechanical ventilation and invasive mechanical ventilation) and continuous renal replace therapy were adopted more in high-SII group patients ($P < 0.001$, respectively). Furthermore, we found that patients in high-SII group with a higher chance of severe complications, such as multiple organ dysfunction syndrome, ARDS, major cardiovascular adverse events, disseminated intravascular coagulation, secondary infection, sepsis-shock and acidosis ($P < 0.001$, respectively).

Table 1
Demographics and clinical characteristics of study population

	All patients (n = 326)	SII < 1293.11 (n = 190)	SII ≥ 1293.11 (n = 136)	P
Gender, (male), n (%)	143 (43.87%)	93 (48.95%)	50 (36.76%)	0.029
Age, year	61.22 ± 0.86	57.49 ± 1.18	66.43 ± 1.09	< 0.001
Smoking, n (%)	41 (12.58%)	11 (5.79%)	30 (22.06%)	< 0.001
Comorbidity, n (%)				
CHD	46 (14.11%)	15 (7.89%)	31 (22.79%)	< 0.001
Hypertension	115 (35.28%)	54 (28.42%)	61 (44.85%)	0.002
Diabetes	111 (34.05%)	45 (23.68%)	66 (48.53%)	< 0.001
Chronic lung disease	26 (7.98%)	11 (5.79%)	15 (11.03%)	0.085
Chronic kidney disease	8 (2.45%)	4 (2.11%)	4 (2.94%)	0.631
Chronic liver disease	14 (4.29%)	9 (4.74%)	5 (3.68%)	0.641
Autoimmune diseases	8 (2.45%)	6 (3.16%)	2 (1.47%)	0.332
Tumor	19 (5.83%)	14 (7.37%)	5 (3.68%)	0.161
Cerebrovascular disease	17 (5.21%)	8 (4.21%)	9 (6.62%)	0.335
Gastrointestinal disease	16 (4.91%)	6 (3.16%)	10 (7.35%)	0.084
Time of illness onset, days	10.81 ± 0.34	10.14 ± 0.42	11.75 ± 0.55	0.018
Hospital admission, days	14.50 ± 0.42	16.21 ± 0.51	12.10 ± 0.66	< 0.001
Initial common symptoms, n (%)				
Fever	288(88.34%)	171 (90.00%)	117 (86.03%)	0.271
Cough	191(58.59%)	121 (63.68%)	70 (51.47%)	0.027
Sputum	121(37.12%)	68 (35.79%)	53 (38.97%)	0.558

Abbreviations: Mean ± SEM and n (%) are reported for continuous and categorical variables, respectively. SEM – standard error of the mean. *SII* systemic immune-inflammation index, *CHD* coronary heart disease, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HR* heart rate, *SPO_2* surplus pulse O_2, *ACEI/ARB* angiotensin-converting enzyme inhibitor / angiotensin II receptor blocker, *GCS* glucocorticoid, *NMV* noninvasive mechanical ventilation; *IMV* invasive mechanical ventilation; *CRRT* continuous renal replacement therapy, *ECMO* extracorporeal membrane oxygenation, *MODS* multiple organ dysfunction syndrome, *ARDS* acute respiratory distress syndrome, *DIC* disseminated intravascular coagulation, *MACE* major adverse cardiac events, *VMC* viral myocarditis, *AKI* acute kidney injury, *GIB* gastrointestinal bleeding

	All patients (n = 326)	SII < 1293.11 (n = 190)	SII ≥ 1293.11 (n = 136)	P
Pharyngalgia	19 (5.83%)	11 (5.79%)	8 (5.88%)	0.932
Dyspnea	193(59.20%)	90 (47.37%)	103 (75.74%)	< 0.001
Fatigue	148(45.40%)	76 (40.00%)	72 (52.94%)	0.021
Myalgia	97 (29.75%)	55 (28.95%)	42 (30.88%)	0.706
Stomachache	31 (9.51%)	17 (8.95%)	14 (10.29%)	0.683
Anorexia	92 (28.22%)	49 (25.79%)	43 (31.62%)	0.249
Diarrhea	103(31.60%)	61 (32.11%)	42 (30.88%)	0.815
Disgusting vomits	47 (14.42%)	30 (15.79%)	17 (12.50%)	0.404
Chest distress	80 (24.54%)	29 (15.26%)	51 (37.50%)	< 0.001
Chest pain	24 (7.36%)	7 (3.68%)	17 (12.50%)	0.003
Palpitation	32 (9.82%)	14 (7.37%)	18 (13.24%)	0.079
Dizziness	32 (9.82%)	19 (10.00%)	13 (9.56%)	0.895
Headache	61 (18.71%)	34 (17.89%)	27 (19.85%)	0.655
Consciousness disorders	15 (4.60%)	4 (2.11%)	11 (8.09%)	0.011
Temperature, ℃	37.36 ± 0.05	37.23 ± 0.07	37.55 ± 0.09	< 0.001
SBP (mmHg)	129.98 ± 1.20	127.95 ± 1.56	132.81 ± 1.84	0.042
DBP (mmHg)	81.56 ± 1.87	79.71 ± 1.19	84.12 ± 4.14	0.242
HR (beats/min)	96.43 ± 1.09	94.66 ± 1.38	98.89 ± 1.76	0.083
SPO_2, %	90.30 ± 0.62	94.19 ± 0.49	85.16 ± 1.15	< 0.001
Pharmacotherapy in hospital, n (%)				
Antibiotic therapy	301(92.33%)	171 (90.00%)	130 (95.59%)	0.062
Antiviral therapy				

Abbreviations: Mean ± SEM and n (%) are reported for continuous and categorical variables, respectively. SEM – standard error of the mean. *SII* systemic immune-inflammation index, *CHD* coronary heart disease, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HR* heart rate, *SPO_2* surplus pulse O_2, *ACEI/ARB* angiotensin-converting enzyme inhibitor / angiotensin II receptor blocker, *GCS* glucocorticoid, *NMV* noninvasive mechanical ventilation; *IMV* invasive mechanical ventilation; *CRRT* continuous renal replacement therapy, *ECMO* extracorporeal membrane oxygenation, *MODS* multiple organ dysfunction syndrome, *ARDS* acute respiratory distress syndrome, *DIC* disseminated intravascular coagulation, *MACE* major adverse cardiac events, *VMC* viral myocarditis, *AKI* acute kidney injury, *GIB* gastrointestinal bleeding

	All patients (n = 326)	SII < 1293.11 (n = 190)	SII ≥ 1293.11 (n = 136)	P
Arbidol	136 (56.44%)	51 (26.84%)	85 (62.50%)	< 0.001
Oseltamivir	7 (2.15%)	3 (1.58%)	4 (2.94%)	0.403
Lopinavir and Ritonavir	15 (4.60%)	8 (4.21%)	7 (5.15%)	0.691
Combined antiviral therapy	113 (34.66%)	77 (40.53%)	36 (26.47%)	0.008
Interferon therapy	91 (27.91%)	55 (28.95%)	36 (26.47%)	0.623
ACEI/ARB	9 (2.76%)	6 (3.16%)	3 (2.21%)	0.605
GCS	224 (68.71%)	108 (56.84%)	116 (85.29%)	< 0.001
Days of GCS use, days	4.82 ± 0.31	4.02 ± 0.38	5.93 ± 0.49	0.001
Immune globulin	130 (39.88%)	62 (32.63%)	68 (50.00%)	0.002
Oxygen therapy in hospital, n (%)				
NMV	155 (47.55%)	57 (30.00%)	98 (72.06%)	< 0.001
IMV	86 (26.38%)	21 (11.05%)	65 (47.79%)	< 0.001
Time of starting IMV, days	1.79 ± 0.22	0.82 ± 0.21	3.15 ± 0.41	< 0.001
Other treatment in hospital, n (%)				
CRRT	19 (5.83%)	5 (2.63%)	14 (10.29%)	0.004
Time of starting CRRT, days	0.75 ± 0.19	0.24 ± 0.11	1.47 ± 0.41	< 0.001
ECMO	5 (1.53%)	2 (1.05%)	3 (2.21%)	0.403
Time of starting ECMO, days	0.15 ± 0.09	0.09 ± 0.08	0.24 ± 0.19	0.013
Complications, n (%)				
Death	147 (45.09%)	45 (23.68%)	102 (75.00%)	< 0.001
MODS	139 (42.64%)	43 (22.63%)	96 (70.59%)	< 0.001
ARDS	116 (35.58%)	38 (20.00%)	78 (57.35%)	< 0.001

Abbreviations: Mean ± SEM and n (%) are reported for continuous and categorical variables, respectively. SEM – standard error of the mean. *SII* systemic immune-inflammation index, *CHD* coronary heart disease, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HR* heart rate, *SPO_2* surplus pulse O_2, *ACEI/ARB* angiotensin-converting enzyme inhibitor / angiotensin II receptor blocker, *GCS* glucocorticoid, *NMV* noninvasive mechanical ventilation; *IMV* invasive mechanical ventilation; *CRRT* continuous renal replacement therapy, *ECMO* extracorporeal membrane oxygenation, *MODS* multiple organ dysfunction syndrome, *ARDS* acute respiratory distress syndrome, *DIC* disseminated intravascular coagulation, *MACE* major adverse cardiac events, *VMC* viral myocarditis, *AKI* acute kidney injury, *GIB* gastrointestinal bleeding

	All patients (n = 326)	SII < 1293.11 (n = 190)	SII ≥ 1293.11 (n = 136)	P
DIC	75 (23.01%)	24 (12.63%)	51 (37.50%)	< 0.001
Secondary infection	42 (12.88%)	13 (6.84%)	29 (21.32%)	< 0.001
MACE	81 (24.85%)	21 (11.05%)	60 (44.12%)	< 0.001
VMC	41 (12.58%)	11 (5.79%)	30 (22.06%)	< 0.001
AKI	53 (16.26%)	17 (8.95%)	36 (26.47%)	< 0.001
Rhabdomyolysis	7 (2.15%)	1 (0.53%)	6 (4.41%)	0.017
Spesis shock	52 (15.95%)	15 (7.89%)	37 (27.21%)	< 0.001
Myelosuppression	79 (24.23%)	23 (12.11%)	56 (41.18%)	< 0.001
Acidosis	64 (19.63%)	13 (6.84%)	51 (37.50)	< 0.001
Low T3 syndrome	15 (4.60%)	2 (1.05%)	13 (9.56%)	< 0.001
Cerebrovascular accident	5 (1.53%)	3 (1.58%)	2 (1.47%)	0.937
GIB	14 (4.29%)	5 (2.63%)	9 (6.62%)	0.080
Liver function impairment	81 (24.85%)	33 (17.37%)	48 (35.29%)	< 0.001
Pneumothorax	9 (2.76%)	3 (1.58%)	6 (4.41%)	0.124

Abbreviations: Mean ± SEM and n (%) are reported for continuous and categorical variables, respectively. SEM – standard error of the mean. *SII* systemic immune-inflammation index, *CHD* coronary heart disease, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HR* heart rate, SPO_2 surplus pulse O_2, *ACEI/ARB* angiotensin-converting enzyme inhibitor / angiotensin II receptor blocker, *GCS* glucocorticoid, *NMV* noninvasive mechanical ventilation; *IMV* invasive mechanical ventilation; *CRRT* continuous renal replacement therapy, *ECMO* extracorporeal membrane oxygenation, *MODS* multiple organ dysfunction syndrome, *ARDS* acute respiratory distress syndrome, *DIC* disseminated intravascular coagulation, *MACE* major adverse cardiac events, *VMC* viral myocarditis, *AKI* acute kidney injury, *GIB* gastrointestinal bleeding

Laboratory and radiological imaging findings

As shown in Table 2, blood routine tests showed that the levels of white blood cell count, neutrophil, neutrophil%, monocyte%, hemoglobin and platelet were higher in high-SII group compared with low-SII group ($P < 0.001$, respectively). On the contrary, the lymphocyte value and lymphocyte% value were much lower in high-SII group ($P < 0.001$, respectively). Biochemical examining reports indicated that there was significant difference in cardiac parameters, liver function index, renal function index between the two groups ($P < 0.001$, respectively). The patients in high-SII group were more likely to have higher concentration of immuno-inflammatory indices (such as high-sensitivity C-reactive protein,

ferritin,procalcitonin, cytokines etc.) ($P < 0.001$, respectively). Besides, there were also significant differences in blood coagulation function between the two groups ($P < 0.050$), except for fibrinogen.

Table 2
Laboratory, and radiographic characteristics of study population

	All patients (n = 326)	SII < 1293.11 (n = 190)	SII ≥ 1293.11 (n = 136)	P
Blood routine index, 10^9/L				
WBC, 10^9/L	7.55 ± 0.27	5.16 ± 0.18	10.90 ± 0.46	< 0.001
Neutrophil%, %	75.95 ± 0.83	67.10 ± 0.96	88.32 ± 0.48	< 0.001
Neutrophil, 10^9/L	6.21 ± 0.27	3.65 ± 0.18	9.79 ± 0.45	< 0.001
Lymphocyte%, %	16.14 ± 0.63	22.88 ± 0.74	6.73 ± 0.33	< 0.001
Lymphocyte, 10^9/L	0.90 ± 0.04	1.11 ± 0.06	0.61 ± 0.03	< 0.001
Monocyte%, %	6.87 ± 0.22	8.48 ± 0.29	4.63 ± 0.23	< 0.001
Monocyte, 10^9/L	0.47 ± 0.02	0.43 ± 0.02	0.47 ± 0.03	0.291
Hemoglobin, mg/dL	124.74 ± 1.33	122.19 ± 1.75	128.30 ± 2.01	0.027
Platelet, 10^9/L	194.05 ± 5.03	183.87 ± 6.53	208.06 ± 7.73	< 0.001
Coagulation function				
PT, sec	15.32 ± 0.33	15.09 ± 0.55	15.64 ± 0.22	< 0.001
PTA, %	87.09 ± 3.03	93.98 ± 5.04	77.56 ± 1.52	< 0.001
FIB, g/L	4.90 ± 0.10	4.74 ± 0.12	5.13 ± 0.19	0.110
APTT, sec	42.23 ± 0.75	43.80 ± 1.17	40.04 ± 0.66	0.012
D-dimer, ug/mL FEU	4.78 ± 0.41	2.59 ± 0.38	7.92 ± 0.75	< 0.001
FDP, ug/mL	30.46 ± 3.85	15.30 ± 3.47	51.76 ± 7.15	< 0.001
Biochemical indexes				
CTnI, pg/ml	604.50 ± 195.76	511.62 ± 191.65	712.21 ± 360.45	< 0.001

Mean ± SEM and n (%) are reported for continuous and categorical variables, respectively. NA-not available. Abbreviations: *SII* systemic immune-inflammation index, *WBC* white blood cell count, *PT* prothrombin time, *PTA* prothrombin activity, *FIB* fibrinogen, *APTT* activated partial thromboplastin time, *FDP* fibrinogen degradation product, *CTnI* cardiac troponin I, *NT-proBNP* N-terminal pro brain natriuretic peptide, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *TBiL* total bilirubin, *TC* total cholesterol, *TG* triglyceride, *HDL-C* high density lipoprotein cholesterol, *LDL-C* low density lipoprotein cholesterol, *CK* creatine kinase, *LDH* lactate dehydrogenase, *eGFR* estimated glomerular filtration rate, *$HCO3^-$* bicarbonate ion, *Hs-CRP* high-sensitivity C-reactive protein, *ESR* erythrocyte sedimentation rate, *PCT* procalcitonin, *Ig A* immunoglobulin A, *Ig G* immunoglobulin G, *Ig M* immunoglobulin M, *IL-1β* interleukin-1, *IL-2R* interleukin-2 receptor, *IL-6* interleukin-6, *IL-8* interleukin-8, *IL-10* interleukin-10, *TNF-α* tumor necrosis factor α, *HIV* human immunodeficiency virus

	All patients (n = 326)	SII < 1293.11 (n = 190)	SII ≥ 1293.11 (n = 136)	P
NT-proBNP, pg/ml	2420.50 ± 511.69	1420.68 ± 432.13	3532.36 ± 960.08	< 0.001
ALT, u/L	37.25 ± 3.49	36.74 ± 5.69	37.96 ± 2.72	< 0.001
AST (u/L)	47.97 ± 5.32	47.69 ± 8.90	48.34 ± 3.06	< 0.001
Albumin, g/L	33.31 ± 0.30	35.22 ± 0.37	30.67 ± 0.41	< 0.001
Globulin, g/L	34.14 ± 0.35	32.86 ± 0.49	35.09 ± 0.47	< 0.001
TBiL, umol/L	15.68 ± 2.23	13.46 ± 2.74	18.76 ± 3.74	< 0.001
TC, mmol/l	3.57 ± 0.05	3.61 ± 0.07	3.51 ± 0.08	0.288
TG, mmol/L	1.65 ± 0.07	1.54 ± 0.12	1.77 ± 0.08	< 0.001
HDL-C, mmol/l	0.85 ± 0.02	0.93 ± 0.03	0.76 ± 0.03	< 0.001
LDL-C, mmol/l	2.18 ± 0.06	2.21 ± 0.07	2.15 ± 0.11	0.653
CK, u/L	253.06 ± 37.77	209.91 ± 37.50	304.14 ± 69.40	< 0.001
LDH, u/L	425.99 ± 16.16	351.32 ± 20.14	529.97 ± 23.98	< 0.001
Potassium, mmol/L	4.31 ± 0.04	4.22 ± 0.04	4.43 ± 0.06	0.003
Sodium, mmol/L	140.08 ± 0.34	140.10 ± 0.41	140.05 ± 0.57	0.846
Calcium, mmol/L	2.36 ± 0.01	2.34 ± 0.02	2.38 ± 0.02	0.082
Urea, mmol/L	7.67 ± 0.44	6.34 ± 0.62	9.52 ± 0.58	< 0.001
Creatinine, mmol/L	95.16 ± 4.95	89.83 ± 5.79	102.57 ± 8.65	< 0.001
eGFR, ml/min/1.73 m^2/L	82.35 ± 1.52	87.98 ± 1.99	74.46 ± 2.17	< 0.001
HCO_3^-, mmol/L	22.85 ± 0.19	23.46 ± 0.24	21.99 ± 0.32	< 0.001
Immuno-inflammatory indices				

Mean ± SEM and n (%) are reported for continuous and categorical variables, respectively. NA-not available. Abbreviations: *SII* systemic immune-inflammation index, *WBC* white blood cell count, *PT* prothrombin time, *PTA* prothrombin activity, *FIB* fibrinogen, *APTT* activated partial thromboplastin time, *FDP* fibrinogen degradation product, *CTnI* cardiac troponin I, *NT-proBNP* N-terminal pro brain natriuretic peptide, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *TBiL* total bilirubin, *TC* total cholesterol, *TG* triglyceride, *HDL-C* high density lipoprotein cholesterol, *LDL-C* low density lipoprotein cholesterol, *CK* creatine kinase, *LDH* lactate dehydrogenase, *eGFR* estimated glomerular filtration rate, *HCO3*$^-$ bicarbonate ion, *Hs-CRP* high-sensitivity C-reactive protein, *ESR* erythrocyte sedimentation rate, *PCT* procalcitonin, *Ig A* immunoglobulin A, *Ig G* immunoglobulin G, *Ig M* immunoglobulin M, *IL-1β* interleukin-1, *IL-2R* interleukin-2 receptor, *IL-6* interleukin-6, *IL-8* interleukin-8, *IL-10* interleukin-10, *TNF-α* tumor necrosis factor α, *HIV* human immunodeficiency virus

	All patients (n = 326)	SII < 1293.11 (n = 190)	SII ≥ 1293.11 (n = 136)	P
Hs-CRP, mg/L	76.31 ± 3.95	53.29 ± 4.27	108.15 ± 6.38	< 0.001
ESR, mm/H	38.78 ± 1.55	33.38 ± 1.92	45.95 ± 2.42	0.024
Ferritin, ug/L	1483.87 ± 188.08	1404.84 ± 305.74	1598.54 ± 127.02	< 0.001
PCT, ng/mL	1.39 ± 0.47	1.051 ± 0.49	1.90 ± 0.89	< 0.001
Ig A, g/L	2.40 ± 0.09	2.27 ± 0.11	2.57 ± 0.15	0.106
Ig G, g/L	12.43 ± 0.29	11.95 ± 0.37	13.07 ± 0.47	0.061
Ig M, g/L	1.06 ± 0.04	1.07 ± 0.06	1.05 ± 0.07	0.462
Alexin C3, g/L	0.83 ± 0.02	0.86 ± 0.02	0.80 ± 0.02	0.046
Alexin C4, g/L	0.24 ± 0.01	0.26 ± 0.01	0.21 ± 0.01	< 0.001
IL-1β, pg/ml	5.93 ± 0.26	5.83 ± 0.25	6.08 ± 0.54	0.313
IL-2R, pg/ml	1008.15 ± 51.85	829.88 ± 65.14	1267.62 ± 78.46	< 0.001
IL-6, pg/ml	113.32 ± 31.35	78.74 ± 34.47	163.64 ± 58.25	< 0.001
IL-8, pg/ml	68.94 ± 30.36	32.12 ± 4.93	122.55 ± 74.10	< 0.001
IL-10, pg/ml	12.44 ± 1.25	10.12 ± 0.90	15.81 ± 2.76	< 0.001
TNF-α, pg/ml	11.70 ± 0.63	11.24 ± 0.83	12.36 ± 0.98	< 0.001
Pathogen infection, n (%)				
Influenza virus A	66 (20.25%)	37 (19.47%)	29 (21.32%)	0.682
Influenza virus B	14 (4.29%)	7 (3.68%)	7 (5.15%)	0.521
Sendai virus	3 (0.92%)	2 (1.05%)	1 (0.74%)	0.767
Mycoplasma	2 (0.61%)	2 (1.05%)	0 (0.00%)	0.230
Chlamydia	0 (0.00%)	0 (0.00%)	0 (0.00%)	NA

Mean ± SEM and n (%) are reported for continuous and categorical variables, respectively. NA-not available. Abbreviations: *SII* systemic immune-inflammation index, *WBC* white blood cell count, *PT* prothrombin time, *PTA* prothrombin activity, *FIB* fibrinogen, *APTT* activated partial thromboplastin time, *FDP* fibrinogen degradation product, *CTnI* cardiac troponin I, *NT-proBNP* N-terminal pro brain natriuretic peptide, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *TBiL* total bilirubin, *TC* total cholesterol, *TG* triglyceride, *HDL-C* high density lipoprotein cholesterol, *LDL-C* low density lipoprotein cholesterol, *CK* creatine kinase, *LDH* lactate dehydrogenase, *eGFR* estimated glomerular filtration rate, *$HCO3^-$* bicarbonate ion, *Hs-CRP* high-sensitivity C-reactive protein, *ESR* erythrocyte sedimentation rate, *PCT* procalcitonin, *Ig A* immunoglobulin A, *Ig G* immunoglobulin G, *Ig M* immunoglobulin M, *IL-1β* interleukin-1, *IL-2R* interleukin-2 receptor, *IL-6* interleukin-6, *IL-8* interleukin-8, *IL-10* interleukin-10, *TNF-α* tumor necrosis factor α, *HIV* human immunodeficiency virus

	All patients (n = 326)	SII < 1293.11 (n = 190)	SII ≥ 1293.11 (n = 136)	P
Adenovirus	1 (0.31%)	0 (0.00%)	1 (0.74%)	0.236
Hepatitis B virus	15 (4.60%)	8 (4.21%)	7 (5.15%)	0.698
Hepatitis C virus	4 (1.23%)	2 (1.05%)	2 (1.47%)	0.735
HIV	1 (0.31%)	0 (0.00%)	1 (0.74%)	0.236
Syphilis	4 (1.23%)	2 (1.05%)	2 (1.47%)	0.735
Co-infection	14 (4.29%)	11 (5.79%)	3 (2.21%)	0.116
Radiographic findings, n(%)				
Unilateral pneumonia	9 (2.76%)	8 (4.21%)	1 (0.74%)	0.058
Bilateral pneumonia	200 (61.35%)	115 (60.53%)	85 (62.50%)	0.718
Hydrothorax	18 (5.52%)	10 (5.26%)	8 (5.88%)	0.809
Ground-glass opacity	176 (53.99%)	107 (56.32%)	69 (50.74%)	0.319
Consolidation	15 (4.60%)	8 (4.21%)	7 (5.15%)	0.698
MuLBTSA score	7.87 ± 0.21	7.75 ± 0.25	8.02 ± 0.35	0.009

Mean ± SEM and n (%) are reported for continuous and categorical variables, respectively. NA-not available. Abbreviations: *SII* systemic immune-inflammation index, *WBC* white blood cell count, *PT* prothrombin time, *PTA* prothrombin activity, *FIB* fibrinogen, *APTT* activated partial thromboplastin time, *FDP* fibrinogen degradation product, *CTnI* cardiac troponin I, *NT-proBNP* N-terminal pro brain natriuretic peptide, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *TBiL* total bilirubin, *TC* total cholesterol, *TG* triglyceride, *HDL-C* high density lipoprotein cholesterol, *LDL-C* low density lipoprotein cholesterol, *CK* creatine kinase, *LDH* lactate dehydrogenase, *eGFR* estimated glomerular filtration rate, $HCO3^-$ bicarbonate ion, *Hs-CRP* high-sensitivity C-reactive protein, *ESR* erythrocyte sedimentation rate, *PCT* procalcitonin, *Ig A* immunoglobulin A, *Ig G* immunoglobulin G, *Ig M* immunoglobulin M, *IL-1β* interleukin-1, *IL-2R* interleukin-2 receptor, *IL-6* interleukin-6, *IL-8* interleukin-8, *IL-10* interleukin-10, *TNF-α* tumor necrosis factor α, *HIV* human immunodeficiency virus

ROC curve analysis

To clarify the factors that affect COVID-19 prognosis, the ROC curves was used to analyze the prognostic value. The optimized cut-off point of SII value for predicting in-hospital death was 1293.11 with the sensitivity for 69.90% and the specificity for 70.80%. The area under the curve (AUC) for death was 0.789 (95%CI = 0.739–0.840, $P < 0.001$) (Fig. 1A). Besides, in our cohort study, SII was a significantly stronger predictor of in-hospital mortality than MuLBSTA score (AUC = 0.585, 95%CI = 0.521–0.648, $P = 0.009$), The sensitivity and the specificity of SII was also improved than MuLBSTA score (sensitivity = 38.40% ,and the specificity = 80.80%) (Fig. 1A).

The best cut-off point of SII value for predicting the development of ARDS was also 1293.11, with the sensitivity for 67.80% and the specificity for 71.10%. The AUC for developing ARDS was 0.736 (95%CI = 0.679–0.794, $P < 0.001$) (Fig. 1B).

Survival analysis

The mean length of hospitalization in patients with COVID-19 was 14.50 ± 0.42 days (range from 1–33 days). In total, 147 (45.09%) people died and 116 (35.58%) patients developed ARDS during hospitalization. Kaplan-Meier survival curves show that patients with higher SII level had significantly worse in-hospital outcomes than those with lower SII level (log-rank test, all p values were < 0.001) (Fig. 2).

In our study, 86 (26.38%) people with respiratory failure were given invasive ventilation. The mean time for patients starting to be given invasive ventilation was 1.79 ± 0.22 days (range from 0–19 days). Kaplan-Meier survival curves showed that the earlier the invasive ventilation was given, the better the prognosis would be (log-rank test, $P < 0.001$) (Fig. 3).

Cox regression analysis of the factors associated with the outcomes

As shown in Table 3, the univariate Cox regression analysis showed that the HR of SII associated to in-hospital death was 4.286 (95% CI = 3.004–6.114, $P < 0.001$). We also evaluated other factors with the outcomes, such as sex, age, smoking history, comorbidities, blood routine index, serum biochemical index, coagulation function, infection-related indices and so on. The multivariate Cox regression analysis indicated that older age (HR = 1.052, 95% CI = 1.018–1.088, $P = 0.002$), lower albumin levels (HR = 0.912, 95% CI = 0.852–0.975, $P = 0.007$), lower lymphocyte proportion (HR = 0.857, 95% CI = 0.792–0.927, $P < 0.001$), higher IL-6 level (HR = 1.002, 95% CI = 1.001–1.004, $P = 0.043$), and higher SII level (≥ 1293.11) (HR = 2.839, 95% CI = 1.116–7.222, $P = 0.028$) were the risk factors for in-hospital death. Meanwhile, the treatment with glucocorticoid (HR = 0.200, 95% CI = 0.059–0.671, $P = 0.009$) was associated with lower risk of in-hospital death.

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	1.611	1.146–2.264	0.006	**1.052**	**1.018–1.088**	**0.002**
Gender (male)	2.582	1.735–3.841	< 0.001			
Smoking	2.451	1.674–3.588	< 0.001			
Comorbidity						
CHD	1.776	1.175–2.684	0.006			
Hypertension	2.009	1.450–2.782	< 0.001			
Diabetes	2.723	1.967–3.770	< 0.001			
Time of illness onset	1.036	1.009–1.063	0.008			
The use of GCS	3.168	1.956–5.132	< 0.001	**0.200**	**0.059–0.671**	**0.009**
SII	4.286	3.004–6.114	< 0.001	**2.839**	**1.116–7.222**	**0.028**
Blood routine index						
WBC	1.134	1.109–1.159	< 0.001			
Neutrophil	1.139	1.115–1.164	< 0.001			
Neutrophil%	1.096	1.077–1.116	< 0.001			
Lymphocyte	0.116	0.168–0.199	< 0.001			
Lymphocyte%	0.879	0.857–0.902	< 0.001	**0.857**	**0.792–0.927**	**< 0.001**
Monocyte	1.532	1.036–2.267	0.033			
Monocyte%	0.822	0.78–0.867	< 0.001			
Hemoglobin	0.993	0.987–0.999	0.03			
Platelet	0.994	0.992–0.996	< 0.001			
Coagulation function						

Abbreviations: *HR* hazard ratio, *CI* confidence interval, *CHD* coronary heart disease, *GCS* glucocorticoid, *NMV* noninvasive mechanical ventilation, *IMV* invasive mechanical ventilation, *WBC* white blood cell count, *PT* prothrombin time, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *TBiL* total bilirubin, *TG* triglyceride, *HDL-C* high density lipoprotein cholesterol, *LDL-C* low density lipoprotein cholesterol, *LDH* lactate dehydrogenase, *CK* creatine kinase, *eGFR* estimated glomerular filtration rate, *Hs-CRP* high-sensitivity C-reactive protein, *ESR* erythrocyte sedimentation rate, *PCT* procalcitonin, *IL-2R* interleukin-2 receptor, *IL-6* interleukin-6, *IL-8* interleukin-8, *IL-10* interleukin-10, *TNF-α* tumor necrosis factor α

Variables	Univariable			Multivariable		
	HR	95% CI	p	HR	95% CI	p
PT	1.036	1.024–1.048	< 0.001			
D-Dimmer	1.088	1.068–1.108	< 0.001			
Biochemical indexes						
ALT	1.003	1.001–1.005	< 0.001			
AST	1.002	1.001–1.003	< 0.001			
Albumin	0.872	0.845–0.899	< 0.001	**0.912**	**0.852–0.975**	**0.007**
Globulin	1.018	0.997–1.039	0.087			
TBiL	1.005	1.002–1.007	< 0.001			
TG	1.317	1.158–1.497	< 0.001			
HDL-C	0.087	0.037–0.205	< 0.001			
LDL-C	0.568	0.417–0.774	< 0.001			
CK	1.001	1.000-1.001	< 0.001			
LDH	1.002	1.001–1.002	< 0.001			
Creatinine	1.002	1.001–1.003	< 0.001			
eGFR	0.976	0.970–0.982	< 0.001			
Immuno-inflammatory indices						
Hs-CRP	1.009	1.007–1.011	< 0.001			
ESR	1.006	0.999–1.013	0.100			
Ferritin	5.521	3.588–8.497	< 0.001			
PCT	1.027	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			

Abbreviations: *HR* hazard ratio, *CI* confidence interval, *CHD* coronary heart disease, *GCS* glucocorticoid, *NMV* noninvasive mechanical ventilation, *IMV* invasive mechanical ventilation, *WBC* white blood cell count, *PT* prothrombin time, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *TBiL* total bilirubin, *TG* triglyceride, *HDL-C* high density lipoprotein cholesterol, *LDL-C* low density lipoprotein cholesterol, *LDH* lactate dehydrogenase, *CK* creatine kinase, *eGFR* estimated glomerular filtration rate, *Hs-CRP* high-sensitivity C-reactive protein, *ESR* erythrocyte sedimentation rate, *PCT* procalcitonin, *IL-2R* interleukin-2 receptor, *IL-6* interleukin-6, *IL-8* interleukin-8, *IL-10* interleukin-10, *TNF-α* tumor necrosis factor α

Variables	Univariable			Multivariable		
	HR	95% CI	p	HR	95% CI	p
IL-2R	1.001	1.000-1.001	< 0.001			
IL-6	1.001	1.000-1.001	< 0.001	**1.002**	**1.001–1.004**	**0.043**
IL-8	1.001	1.000-1.001	< 0.001			
IL-10	1.012	1.008–1.017	< 0.001			
TNF-α	1.044	1.032–1.056	< 0.001			

Abbreviations: *HR* hazard ratio, *CI* confidence interval, *CHD* coronary heart disease, *GCS* glucocorticoid, *NMV* noninvasive mechanical ventilation, *IMV* invasive mechanical ventilation, *WBC* white blood cell count, *PT* prothrombin time, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *TBiL* total bilirubin, *TG* triglyceride, *HDL-C* high density lipoprotein cholesterol, *LDL-C* low density lipoprotein cholesterol, *LDH* lactate dehydrogenase, *CK* creatine kinase, *eGFR* estimated glomerular filtration rate, *Hs-CRP* high-sensitivity C-reactive protein, *ESR* erythrocyte sedimentation rate, *PCT* procalcitonin, *IL-2R* interleukin-2 receptor, *IL-6* interleukin-6, *IL-8* interleukin-8, *IL-10* interleukin-10, *TNF-α* tumor necrosis factor α

We also evaluated the factors with the outcomes of developed ARDS. The univariate Cox regression analysis showed that the HR of SII associated to the development of ARDS was 3.836 (95% CI = 2.589–5.685, $P < 0.001$). The multivariate Cox regression analysis indicated that higher SII level (≥ 1293.11) (HR = 6.832, 95% CI = 2.583–18.074, $P < 0.001$) was the independent risk factors for developing ARDS. Nevertheless, the lymphocyte proportion (HR = 0.776, 95% CI = 0.713–0.845, $P < 0.001$) was negatively correlated with the risk of the development of ARDS (Table 4).

Table 4
Predictors of developed ARDS in univariable and multivariable Cox regression analyses.

Variables	Univariable			Multivariable		
	HR	95% CI	p	HR	95% CI	p
Age	3.33	2.055–5.398	< 0.001			
Gender (male)	2.541	1.255–5.145	0.01			
Smoking	2.109	1.353–3.288	0.001			
Comorbidity						
CHD	1.666	1.036–2.677	0.035			
Hypertension	2.160	1.498–3.115	< 0.001			
Diabetes	2.683	1.861–3.868	< 0.001			
Time of illness onset	1.005	0.972–1.039	0.784			
The use of GCS	2.927	1.726–4.965	< 0.001			
SII	3.836	2.589–5.685	< 0.001	**6.832**	**2.583–18.074**	**< 0.001**
Blood routine index						
WBC	1.131	1.103–1.160	< 0.001			
Neutrophil	1.137	1.110–1.166	< 0.001			
Neutrophil%	1.099	1.077–1.122	< 0.001			
Lymphocyte	0.103	0.056–0.190	< 0.001			
Lymphocyte%	0.877	0.852–0.904	< 0.001	**0.776**	**0.713–0.845**	**< 0.001**
Monocyte	1.404	0.868–2.270	0.167			
Monocyte%	0.808	0.761–0.859	< 0.001			
Hemoglobin	0.992	0.985–0.999	0.020			
Platelet	0.993	0.991–0.996	< 0.001			
Coagulation function						

Abbreviations: *ARDS* acute respiratory distress syndrome,*HR* hazard ratio，*CI* confidence interval，*CHD* coronary heart disease，*GCS* glucocorticoid，*NMV* noninvasive mechanical ventilation，*IMV* invasive mechanical ventilation，*WBC* white blood cell count，*PT* prothrombin time，*ALT* alanine aminotransferase，*AST* aspartate aminotransferase，*TBiL* total bilirubin，*TG* triglyceride，*HDL-C* high density lipoprotein cholesterol，*LDL-C* low density lipoprotein cholesterol，*LDH* lactate dehydrogenase，*CK* creatine kinase，*eGFR* estimated glomerular filtration rate，*Hs-CRP* high-sensitivity C-reactive protein，*ESR* erythrocyte sedimentation rate，*PCT* procalcitonin，*IL-2R* interleukin-2 receptor，*IL-6* interleukin-6，*IL-8* interleukin-8，*IL-10* interleukin-10，*TNF-α* tumor necrosis factor α

Variables	Univariable			Multivariable		
	HR	95% CI	p	HR	95% CI	p
PT	1.036	1.023–1.050	< 0.001			
D-Dimmer	1.083	1.061–1.106	< 0.001			
Biochemical indexes						
ALT	1.003	1.001–1.005	0.016			
AST	1.002	1.001–1.003	< 0.001			
Albumin	0.883	0.853–0.914	< 0.001			
Globulin	1.012	0.987–1.037	0.362			
TBiL	1.005	1.002–1.007	< 0.001			
TG	1.343	1.165–1.548	< 0.001			
HDL-C	0.125	0.047–0.334	< 0.001			
LDL-C	0.574	0.402–0.820	0.002			
CK	1.001	1.000-1.001	0.012			
LDH	1.002	1.001–1.002	< 0.001			
CR	1.002	1.001–1.003	< 0.001			
eGFR	0.974	0.968–0.980	< 0.001			
Immuno-inflammatory indices						
Hs-CRP	1.009	1.007–1.010	< 0.001			
ESR	1.002	0.994–1.010	0.606			
Ferritin	6.967	3.677–13.200	< 0.001			
PCT	1.029	1.017–1.042	< 0.001			
Alexin C3	0.057	0.017–0.192	< 0.001			
Alexin C4	0.003	0.001–0.070	< 0.001			

Abbreviations: *ARDS* acute respiratory distress syndrome,*HR* hazard ratio，*CI* confidence interval，*CHD* coronary heart disease，*GCS* glucocorticoid，*NMV* noninvasive mechanical ventilation，*IMV* invasive mechanical ventilation，*WBC* white blood cell count，*PT* prothrombin time，*ALT* alanine aminotransferase，*AST* aspartate aminotransferase，*TBiL* total bilirubin，*TG* triglyceride，*HDL-C* high density lipoprotein cholesterol，*LDL-C* low density lipoprotein cholesterol，*LDH* lactate dehydrogenase，*CK* creatine kinase，*eGFR* estimated glomerular filtration rate，*Hs-CRP* high-sensitivity C-reactive protein，*ESR* erythrocyte sedimentation rate，*PCT* procalcitonin，*IL-2R* interleukin-2 receptor，*IL-6* interleukin-6，*IL-8* interleukin-8，*IL-10* interleukin-10，*TNF-α* tumor necrosis factor α

Variables	Univariable			Multivariable		
	HR	95% CI	p	HR	95% CI	p
IL-2R	1.001	1.000-1.001	< 0.001			
IL-6	1.001	1.000-1.001	< 0.001			
IL-8	1.001	1.000-1.001	0.005			
IL-10	1.013	1.008–1.018	< 0.001			
TNF-α	1.047	1.034–1.060	< 0.001			

Abbreviations: *ARDS* acute respiratory distress syndrome, *HR* hazard ratio, *CI* confidence interval, *CHD* coronary heart disease, *GCS* glucocorticoid, *NMV* noninvasive mechanical ventilation, *IMV* invasive mechanical ventilation, *WBC* white blood cell count, *PT* prothrombin time, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *TBiL* total bilirubin, *TG* triglyceride, *HDL-C* high density lipoprotein cholesterol, *LDL-C* low density lipoprotein cholesterol, *LDH* lactate dehydrogenase, *CK* creatine kinase, *eGFR* estimated glomerular filtration rate, *Hs-CRP* high-sensitivity C-reactive protein, *ESR* erythrocyte sedimentation rate, *PCT* procalcitonin, *IL-2R* interleukin-2 receptor, *IL-6* interleukin-6, *IL-8* interleukin-8, *IL-10* interleukin-10, *TNF-α* tumor necrosis factor α

The dynamic changes of SII in study population

The dynamic change of SII value in-hospital was described in Fig. 4. The SII level on admission was generally lower than that before discharge and there was significantly different between two groups (survival group P = 0.002, dead group $P = 0.016$). Similar findings were seen in the non-ARDS group patients ($P < 0.001$). It suggested that the changes of the value of SII was correlated with the outcomes to some extent.

Discussion

In our study, 147 (45.09%) people died and 116 (35.58%) patients developed ARDS during hospitalization. People with higher level of SII associated with an increased risk of in-hospital mortality or developing ARDS, the same as the lower lymphocyte proportion. Older age, lower albumin levels, lower lymphocyte proportion and higher IL-6 levels were the risk factors for in-hospital death. We also found that the treatment with glucocorticoids may help to reduce the mortality. From the accumulated data, it seems that the earlier the invasive ventilation was adopted, the better the outcomes would be in patients with respiratory failure. Our research for the first time demonstrated that the relationship between SII score and the risk of patients with COVID-19 progressing to in-hospital death or ARDS.

Up to now, the pathogenesis of COVID-19 is still under investigation. Some researchers found that the increased neutrophils and platelet as well as the reduced lymphocytes were correlated with disease severity and mortality [18, 19]. These findings suggested that the immuno-inflammatory responses may play an important role in the pathogenesis of COVID-19 and in the disease progression (including a series of complications) [10, 20]. The novel biomarker, SII, including the levels of neutrophils, platelets and

lymphocytes and the changes in value could generally reflect the balance between host immune and inflammatory status. The inflammatory cells aforementioned played their respective role in the development and progression of virus-induced diseases [21, 22].

The present study analyzed that the adverse clinical prognosis (in-hospital mortality and the developed ARDS) was closely associated with the higher value of SII. The changes of hematological parameters were common in patients with COVID-19. According to current study, the high SII level resulted from increased neutrophil counts along with platelets whereas the decreased lymphocyte counts. The results of some recent clinical and experimental researches may give some explanations for our study. There are several studies have described the clinical characteristics of COVID-19 patients and they indicated that the levels of neutrophils was increased [23–25]. And our results were consistent with previous studies. Furthermore, it was reported that neutrophilia was a predictive factor with poor outcomes in patients with COVID-19 [26]. Retrospective analysis showed that about one-third of the study population suffered thrombocytopenia which suggested organ dysfunction and physiological disorder [27]. Clinically, Yang et al indicated that the nadir platelet counts were related with increased risk of in-hospital mortality and the lower the platelet count has a greater risk in death [28]. What's more, lymphocytes played a vital function in maintaining the homeostasis of immune and inflammatory response [29]. Lymphocytopenia was a prominent clinical characteristic of patients with COVID-19 and this alteration also existed in severe acute respiratory syndrome and middle east respiratory syndrome people. According to the existing literature, the potential mechanisms leading to the reduction of lymphocyte might be related to the lymphocyte necrocytosis and the lymphatic organs damage caused by SARS-CoV-2 infected [30], the lymphocyte apoptosis induced by inflammatory cytokines [31], and the inhibition of lymphocytes by metabolize dysfunction [32].

Additionally, researches have shown that the lower lymphocyte counts and the lower lymphocyte proportion both were a predictor of prognosis in COVID-19 patients and were helpful in distinguishing the severity [33, 34]. Similarly, our results showed that the lower lymphocyte proportion was negatively connected with in-hospital mortality or developed ARDS. However, the lymphocyte count was not statistically significant in multivariate analysis. This was probably because the differences in study design, population selection, statistical methods, outcome measurements and so on.

Besides, the MuLBSTA score, developed by Guo et al, was a prognostic tool for evaluating the mortality risk of viral pneumonia [35]. The scoring system was consisting of six parameters including age, hypertension, smoking, quit smoking, bacterial infection, lymphocyte and multilobe infiltrate. In our study, we found that SII had a better predictive ability than MuLBSTA score according to the ROC analysis. Therefore, the value of SII could be easier and quickily to calculate on basis of the blood routine at admission. It might be applied in clinic because of its convenience and cost-effectiveness.

It is still unclear what is the crucial cause for mortality in COVID-19. In our study, the levels of IL-2R, IL-6, IL-8, IL-10 and TNF-α were observed higher in patients in the death group than the survival group. Especially the IL-6 level was significantly positively correlated with in-hospitalization death. Our results

are similar to those of a recent study, which also reported the immune status of severe SARS-CoV-2 infected patients, with higher levels of proinflammatory and chemokines cytokines including IL-2R, IL-7, IL-10, G-CSF, IP-10, MCP1, MIP1α and TNF-α [36]. In another study, higher expression of IL-6 was also existed in critical intensive care unit (ICU) COVID-19 patients [37, 38]. These findings are consistent with SARS and MERS in that the “cytokine storm” may play an important role in the pathogenesis of COVID-19 and progression [39–41]. It suggesting that IL-6 may be a potential blocking target to calm inflammatory storm [38]. The excessive and uncontrolled inflammatory response contributes to both viral control and tissue damage. In the context of the high amounts of cytokines induced by SARS-CoV-2, the use of glucocorticoids in the severe patients may do much good than harm by reducing inflammatory-induced injury in our study. In our cohort study, glucocorticoid was given to most severe patients who was sicker and with more severe lung damage or organ damage. However, current evidence about the benefit of glucocorticoids in patients with SARS, MERS or COVID-19 is still controversial [15, 36, 42, 43]. Further evidence is still needed to assess the benefits of the treatment of glucocorticoid for patients infected with COVID-19.

The median age of the patients enrolled in our research were much older than previous reports [26, 36, 44]. Older patients are more susceptible to SARS-CoV-2 infection and also associated with higher frequency of comorbidities and low immune function [26, 44]. We also found that the serum level of albumin was negatively correlated with the outcomes of death. Albumin is the indicator of the body's nutritional status and liver function status. Previous studies have reported that liver damage was a risk factor for severe outcome and death in patients with COVID-19 [45]. Our research shows that COVID-19 patients with respiratory failure were given an early application of invasive ventilation was associated with better outcomes. Our result was different from the report of the LUNG SAFE multicenter study, which indicate that no significant difference can be observed in ICU and hospital mortality rates of patients with ARDS receiving non-invasive ventilation or mechanical ventilation [46, 47]. The application of non-invasive ventilation versus invasive ventilation in the management of COVID-19 patients with ARDS continues to be controversial [47].

We have to acknowledge that there are some limitations in this study. Firstly, the retrospective design of the study sets 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, our current work was based on a small sampling of patients with COVID-19. Thus, more prospective and larger population studies are needed to validate our conclusions. Thirdly, our work was lack of a formal follow-up protocol to assess for the condition outside of hospital due to the limits of the objective conditions.

Conclusion

The elevated SII was a novel prognostic indicator in predicting in-hospital mortality and developed ARDS. And the lymphocyte proportion was found to be negatively correlated with the risk of adverse outcomes. What’more, it seems that the invasive ventilation performed in the early stage of disease progression may improve the poor prognosis.

Abbreviations

SII: Systemic immune-inflammation index; COVID-19: Coronavirus disease 2019; ROC: Receiver operating characteristic; ARDS: Acute respiratory distress syndrome; AUC: Area under the curve; HR: Hazard ratio; WHO: World Health Organization; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus – 2; SARS-CoV: Severe acute respiratory syndrome-CoV; MERS-CoV: Middle east respiratory syndrome-CoV; GCS: Glucocorticoids; ICU: Critical intensive care unit.

Declarations

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Author's contributions

L.H. and H.B. designed the study. L.H., H.B., C.Y. and Y.Y. finished the initial draft writing. C.Y. and Y.Y. contributed to the acquirement of institutional permission. P.W. contributed to the draft correction and reviewed the final manuscript. All the authors participated in clinical data collection, follow-up, data analysis and data examination. All authors read and approved the final manuscript.

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Availability of data and materials

The raw data required to reproduce these findings cannot be shared at this time as the data also forms part of an ongoing study.

Ethics approval and consent to participate

The study was reviewed and approved by the Ethics Committee at the hospital (TJ-IRB20200362) and in accordance with the Helsinki Declaration. The requirement for Written informed consent was waived by

the Ethics Commission of the designated hospital for COVID-19 treatment due to the outbreak of this infectious disease.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflict of interest

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Figures

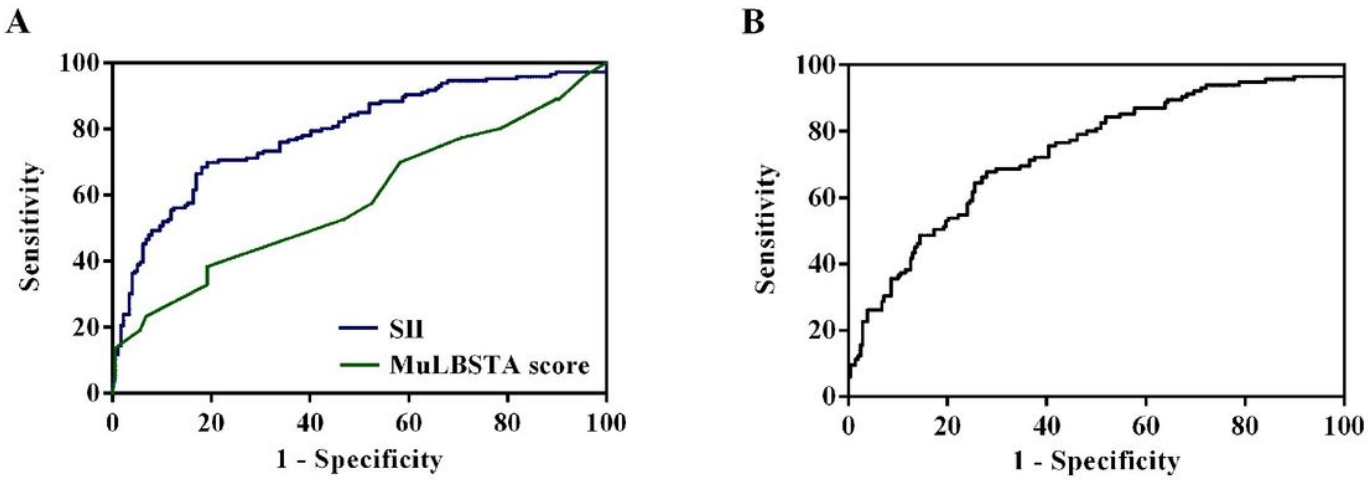

Figure 1

Analysis showing the predictive cutoff value of SII in COVID-19 patients. (A) ROC curves of SII (AUC=0.789; 95%CI=0.739–0.840; P<0.001) and MuLBSTA score (AUC=0.585; 95%CI=0.521–0.648; p=0.009) for in-hospital mortality. (B) ROC curves of SII (AUC=0.736; 95%CI=0.679–0.794; P<0.001) for developed ARDS. ROC, receiver operator characteristic; SII, systemic immune-inflammatory index; COVID-

19, coronavirus disease 2019; AUC, area under the curve; CI, confidence interval; ARDS, acute respiratory distress syndrome

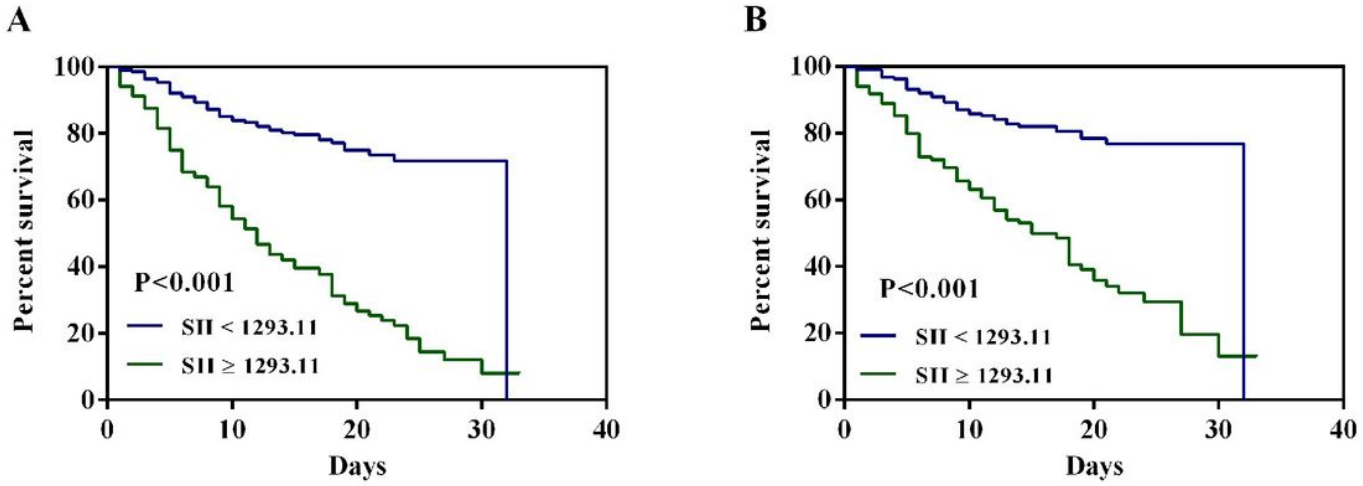

Figure 2

Kaplan-Meier curves for COVID-19 patients with in-hospital mortality and developed ARDS. (A) Kaplan-Meier survival curves of in-hospital mortality (log-rank test: P<0.001). (B) Kaplan-Meier survival curves of developed ARDS (log-rank test: P<0.001). COVID-19, coronavirus disease 2019; ARDS, acute respiratory distress syndrome; SII, systemic immune-inflammatory index.

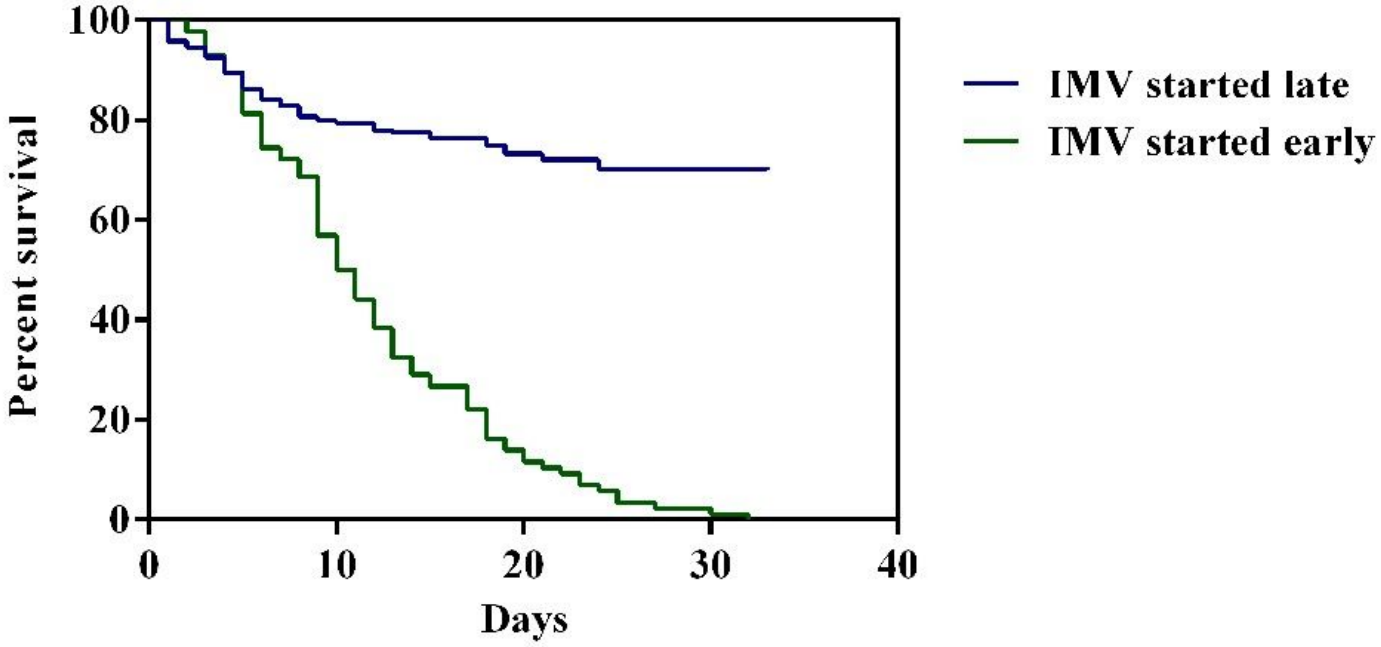

Figure 3

Kaplan-Meier curves for COVID-19 patients who received IMV in early or later stage of disease. COVID-19, coronavirus disease 2019; IMV, invasive mechanical ventilation.

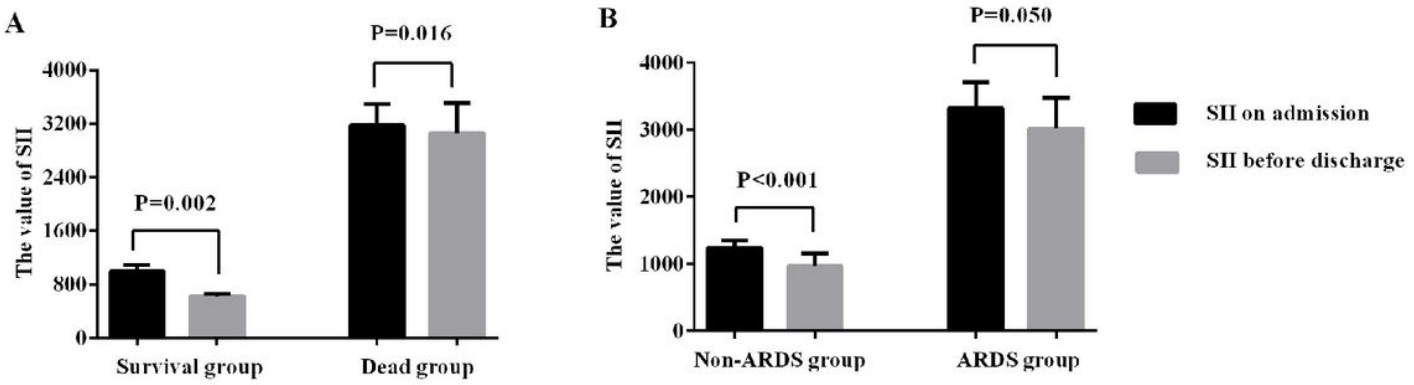

Figure 4

The dynamic changes of SII in patients with COVID-19. (A) The dynamic changes of SII between survival group and dead group. (B) The dynamic changes of SII between ARDS group and non-ARDS group. COVID-19, coronavirus disease 2019; SII, systemic immune-inflammatory index; ARDS, acute respiratory distress syndrome